CHAPTER 82

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.

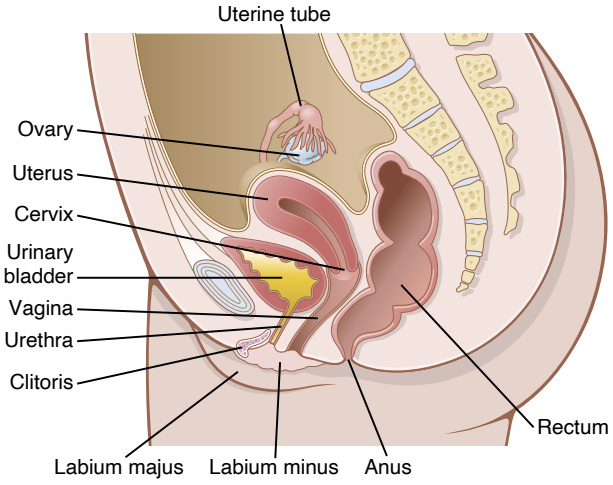

Figure 82-1. The female reproductive organs.

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

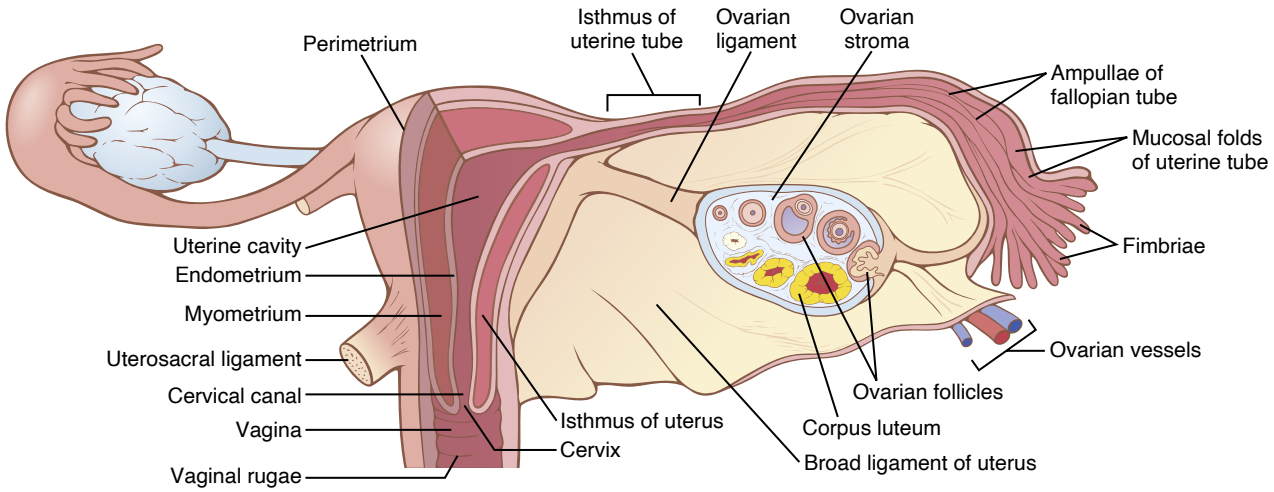

Figure 82-2. Internal structures of the uterus, ovary, and a uterine tube.

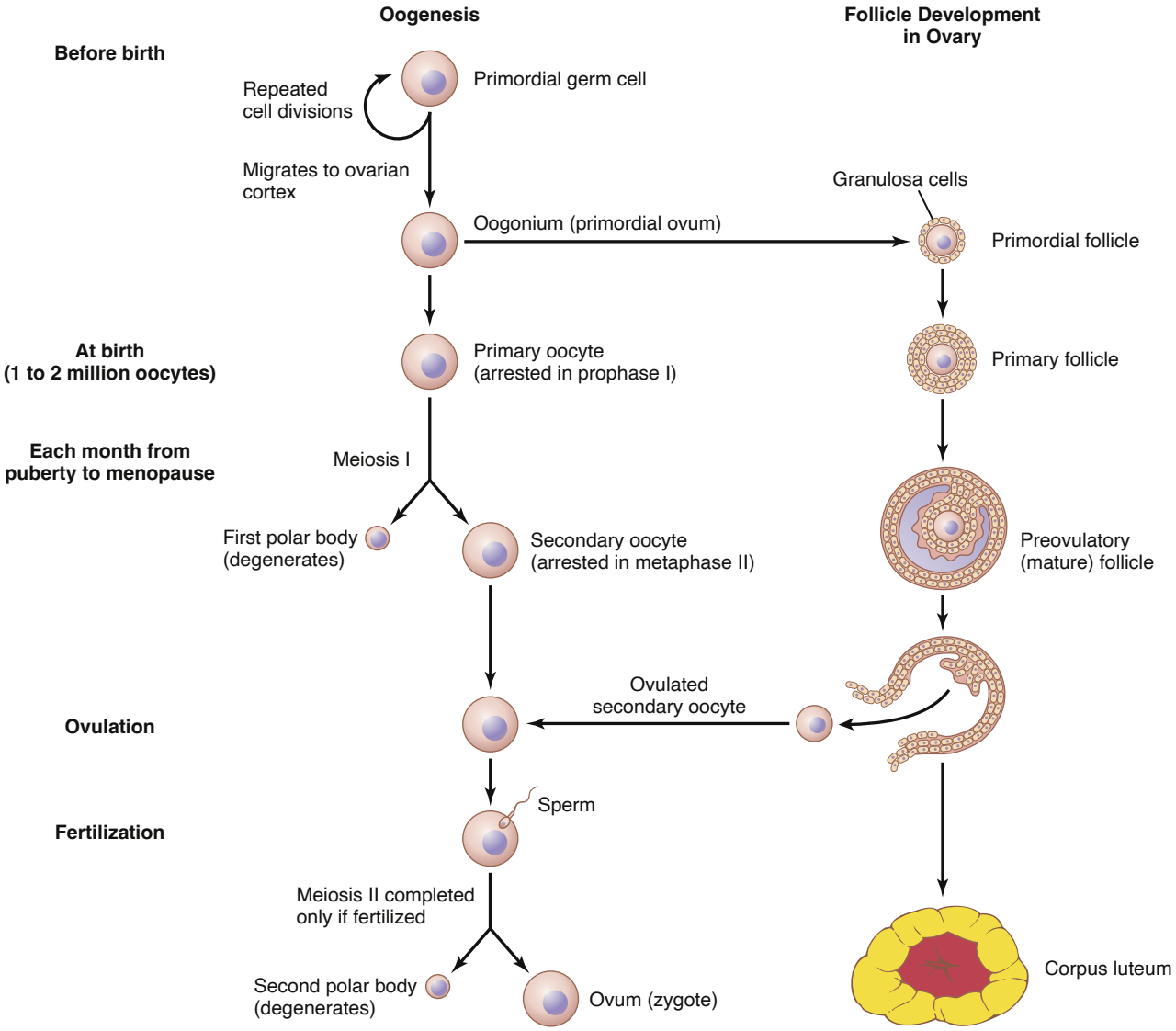

Figure 82-3. Oogenesis and follicle development.

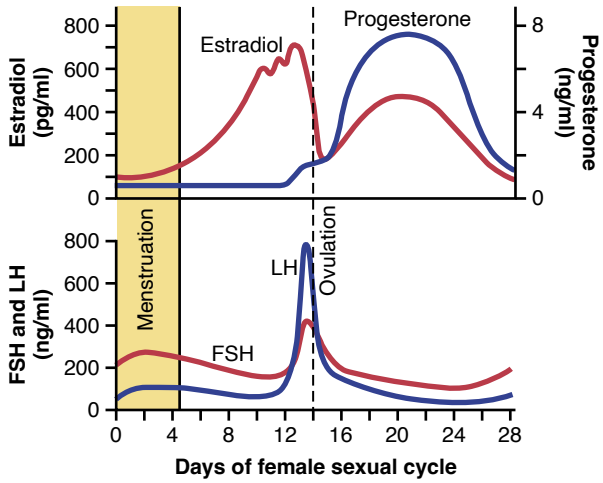

Figure 82-4. Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle. FSH, Follicle-stimulating hormone; LH, luteinizing hormone.

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,

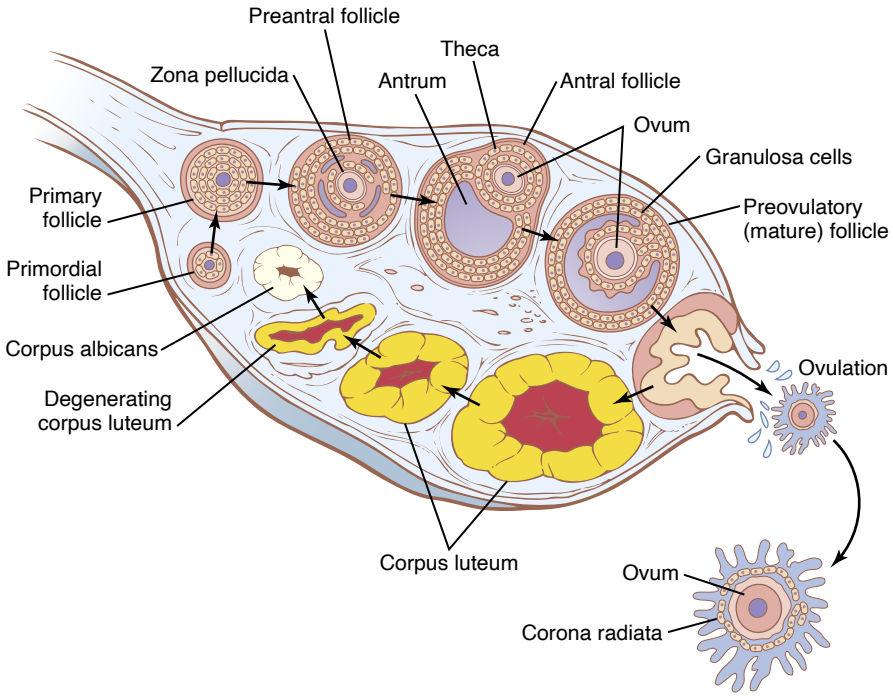

Figure 82-5. Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

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 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.

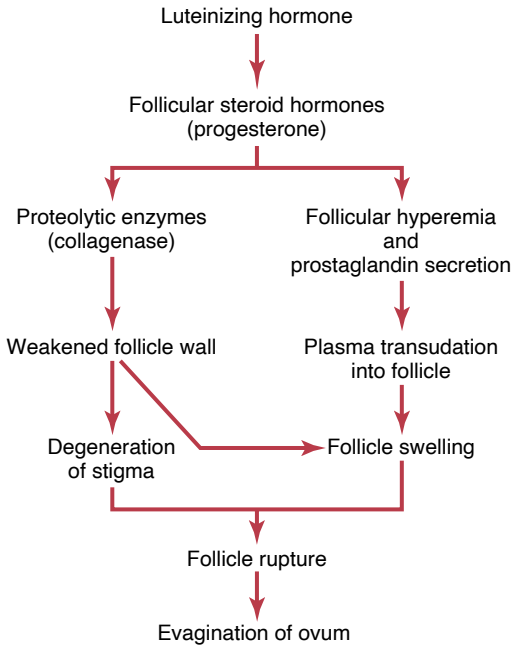

Figure 82-6. The postulated mechanism of ovulation.

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**).

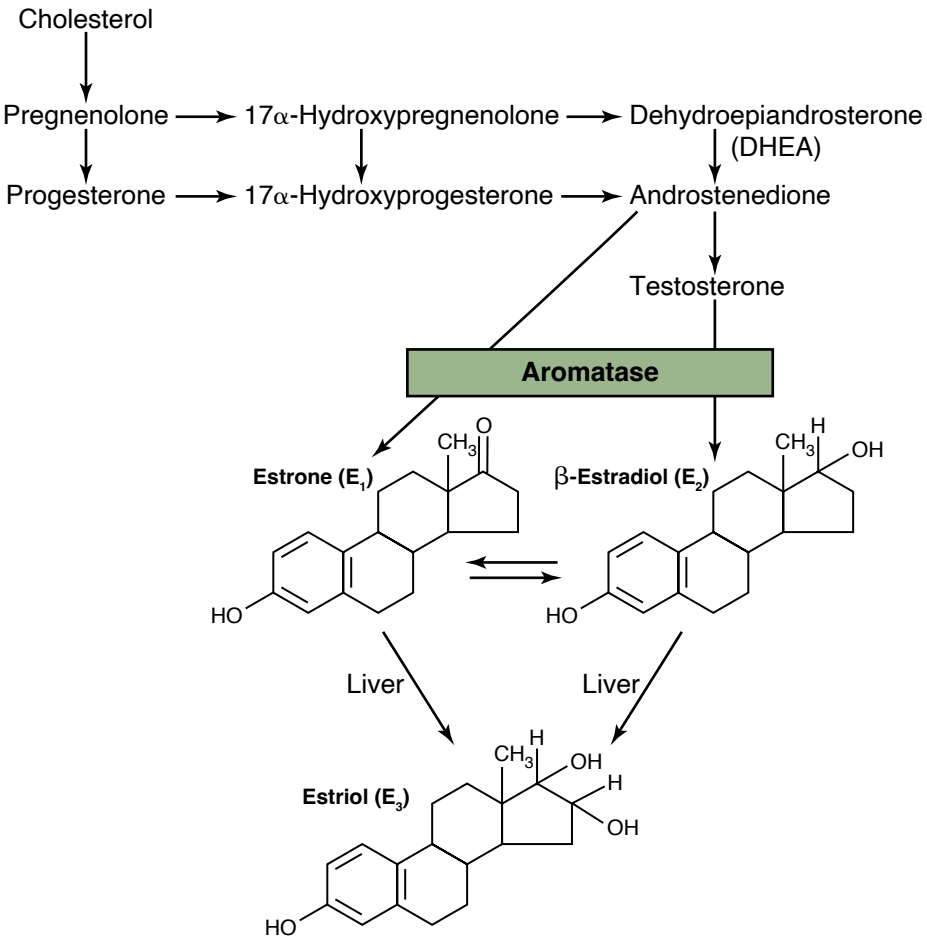

Figure 82-7. Synthesis of the principal female hormones. The chemical structures of the precursor hormones, including progesterone, are shown in Figure 78-2.

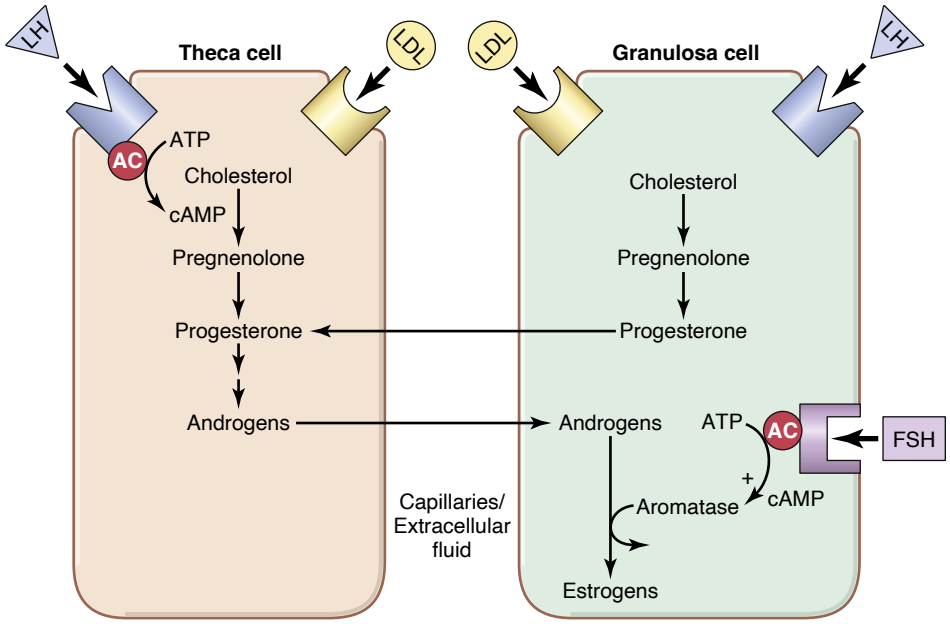

Figure 82-8. Interaction of follicular theca and granulosa cells for production of estrogens. The theca cells, under the control of luteinizing hormone (LH), produce androgens that diffuse into the granulosa cells. In mature follicles, follicle-stimulating hormone (FSH) acts on granulosa cells to stimulate 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.

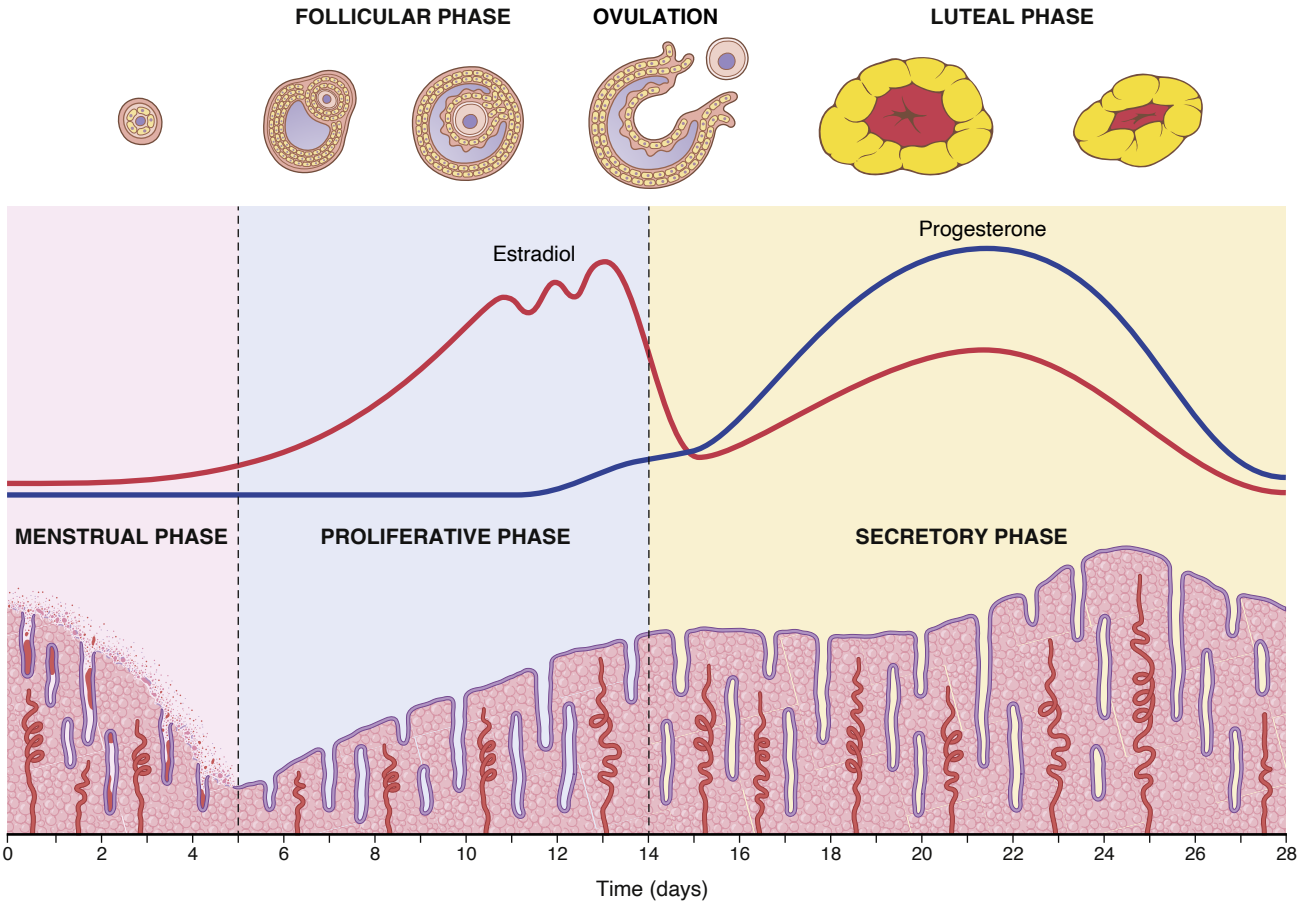

Figure 82-9. Phases of endometrial growth and menstruation during each monthly female sexual cycle.

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:

Glu - His - Trp - Ser - Tyr - Gly - Leu - Arg - Pro - Gly - NH_2

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

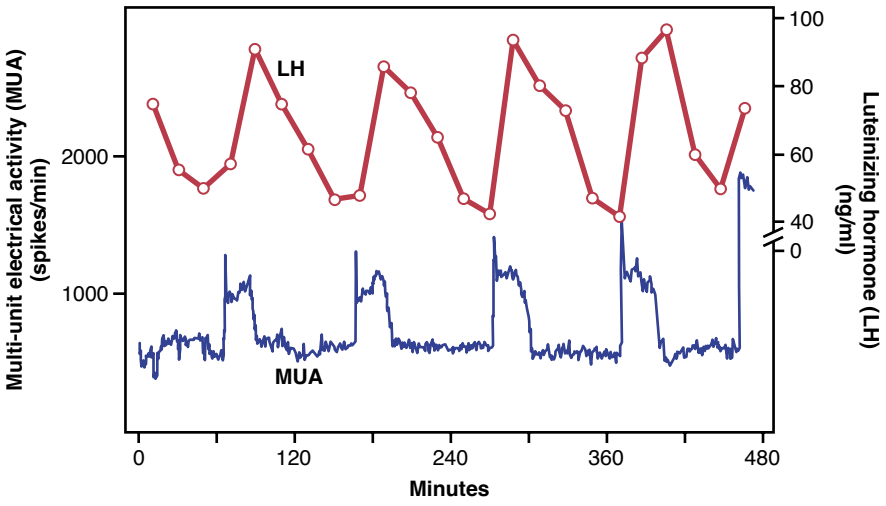

Figure 82-10. Shown is a pulsatile change in luteinizing hormone (LH) in the peripheral circulation of a pentobarbital-anesthetized ovariectomized rhesus monkey *(red line)* and a minute by minute recording of *multi-unit electrical activity* (MUA) in the mediobasal hypothalamus *(blue line). (Data from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

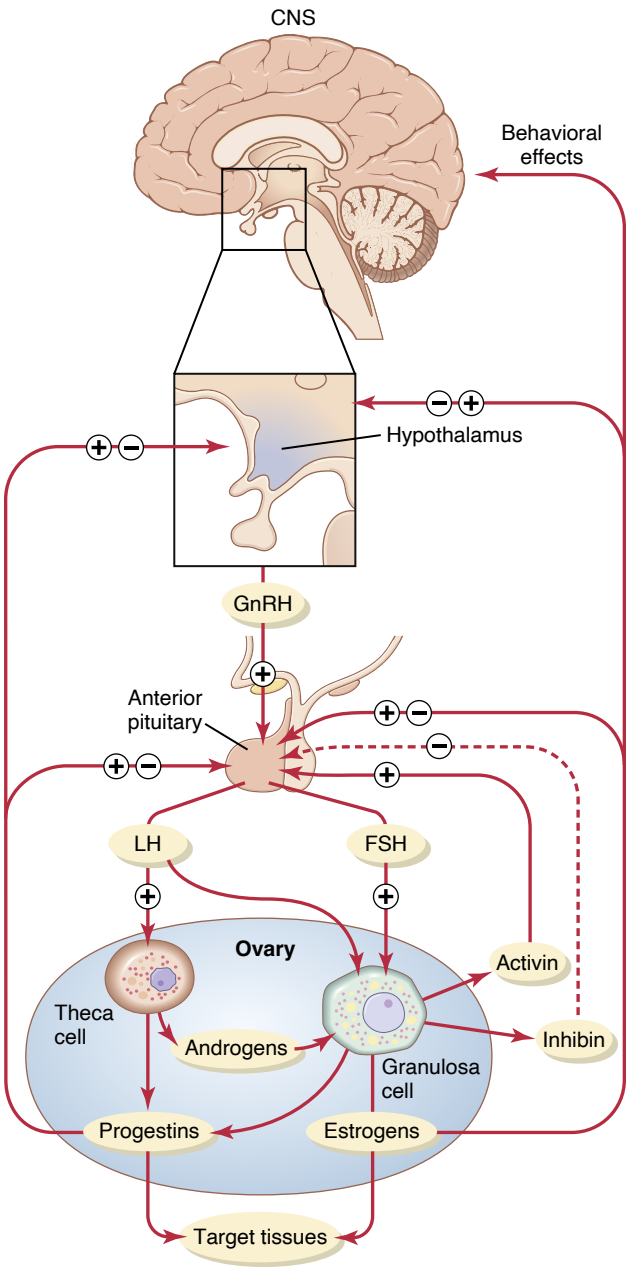

Figure 82-11. Feedback regulation of the hypothalamic-pituitary-ovarian axis in females. Stimulatory effects are shown by plus signs (+); negative feedback inhibitory effects are shown by minus signs (–). Estrogens and progestins exert negative and positive feedback effects on the anterior pituitary 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).

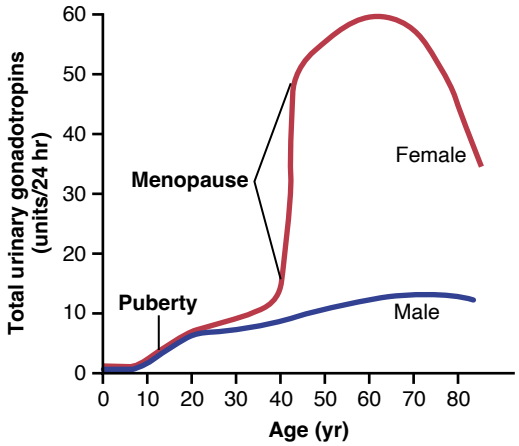

Figure 82-12. Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.

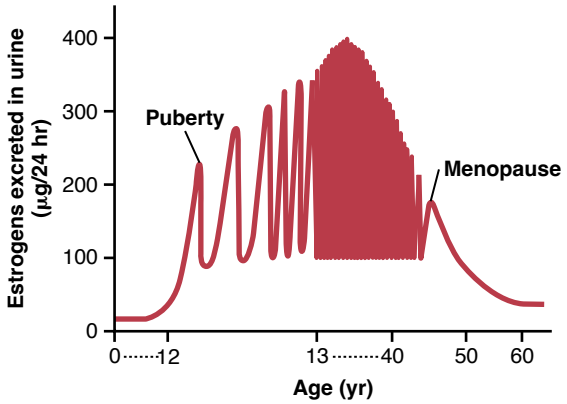

Figure 82-13. Estrogen secretion throughout the sexual life of the female human being.

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.

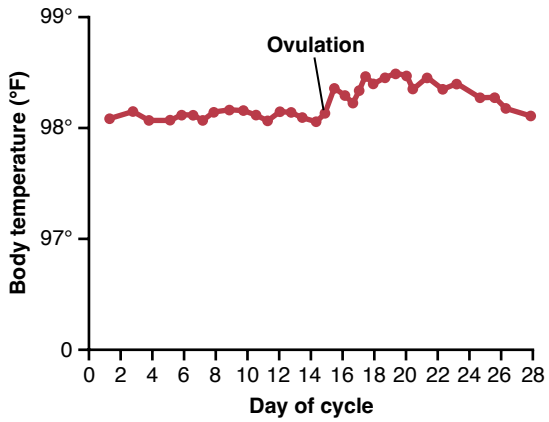

Figure 82-14. Elevation in body temperature shortly after ovulation.

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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CHAPTER 83

Pregnancy and Lactation

In Chapters 81 and 82, the sexual functions of the male and female are described to the point of fertilization of the ovum. If the ovum becomes fertilized, a new sequence of events called *gestation* or *pregnancy* takes place, and the fertilized ovum eventually develops into a full-term fetus. The purpose of this chapter is to discuss the early stages of ovum development after fertilization and then to discuss the physiology of pregnancy. In Chapter 84, some special aspects of fetal and early childhood physiology are discussed.

MATURATION AND FERTILIZATION OF THE OVUM

While still in the ovary, the ovum is in the *primary oocyte* stage. Shortly before it is released from the ovarian follicle, its nucleus divides by meiosis and a *first polar body* is expelled from the nucleus of the oocyte (see **Figure 82-3**). The primary oocyte then becomes the *secondary oocyte.* In this process, each of the 23 pairs of chromosomes loses one of its partners, which becomes incorporated in a *polar body* that is expelled. This leaves 23 *unpaired* chromosomes in the secondary oocyte. It is at this time that the ovum, which is still in the secondary oocyte stage, is ovulated into the abdominal cavity. Then, almost immediately, it enters the fimbriated end of one of the fallopian tubes.

Entry of the Ovum Into the Fallopian Tube (Uterine Tube). When ovulation occurs, the ovum, along with a hundred or more attached granulosa cells that constitute the *corona radiata,* is expelled directly into the peritoneal cavity and must then enter one of the fallopian tubes (also called *uterine tubes*) to reach the cavity of the uterus. The fimbriated ends of each fallopian tube fall naturally around the ovaries. The inner surfaces of the fimbriated tentacles are lined with ciliated epithelium, and the *cilia* are activated by estrogen from the ovaries, which causes the cilia to beat toward the opening, or *ostium,* of the involved fallopian tube. One can actually see a slow fluid current flowing toward the ostium. By this means, the ovum enters one of the fallopian tubes.

Although one might suspect that many ova fail to enter the fallopian tubes, conception studies suggest that up to 98% of ova succeed in this task. Indeed, in some recorded cases, women with one ovary removed and the opposite fallopian tube removed have had several children with relative ease of conception, thus demonstrating that ova can even enter the opposite fallopian tube.

Fertilization of the Ovum. After the male ejaculates semen into the vagina during intercourse, a few sperm are transported within 5 to 10 minutes upward from the vagina and through the uterus and fallopian tubes to the *ampullae* of the fallopian tubes near the ovarian ends of the tubes. This transport of the sperm is aided by contractions of the uterus and fallopian tubes stimulated by prostaglandins in the male seminal fluid and also by oxytocin released from the posterior pituitary gland of the female during her orgasm. Of the almost half a billion sperm deposited in the vagina, a few thousand succeed in reaching each ampulla.

Fertilization of the ovum **(Figure 83-1)** normally takes place in the ampulla of one of the fallopian tubes soon after both the sperm and the ovum enter the ampulla. Before a sperm can enter the ovum, however, it must first penetrate the multiple layers of granulosa cells attached to the outside of the ovum (the *corona radiata*) and then bind to and penetrate the *zona pellucida* surrounding the ovum. The mechanisms used by the sperm for these purposes are presented in Chapter 81.

Once a sperm has entered the ovum (which is still in the secondary oocyte stage of development), the oocyte divides again to form the *mature ovum* plus a *second polar body* that is expelled (see **Figure 82-3**). The mature ovum still carries in its nucleus (now called the *female pronucleus*) 23 chromosomes. One of these chromosomes is the female chromosome, known as the *X chromosome.*

In the meantime, the fertilizing sperm has also changed. On entering the ovum, its head swells to form a *male pronucleus,* shown in **Figure 83-1*D***. Later, the 23 unpaired chromosomes of the male pronucleus and the 23 unpaired chromosomes of the female pronucleus align themselves to re-form a complete complement of 46 chromosomes (23 pairs) in the *fertilized ovum* or *zygote* (see **Figure 83-1*E***).

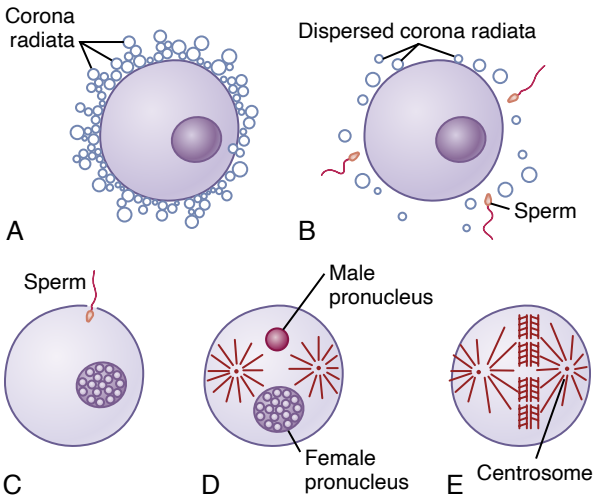

Figure 83-1. Fertilization of the ovum. **A,** The mature ovum surrounded by the corona radiata. **B,** Dispersal of the corona radiata. **C,** Entry of the sperm. **D,** Formation of the male and female pronuclei. **E,** Reorganization of a full complement of chromosomes and beginning division of the ovum. *(Modified from Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, 7th ed. Philadelphia: WB Saunders, 1974.)*

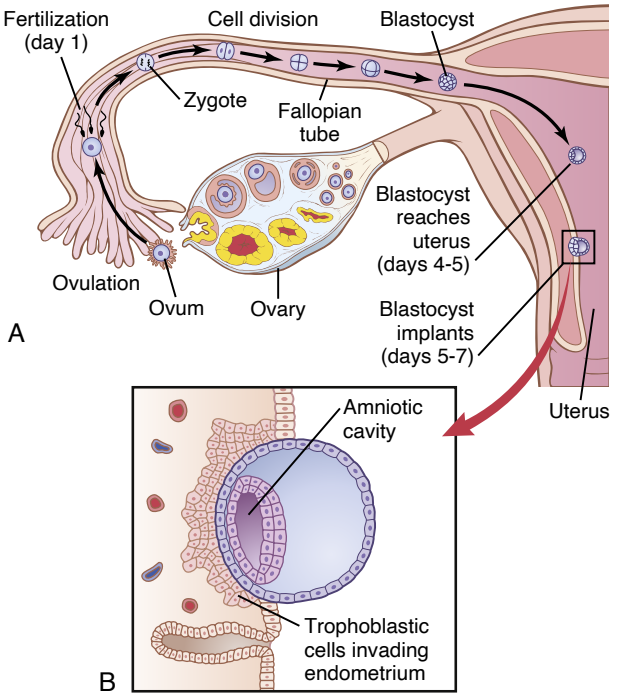

Figure 83-2. A, Ovulation, fertilization of the ovum in the fallopian tube, and implantation of the blastocyst in the uterus. **B,** The action of trophoblast cells in implantation of the blastocyst in the uterine endometrium.

WHAT DETERMINES THE SEX OF THE FETUS THAT IS CREATED?

Half of the mature sperm carry in their genome an X chromosome (the female chromosome) and half carry a Y chromosome (the male chromosome). Therefore, if an X chromosome from a sperm combines with an X chromosome from an ovum, giving an XX combination, a female child will be born, as explained in Chapter 81. If a Y chromosome from a sperm is paired with an X chromosome from an ovum, giving an XY combination, a male child will be born.

TRANSPORT OF THE FERTILIZED OVUM IN THE FALLOPIAN TUBE

After fertilization has occurred, an additional 3 to 5 days is normally required for transport of the fertilized ovum through the remainder of the fallopian tube into the cavity of the uterus (**Figure 83-2**). This transport is effected mainly by a feeble fluid current in the tube resulting from epithelial secretion plus action of the ciliated epithelium that lines the tube; the cilia always beat toward the uterus. Weak contractions of the fallopian tube may also aid passage of the ovum.

The fallopian tubes are lined with a rugged cryptoid surface that impedes passage of the ovum despite the fluid current. Also, the *isthmus* of the fallopian tube (the last 2 centimeters before the tube enters the uterus) remains spastically contracted for about the first 3 days after ovulation. After this time, the rapidly increasing progesterone secreted by the ovarian corpus luteum first promotes increasing progesterone receptors on the fallopian tube smooth muscle cells; then the progesterone activates the receptors, relaxing the tubules and allowing entry of the ovum into the uterus.

This delayed transport of the fertilized ovum through the fallopian tube allows several stages of cell division to occur before the dividing ovum—now called a *blastocyst,* with about 100 cells—enters the uterus. During this time, the fallopian tube secretory cells produce large quantities of secretions used for nutrition of the developing blastocyst.

IMPLANTATION OF THE BLASTOCYST IN THE UTERUS

After reaching the uterus, the developing blastocyst usually remains in the uterine cavity an additional 1 to 3 days before it implants in the endometrium; thus, implantation ordinarily occurs on about the fifth to seventh day after ovulation. Before implantation, the blastocyst obtains its nutrition from the uterine endometrial secretions, called "uterine milk."

Implantation results from the action of *trophoblast cells* that develop over the surface of the blastocyst. These cells secrete proteolytic enzymes that digest and liquefy the adjacent cells of the uterine endometrium. Some of the fluid and nutrients released are actively transported by the same trophoblast cells into the blastocyst, adding more sustenance for growth. **Figure 83-3** shows an early implanted human blastocyst with a small embryo. Once implantation has taken place, the trophoblast cells and other adjacent cells (from the blastocyst and the uterine

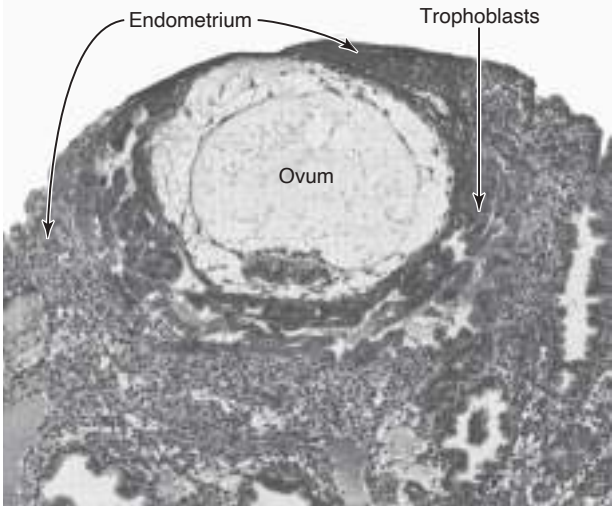

Figure 83-3. Implantation of the early human embryo, showing trophoblastic digestion and invasion of the endometrium. *(Courtesy Dr. Arthur Hertig.)*

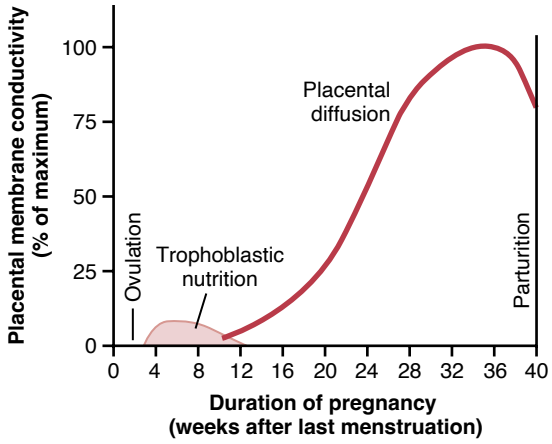

Figure 83-4. Nutrition of the fetus. Most of the early nutrition is due to trophoblastic digestion and absorption of nutrients from the endometrial decidua, and essentially all the later nutrition results from diffusion through the placental membrane.

endometrium) proliferate rapidly, forming the placenta and the various membranes of pregnancy.

EARLY NUTRITION OF THE EMBRYO

In Chapter 82, we pointed out that the progesterone secreted by the ovarian corpus luteum during the latter half of each monthly sexual cycle has an effect on the uterine endometrium, converting the endometrial stromal cells into large swollen cells containing extra quantities of glycogen, proteins, lipids, and even some minerals necessary for development of the *conceptus* (the embryo and its adjacent parts or associated membranes). Then, when the conceptus implants in the endometrium, continued secretion of progesterone causes the endometrial cells to swell further and to store even more nutrients. These cells are now called *decidual cells,* and the total mass of cells is called the *decidua.*

As the trophoblast cells invade the decidua, digesting and imbibing it, the stored nutrients in the decidua are used by the embryo for growth and development. During the first week after implantation, this is the only means by which the embryo can obtain nutrients; the embryo continues to obtain at least some of its nutrition in this way for up to 8 weeks, although the placenta also begins to provide nutrition after about the 16th day beyond fertilization (a little more than 1 week after implantation). **Figure 83-4** shows this trophoblastic period of nutrition, which gradually gives way to placental nutrition.

ANATOMY AND FUNCTION OF THE PLACENTA

While the trophoblastic cords from the blastocyst are attaching to the uterus, blood capillaries grow into the cords from the vascular system of the newly forming embryo. About 21 days after fertilization, blood also begins to be pumped by the heart of the human embryo. Simultaneously, *blood sinuses* supplied with blood from the mother develop around the outsides of the trophoblastic cords. The trophoblast cells send out more and more projections, which become *placental villi* into which fetal capillaries grow. Thus, the villi, carrying fetal blood, are surrounded by sinuses that contain maternal blood.

The final structure of the placenta is shown in **Figure 83-5**. Note that the blood of the fetus flows through two *umbilical arteries,* then into the capillaries of the villi, and finally back through a single *umbilical vein* into the fetus. At the same time, the mother's blood flows from her *uterine arteries* into large *maternal sinuses* that surround the villi and then back into the *uterine veins* of the mother. The lower part of **Figure 83-5** shows the relationship between the fetal blood of each fetal placental villus and the blood of the mother surrounding the outsides of the villus in the fully developed placenta.

The total surface area of all the villi of the mature placenta is only a few square meters—many times less than the area of the pulmonary membrane in the lungs. Nevertheless, nutrients and other substances pass through this placental membrane mainly by diffusion in much the same manner that diffusion occurs through the alveolar membranes of the lungs and the capillary membranes elsewhere in the body.

PLACENTAL PERMEABILITY AND MEMBRANE DIFFUSION CONDUCTANCE

The major function of the placenta is to provide for diffusion of foodstuffs and oxygen from the mother's blood into the fetus's blood and diffusion of excretory products from the fetus back into the mother.

In the early months of pregnancy, the placental membrane is still thick because it is not fully developed. Therefore, its permeability is low. Further, the surface area is small because the placenta has not grown significantly.

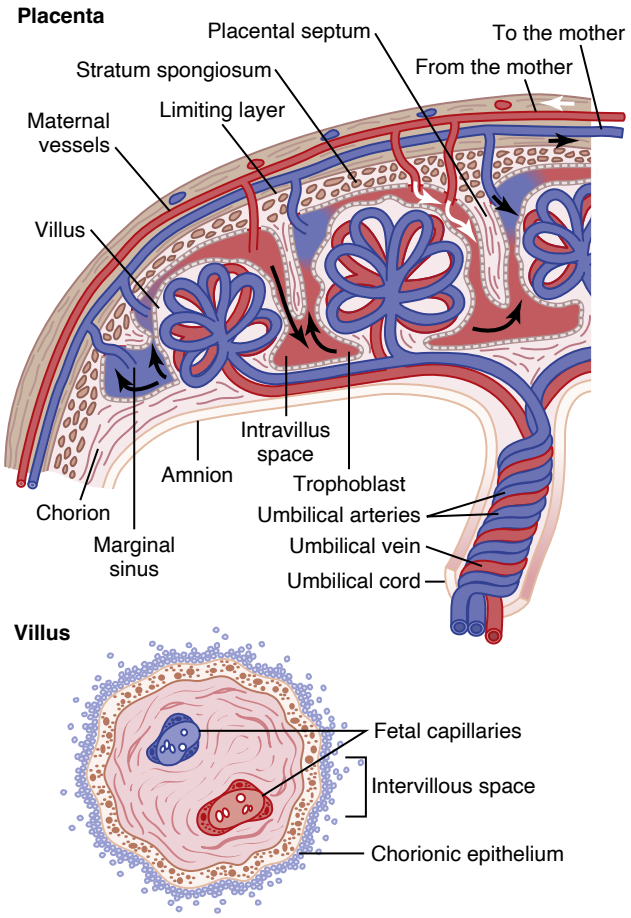

Figure 83-5. *Top,* Organization of the mature placenta. *Bottom,* Relationship of the fetal blood in the villus capillaries to the mother's blood in the intervillous spaces.

Therefore, the total diffusion conductance is minuscule at first. In later pregnancy, the permeability increases because of thinning of the membrane diffusion layers and because the surface area expands many times over, thus giving the tremendous increase in placental diffusion shown in **Figure 83-4**.

Rarely, "breaks" occur in the placental membrane, which allows fetal blood cells to pass into the mother or, even less commonly, the mother's cells to pass into the fetus. Fortunately, it is rare for the fetus to bleed severely into the mother's circulation because of a ruptured placental membrane.

Diffusion of Oxygen Through the Placental Membrane. Almost the same principles for diffusion of oxygen through the pulmonary membrane (discussed in detail in Chapter 40) are applicable for diffusion of oxygen through the placental membrane. The dissolved oxygen in the blood of the large maternal sinuses passes into the fetal blood by *simple diffusion,* driven by an oxygen pressure gradient from the mother's blood to the fetus's blood. Near the end of pregnancy, the mean partial pressure of oxygen (P_{O_2}) of the mother's blood in the placental sinuses is about 50 mm Hg, and the mean P_{O_2} in the fetal blood

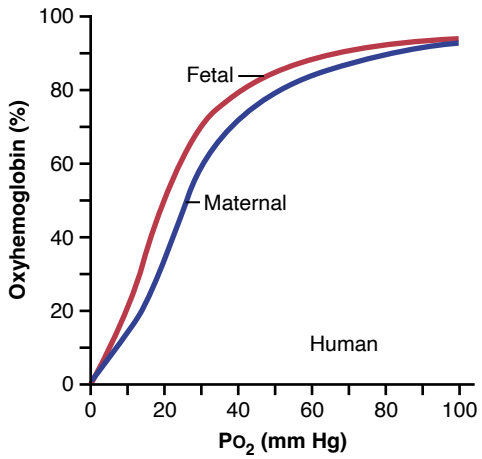

Figure 83-6. Oxyhemoglobin dissociation curves for maternal *(blue curve)* and fetal *(red curve)* blood, showing that fetal blood can carry a greater quantity of oxygen than can maternal blood for a given blood P_{O_2}. *(Data from Metcalfe J, Moll W, Bartels H: Gas exchange across the placenta. Fed Proc 23:775, 1964.)*

after it becomes oxygenated in the placenta is about 30 mm Hg. Therefore, the mean pressure gradient for diffusion of oxygen through the placental membrane is about 20 mm Hg.

One might wonder how it is possible for a fetus to obtain sufficient oxygen when the fetal blood leaving the placenta has a P_{O_2} of only 30 mm Hg. There are three reasons why even this low P_{O_2} is capable of allowing the fetal blood to transport almost as much oxygen to the fetal tissues as is transported by the mother's blood to her tissues.

First, the hemoglobin of the fetus is mainly *fetal hemoglobin,* which is a type of hemoglobin synthesized in the fetus before birth. **Figure 83-6** shows the comparative oxygen dissociation curves for maternal hemoglobin and fetal hemoglobin, demonstrating that the curve for fetal hemoglobin is shifted to the left of that for maternal hemoglobin. This means that at the low P_{O_2} levels in fetal blood, the fetal hemoglobin can carry 20% to 50% more oxygen than can maternal hemoglobin.

Second, the *hemoglobin concentration of fetal blood is about 50% greater than that of the mother,* which is an even more important factor in enhancing the amount of oxygen transported to the fetal tissues.

Third, the *Bohr effect,* which is explained in relation to the exchange of carbon dioxide and oxygen in the lung in Chapter 41, provides another mechanism to enhance the transport of oxygen by fetal blood. That is, hemoglobin can carry more oxygen at a low P_{CO_2} than it can at a high P_{CO_2}. The fetal blood entering the placenta carries large amounts of carbon dioxide, but much of this carbon dioxide diffuses from the fetal blood into the maternal blood. Loss of the carbon dioxide makes the fetal blood more alkaline, whereas the increased carbon dioxide in the maternal blood makes it more acidic.

These changes increase the capacity of fetal blood to combine with oxygen and decrease oxygen binding of maternal blood, which forces still more oxygen from the

maternal blood while enhancing oxygen uptake by the fetal blood. Thus, the Bohr shift operates in one direction in the maternal blood and in the other direction in the fetal blood. These two effects make the Bohr shift twice as important here as it is for oxygen exchange in the lungs; therefore, it is called the *double Bohr effect.*

By these three means, the fetus is capable of receiving more than adequate oxygen through the placental membrane, despite the fact that the fetal blood leaving the placenta has a P_{O_2} of only 30 mm Hg.

The total *diffusing capacity* of the entire placenta for oxygen at term is about 1.2 ml of oxygen per minute per mm Hg oxygen pressure difference across the membrane, which compares favorably with that of the lungs of the newborn baby.

Diffusion of Carbon Dioxide Through the Placental Membrane. Carbon dioxide is continually formed in the fetal tissues in the same way that it is formed in maternal tissues, and the only means for excreting the carbon dioxide from the fetus is through the placenta into the mother's blood. The partial pressure of carbon dioxide (P_{CO_2}) of the fetal blood is 2 to 3 mm Hg higher than that of the maternal blood. This small pressure gradient for carbon dioxide across the membrane is more than sufficient to allow adequate diffusion of carbon dioxide because the extreme solubility of carbon dioxide in the placental membrane allows carbon dioxide to diffuse about 20 times as rapidly as oxygen.

Diffusion of Foodstuffs Through the Placental Membrane. Other metabolic substrates needed by the fetus diffuse into the fetal blood in the same manner **as** oxygen. For example, in the late stages of pregnancy, the fetus often uses as much glucose as is used by the entire body of the mother. To provide this much glucose, the trophoblast cells lining the placental villi provide for *facilitated diffusion* of glucose through the placental membrane—that is, the glucose is transported by carrier molecules in the trophoblast cells of the membrane. Even so, the glucose level in fetal blood is 20% to 30% lower than that in maternal blood.

Because of the high solubility of fatty acids in cell membranes, these fatty acids also diffuse from the maternal blood into the fetal blood, but more slowly than glucose, so glucose is used more easily by the fetus for nutrition. Also, such substances as ketone bodies and potassium, sodium, and chloride ions diffuse with relative ease from the maternal blood into the fetal blood.

Excretion of Waste Products Through the Placental Membrane. In the same manner that carbon dioxide diffuses from the fetal blood into the maternal blood, other excretory products formed in the fetus also diffuse through the placental membrane into the maternal blood and are then excreted along with the excretory products of the mother. These products include especially the *nonprotein nitrogens* such as *urea, uric acid,* and *creatinine.* The level of urea in fetal blood is only slightly greater than that in maternal blood because urea diffuses through the placental membrane with great ease. However, creatinine, which does not diffuse as easily, has a fetal blood concentration considerably higher than that in the mother's blood. Therefore, excretion from the fetus depends mainly, if not entirely, on the diffusion gradients across the placental membrane and its permeability and surface area. Because there are higher concentrations of the excretory products in the fetal blood than in the maternal blood, there is continual diffusion of these substances from the fetal blood to the maternal blood.

HORMONAL FACTORS IN PREGNANCY

In pregnancy, the placenta forms especially large quantities of *human chorionic gonadotropin, estrogens, progesterone,* and *human chorionic somatomammotropin,* the first three of which, and probably the fourth as well, are all essential to a normal pregnancy.

HUMAN CHORIONIC GONADOTROPIN CAUSES PERSISTENCE OF THE CORPUS LUTEUM AND PREVENTS MENSTRUATION

Menstruation normally occurs in a nonpregnant woman about 14 days after ovulation, at which time most of the endometrium of the uterus sloughs away from the uterine wall and is expelled to the exterior. If this happens after an ovum has implanted, the pregnancy will terminate. However, this sloughing is prevented by secretion of *human chorionic gonadotropin* by the newly developing embryonic tissues.

Coincidental with the development of the trophoblast cells from the early fertilized ovum, human chorionic gonadotropin is secreted by the syncytial trophoblast cells into the fluids of the mother, as shown in **Figure 83-7**. Secretion of this hormone can first be measured in the blood 8 to 9 days after ovulation, shortly after the blastocyst implants in the endometrium. Then, the secretion rate rises rapidly to reach a maximum at about 10 to 12 weeks of pregnancy and decreases back to a lower value by 16 to 20 weeks. It continues at this level for the remainder of the pregnancy.

Function of Human Chorionic Gonadotropin. Human chorionic gonadotropin is a glycoprotein having a molecular weight of about 39,000 and much the same molecular structure and function as luteinizing hormone secreted by the pituitary gland. The most important function of human chorionic gonadotropin is to prevent involution of the corpus luteum at the end of the monthly female sexual cycle. Instead, it causes the corpus luteum to secrete even larger quantities of its sex hormones—progesterone and estrogens—for the next few months. These sex hormones prevent menstruation and cause the endometrium

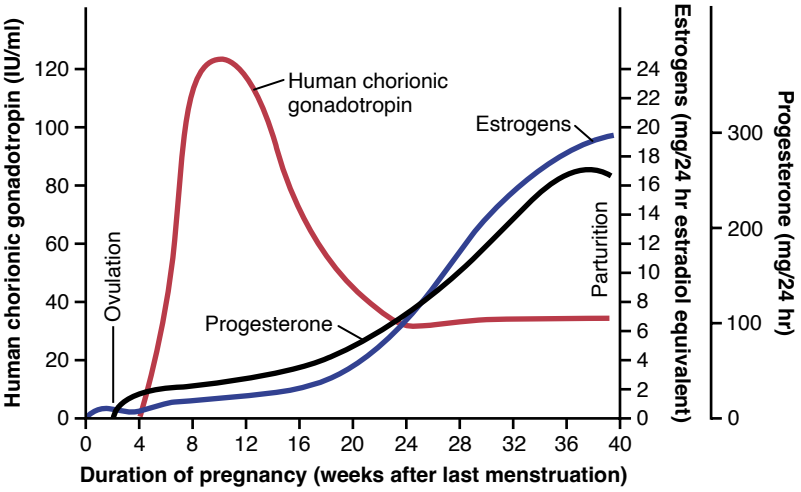

Figure 83-7. Rates of secretion of estrogens *(blue curve)* and progesterone *(black curve)* and concentration of human chorionic gonadotropin *(red curve)* at different stages of pregnancy.

to continue to grow and store large amounts of nutrients rather than being shed in the menstruum. As a result, the *decidua-like cells* that develop in the endometrium during the normal female sexual cycle become actual *decidual cells*—greatly swollen and nutritious—at about the time that the blastocyst implants.

Under the influence of human chorionic gonadotropin, the corpus luteum in the mother's ovary grows to about twice its initial size by a month or so after pregnancy begins. Its continued secretion of estrogens and progesterone maintains the decidual nature of the uterine endometrium, which is necessary for early development of the fetus.

If the corpus luteum is removed before approximately the seventh week of pregnancy, spontaneous abortion almost always occurs, sometimes even up to the 12th week. After that time, the placenta secretes sufficient quantities of progesterone and estrogens to maintain pregnancy for the remainder of the gestation period. The corpus luteum involutes slowly after the 13th to 17th week of gestation.

Human Chorionic Gonadotropin Stimulates the Male Fetal Testes to Produce Testosterone. Human chorionic gonadotropin also exerts an *interstitial cell*–stimulating effect on the testes of the male fetus, resulting in production of testosterone in male fetuses until the time of birth. This small secretion of testosterone during gestation is what causes the fetus to grow male sex organs instead of female organs. Near the end of pregnancy, testosterone secreted by the fetal testes also causes the testes to descend into the scrotum.

SECRETION OF ESTROGENS BY THE PLACENTA

The placenta, like the corpus luteum, secretes estrogens and progesterone. Histochemical and physiological studies show that these two hormones, like most other placental hormones, are secreted by the *syncytial trophoblast* cells of the placenta.

Figure 83-7 shows that toward the end of pregnancy, the daily production of placental estrogens increases to about 30 times the mother's normal level of production. However, secretion of estrogens by the placenta is quite different from secretion by the ovaries. Most important, the estrogens secreted by the placenta are not synthesized de novo from basic substrates in the placenta. Instead, they are formed almost entirely from androgenic steroid compounds, *dehydroepiandrosterone* and *16-hydroxydehydroepiandrosterone,* which are formed in the mother's adrenal glands and in the fetus's adrenal glands. These weak androgens are transported by the blood to the placenta and converted by the trophoblast cells into estradiol, estrone, and estriol. The cortices of the fetal adrenal glands are extremely large, and about 80% consists of a so-called *fetal zone,* the primary function of which seems to be to secrete dehydroepiandrosterone during pregnancy.

Function of Estrogen in Pregnancy. In Chapter 82, we pointed out that estrogens exert mainly a proliferative function on most reproductive and associated organs of the mother. During pregnancy, the extreme quantities of estrogens cause (1) enlargement of the mother's uterus, (2) enlargement of the mother's breasts and growth of the breast ductal structure, and (3) enlargement of the mother's female external genitalia.

The estrogens also relax the pelvic ligaments of the mother, so the sacroiliac joints become relatively limber, and the symphysis pubis becomes elastic. These changes allow easier passage of the fetus through the birth canal. There is reason to believe that estrogens also affect many general aspects of fetal development during pregnancy—for example, by affecting the rate of cell reproduction in the early embryo.

SECRETION OF PROGESTERONE BY THE PLACENTA

Progesterone is just as essential as estrogen for a successful pregnancy. In addition to being secreted in moderate

quantities by the corpus luteum at the beginning of pregnancy, progesterone is secreted later in tremendous quantities by the placenta, as shown in **Figure 83-7**.

The following special effects of progesterone are essential for the normal progression of pregnancy:

1. Progesterone causes decidual cells to develop in the uterine endometrium. These cells play an important role in nutrition of the early embryo.
2. Progesterone decreases contractility of the pregnant uterus, thus preventing uterine contractions from causing spontaneous abortion.
3. Progesterone contributes to development of the conceptus even before implantation because it specifically increases secretions of the mother's fallopian tubes and uterus to provide appropriate nutrition for the developing *morula* (the spherical mass of 16 to 32 blastomeres formed before the blastula) and *blastocyst.* Progesterone may also affect cell cleavage in the early developing embryo.
4. The progesterone secreted during pregnancy helps estrogen prepare the mother's breasts for lactation, which is discussed later in this chapter.

HUMAN CHORIONIC SOMATOMAMMOTROPIN

Human chorionic somatomammotropin, a protein hormone with a molecular weight of about 22,000, begins to be secreted by the placenta at about the fifth week of pregnancy. Secretion of this hormone increases progressively throughout the remainder of pregnancy in direct proportion to the weight of the placenta. Although the functions of chorionic somatomammotropin are uncertain, it is secreted in quantities several times greater than that of all the other pregnancy hormones combined. It has several possible important effects.

First, when administered to several types of animals, human chorionic somatomammotropin causes at least partial development of the animal's breasts and in some cases causes lactation. Because this was the first function of the hormone that was discovered, it was first named *human placental lactogen* and was believed to have functions similar to those of prolactin. However, attempts to use it to promote lactation in humans have not been successful.

Second, this hormone has weak actions similar to those of growth hormone, causing formation of tissue proteins in the same way that growth hormone does. It also has a chemical structure similar to that of growth hormone, but 100 times as much human chorionic somatomammotropin as growth hormone is required to promote growth.

Third, human chorionic somatomammotropin causes decreased insulin sensitivity and decreased utilization of glucose in the mother, thereby making larger quantities of glucose available to the fetus. Because glucose is the major substrate used by the fetus to energize its growth, the possible importance of such a hormonal effect is obvious. Further, the hormone promotes the release of free fatty acids from fat stores of the mother, thus providing this alternative source of energy for the mother's metabolism during pregnancy. Therefore, it appears that human chorionic somatomammotropin is a general metabolic hormone that has specific nutritional implications for the mother and the fetus.

Other Hormonal Factors in Pregnancy

Almost all the nonsexual endocrine glands of the mother also react markedly to pregnancy. This reaction results mainly from the increased metabolic load on the mother but also, to some extent, from the effects of placental hormones on the pituitary and other glands. The following effects are some of the most notable.

Pituitary Secretion. The anterior pituitary gland of the mother enlarges at least 50% during pregnancy and increases its production of *adrenocorticotropic hormone* (ACTH), *thyrotropin,* and *prolactin.* Conversely, pituitary secretion of follicle-stimulating hormone and luteinizing hormone is almost totally suppressed as a result of the inhibitory effects of estrogens and progesterone from the placenta.

Increased Corticosteroid Secretion. The rate of adrenocortical secretion of *glucocorticoids* is moderately increased throughout pregnancy. It is possible that these glucocorticoids help mobilize amino acids from the mother's tissues to be used for synthesis of fetal tissues.

Pregnant women usually have about a 2-fold increase in *aldosterone* secretion, reaching a peak at the end of gestation. This increase, along with the actions of estrogens, causes a tendency for even a normal pregnant woman to reabsorb excess sodium from her renal tubules and, therefore, to retain fluid.

Increased Thyroid Gland Secretion. The mother's thyroid gland ordinarily enlarges up to 50% during pregnancy and increases its production of thyroxine a corresponding amount. The increased thyroxine production is caused at least partly by a thyrotropic effect of *human chorionic gonadotropin* secreted by the placenta and by small quantities of a specific thyroid-stimulating hormone, *human chorionic thyrotropin,* also secreted by the placenta.

Increased Parathyroid Gland Secretion. The mother's parathyroid glands usually enlarge during pregnancy, especially if her diet is deficient in calcium. Enlargement of these glands causes calcium absorption from the mother's bones, thereby maintaining normal calcium ion concentration in the mother's extracellular fluid, even while the fetus removes calcium to ossify its own bones. This secretion of parathyroid hormone is even greater during lactation after the baby's birth because the growing baby requires many times more calcium than does the fetus.

Secretion of "Relaxin" by the Ovaries and Placenta. A hormone called *relaxin* is also secreted by the corpus luteum of the ovary and by placental tissues. Its secretion is increased by a stimulating effect of human chorionic gonadotropin at the same time that the corpus luteum and the placenta secrete large quantities of estrogens and progesterone.

Relaxin is a 48–amino acid polypeptide with a molecular weight of about 9000. This hormone, when injected, causes relaxation of the ligaments of the symphysis pubis

in the estrous rat and guinea pig. This effect is weak or possibly even absent in pregnant women. Instead, this role is probably played mainly by the estrogens, which also cause relaxation of the pelvic ligaments. It has also been claimed that relaxin softens the cervix of the pregnant woman at the time of delivery. Relaxin is also thought to serve as a vasodilator, contributing to increased blood flow in various tissues, including the kidneys, and increasing venous return and cardiac output in pregnancy.

Response of the Mother's Body to Pregnancy

Most apparent among the many reactions of the mother to the fetus and to the higher levels of pregnancy hormones is the increased size of the various sexual organs. For example, the uterus increases from about 50 to 1100 grams, and the breasts approximately double in size. At the same time, the vagina enlarges and the introitus opens more widely. Also, the various hormones can cause marked changes in a pregnant woman's appearance, sometimes resulting in the development of edema, acne, and masculine or acromegalic features.

Weight Gain in the Pregnant Woman

The average weight gain during pregnancy is about 25 to 35 pounds, with most of this gain occurring during the last two trimesters. Of this added weight, about 8 pounds is fetus and 4 pounds is amniotic fluid, placenta, and fetal membranes. The uterus increases about 3 pounds and the breasts another 2 pounds, still leaving an average weight increase of 8 to 18 pounds. About 5 pounds of this added weight is extra fluid in the blood and extracellular fluid, and the remaining 3 to 13 pounds is generally fat accumulation. The extra fluid is excreted in the urine during the first few days after birth—that is, after loss of the fluid-retaining hormones from the placenta.

During pregnancy, a woman often has a greatly increased desire for food, partly as a result of removal of food substrates from the mother's blood by the fetus and partly because of hormonal factors. Without appropriate prenatal control of diet, the mother's weight gain can be as great as 75 pounds instead of the usual 25 to 35 pounds.

Metabolism During Pregnancy

As a consequence of the increased secretion of many hormones during pregnancy, including thyroxine, adrenocortical hormones, and the sex hormones, the basal metabolic rate of the pregnant woman increases about 15% during the latter half of pregnancy. As a result, she frequently has sensations of becoming overheated. Also, owing to the extra load she is carrying, greater amounts of energy than normal must be expended for muscle activity.

Nutrition During Pregnancy

By far the greatest growth of the fetus occurs during the last trimester of pregnancy; its weight almost doubles during the last 2 months of pregnancy. Ordinarily, the mother does not absorb sufficient protein, calcium, phosphates, and iron from her diet during the last months of pregnancy to supply these extra needs of the fetus. However, in anticipation of these extra needs, the mother's body has already been storing these substances—some in the placenta, but most in the normal storage depots of the mother.

If appropriate nutritional elements are not present in a pregnant woman's diet, several maternal deficiencies can occur, especially in calcium, phosphates, iron, and the vitamins. For example, the fetus needs about 375 milligrams of iron to form its blood, and the mother needs an additional 600 milligrams to form her own extra blood. The normal store of nonhemoglobin iron in the mother at the outset of pregnancy is often only 100 milligrams and almost never more than 700 milligrams. Therefore, without sufficient iron in her food, a pregnant woman may develop *hypochromic anemia*. Also, it is especially important that she receive vitamin D, because although the total quantity of calcium used by the fetus is small, calcium is normally poorly absorbed by the mother's gastrointestinal tract without vitamin D. Finally, shortly before birth of the baby, vitamin K is often added to the mother's diet so the baby will have sufficient prothrombin to prevent hemorrhage, particularly brain hemorrhage, caused by the birth process.

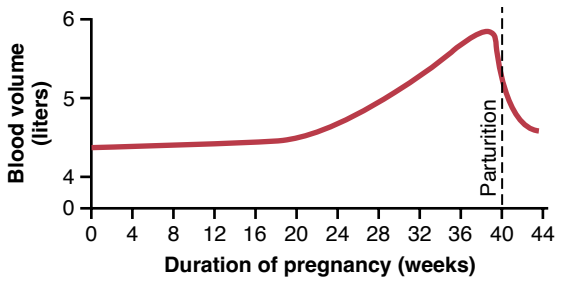

Figure 83-8. Effect of pregnancy on increasing the mother's blood volume.

Changes in the Maternal Circulatory System During Pregnancy

Blood Flow Through the Placenta and Maternal Cardiac Output Increase During Pregnancy. About 625 ml of blood flows through the maternal circulation of the placenta each minute during the last month of pregnancy. This flow, plus the general increase in the mother's metabolism, increases the mother's cardiac output to 30% to 40% above normal by the 27th week of pregnancy; then, for unexplained reasons, the cardiac output falls to only a little above normal during the last 8 weeks of pregnancy, despite the high uterine blood flow, indicating that blood flow in some other tissue(s) may be reduced.

Maternal Blood Volume Increases During Pregnancy. The maternal blood volume shortly before term is about 30% above normal. This increase occurs mainly during the latter half of pregnancy, as shown in **Figure 83-8**. The cause of the increased volume is likely due, at least in part, to aldosterone and estrogens, which are greatly increased in pregnancy, and to increased fluid retention by the kidneys. In addition, the bone marrow becomes increasingly active and produces extra red blood cells to go with the excess fluid volume. Therefore, at the time of the birth of the baby, the mother has about 1 to 2 liters of extra blood in her circulatory system. Only about one-fourth of this amount is normally lost through bleeding during delivery of the baby, thereby allowing a considerable safety factor for the mother.

Maternal Respiration Increases During Pregnancy. Because of the increased basal metabolic rate of a pregnant woman and because of her greater size, the total amount of oxygen used by the mother shortly before the birth of the baby

is about 20% above normal, and a commensurate amount of carbon dioxide is formed. These effects cause the mother's minute ventilation to increase. It is also believed that the high levels of progesterone during pregnancy increase the minute ventilation even more because progesterone increases the sensitivity of the respiratory center to carbon dioxide. The net result is an increase in minute ventilation of about 50% and a decrease in arterial P_{CO_2} to several mm Hg below that in a nonpregnant woman. Simultaneously, the growing uterus presses upward against the abdominal contents, which press upward against the diaphragm, so the total excursion of the diaphragm is decreased. Consequently, the respiratory rate is increased to maintain the extra ventilation.

Maternal Kidney Function During Pregnancy

The rate of urine formation by a pregnant woman is usually slightly increased because of increased fluid intake and increased load of excretory products. In addition, several special alterations of kidney function occur.

First, the renal tubules' reabsorptive capacity for sodium, chloride, and water is increased as much as 50% as a consequence of increased production of salt and water-retaining hormones, especially steroid hormones by the placenta and adrenal cortex.

Second, the renal blood flow and glomerular filtration rate increase up to 50% during normal pregnancy as a result of renal vasodilation. Although the mechanisms that cause renal vasodilation in pregnancy are still unclear, some studies suggest that increased levels of nitric oxide or the ovarian hormone *relaxin* may contribute to these changes. The increased glomerular filtration rate likely occurs, at least in part, as a compensation for increased tubular reabsorption of salt and water. Thus, the *normal* pregnant woman ordinarily accumulates only about 5 pounds of extra water and salt.

Amniotic Fluid and Its Formation

Normally, the volume of *amniotic fluid* (the fluid inside the uterus in which the fetus floats) is between 500 ml and 1 liter, but it can be only a few milliliters or as much as several liters. On average, the water in amniotic fluid is replaced once every 3 hours and the electrolytes sodium and potassium are replaced an average of once every 15 hours. A large portion of the fluid is derived from renal excretion by the fetus. Likewise, a certain amount of absorption occurs by way of the gastrointestinal tract and lungs of the fetus. However, even after in utero death of a fetus, some turnover of the amniotic fluid still occurs, which indicates that some of the fluid is formed and absorbed directly through the amniotic membranes.

Preeclampsia and Eclampsia

About 5% of all pregnant women experience *pregnancy-induced hypertension*, a rapid rise in arterial blood pressure to hypertensive levels during the last few months of pregnancy that may also be associated with leakage of large amounts of protein into the urine. This condition is called *preeclampsia* or *toxemia of pregnancy*. It is often characterized by excess salt and water retention by the mother's kidneys and by weight gain and development of edema and hypertension in the mother. In addition, function of the vascular endothelium is impaired, and arterial spasm occurs in many parts of the mother's body, most significantly in the kidneys, brain, and liver. Renal blood flow and the glomerular filtration rate are decreased, which is exactly opposite to the changes that occur in the normal pregnant woman. The renal effects also include thickened glomerular tufts that contain a protein deposit in the basement membranes.

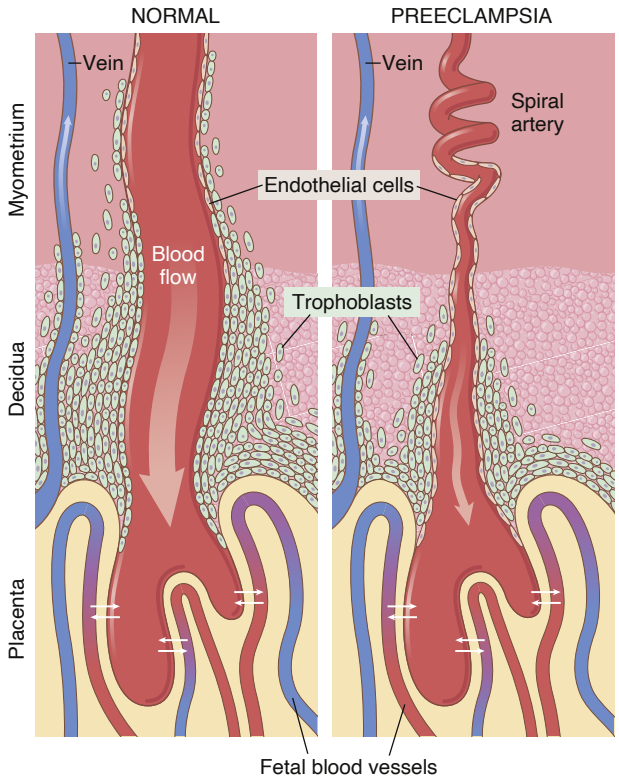

Figure 83-9. Remodeling of the spiral arteries of the uterine endometrium during normal pregnancy and failure of the spiral arteries to remodel adequately in preeclampsia. In normal pregnancy, the trophoblasts migrate into the maternal uterine spiral arteries and transform them into much larger, low-resistance, high-flow vessels. In preeclampsia, the trophoblasts fail to invade the endothelium of the spiral arteries adequately, resulting in narrow placental vessels and relative placental ischemia.

Various attempts have been made to prove that preeclampsia is caused by excessive secretion of placental or adrenal hormones, but proof of a hormonal basis is still lacking. Another theory is that preeclampsia results from some type of autoimmunity or allergy in the mother caused by the presence of the fetus. In support of this theory, the acute symptoms usually disappear within a few days after birth of the baby.

Evidence also indicates that preeclampsia is initiated by *insufficient blood supply to the placenta*, resulting in the placenta's release of substances that cause widespread dysfunction of the maternal vascular endothelium. During normal placental development, the trophoblasts invade the spiral arteries of the uterine endometrium and completely remodel the maternal arteries into much larger blood vessels with low resistance to blood flow (**Figure 83-9**). In women with preeclampsia, the maternal spiral arteries fail to undergo these adaptive changes, for reasons that are still unclear, and blood supply to the placenta is insufficient. This insufficient blood supply, in turn, causes the placenta to release various substances that enter the

mother's circulation and cause impaired vascular endothelial function, decreased blood flow to the kidneys, excess salt and water retention, and increased blood pressure.

Although the factors that link reduced placental blood supply with maternal endothelial dysfunction are still uncertain, some experimental studies suggest a role for increased levels of *inflammatory cytokines* such as *tumor necrosis factor-α and interleukin-6*. Placental factors that impede angiogenesis (blood vessel growth) have also been shown to contribute to increased inflammatory cytokines and preeclampsia. For example, the antiangiogenic proteins *soluble fms-related tyrosine kinase 1* (s-Flt1) and *soluble endoglin* are increased in the blood of women with preeclampsia. These substances are released by the placenta into the maternal circulation in response to ischemia and hypoxia of the placenta. Soluble endoglin and s-Flt1 have multiple effects that may impair function of the maternal vascular endothelium and cause hypertension, proteinuria, and the other systemic manifestations of preeclampsia. However, the precise role of the various factors released from the ischemic placenta in causing the multiple cardiovascular and renal abnormalities in women with preeclampsia is still uncertain.

Eclampsia is an extreme degree of preeclampsia characterized by vascular spasm throughout the body; clonic seizures in the mother, sometimes followed by coma; greatly decreased kidney output; malfunction of the liver; often extreme hypertension; and a generalized toxic condition of the body. It usually occurs shortly before the birth of the baby. Without treatment, a high percentage of mothers with eclampsia die. However, with optimal and immediate use of rapidly acting vasodilating drugs to reduce the arterial pressure to normal, followed by immediate termination of pregnancy—by cesarean section if necessary—the mortality even in mothers with eclampsia has been reduced to 1% or less.

PARTURITION

INCREASED UTERINE EXCITABILITY NEAR TERM

Parturition means birth of the baby. Toward the end of pregnancy, the uterus becomes progressively more excitable, until finally it develops such strong rhythmic contractions that the baby is expelled. The exact cause of the increased activity of the uterus is not known, but at least two major categories of effects lead up to the intense contractions responsible for parturition: (1) progressive hormonal changes that cause increased excitability of the uterine musculature and (2) progressive mechanical changes.

HORMONAL FACTORS THAT INCREASE UTERINE CONTRACTILITY

Increased Ratio of Estrogens to Progesterone. Progesterone inhibits uterine contractility during pregnancy, thereby helping to prevent expulsion of the fetus. Conversely, estrogens have tend to increase the degree of uterine contractility, partly because estrogens increase the number of gap junctions between the adjacent uterine smooth muscle cells, but also because of other poorly understood effects. Both progesterone and estrogen are secreted in progressively greater quantities throughout most of pregnancy, but from the seventh month onward, estrogen secretion continues to increase while progesterone secretion remains constant or perhaps even decreases slightly. Therefore, it has been postulated that the *estrogen-to-progesterone ratio* increases sufficiently toward the end of pregnancy to be at least partly responsible for the increased contractility of the uterus.

Oxytocin Causes Contraction of the Uterus. Oxytocin, a hormone secreted by the neurohypophysis, specifically causes uterine contraction (see Chapter 76). There are four reasons to believe that oxytocin is important in increasing the contractility of the uterus near term:

1. The uterine muscle increases its oxytocin receptors and therefore increases its responsiveness to a given dose of oxytocin during the latter few months of pregnancy.
2. Oxytocin secretion rate by the neurohypophysis is considerably increased at the time of labor.
3. Although hypophysectomized animals can still deliver their young at term, labor is prolonged.
4. Experiments in animals indicate that irritation or stretching of the uterine cervix, as occurs during labor, can cause a neurogenic reflex through the paraventricular and supraoptic nuclei of the hypothalamus that causes the posterior pituitary gland (the neurohypophysis) to increase its secretion of oxytocin.

Effect of Fetal Hormones on the Uterus. The fetus's pituitary gland secretes increasing quantities of oxytocin, which might play a role in exciting the uterus. Also, the fetus's adrenal glands secrete large quantities of cortisol, another possible uterine stimulant. In addition, the fetal membranes release prostaglandins in high concentration at the time of labor. These prostaglandins, too, can increase the intensity of uterine contractions.

Mechanical Factors That Increase Uterine Contractility

Stretch of the Uterine Musculature. Simply stretching smooth muscles usually increases their contractility. Further, intermittent stretch, which occurs repeatedly in the uterus because of fetal movements, can also elicit smooth muscle contraction. Note especially that twins are born, on average, *19 days earlier* than a single child, which emphasizes the importance of mechanical stretch in eliciting uterine contractions.

Stretch or Irritation of the Cervix. There is reason to believe that stretching or irritating the uterine cervix is particularly important in eliciting uterine contractions. For example, obstetricians frequently induce labor by rupturing the membranes so the head of the baby stretches the cervix more forcefully than usual or irritates it in other ways.

The mechanism whereby cervical irritation excites the body of the uterus is not known. It has been suggested that stretching or irritation of nerves in the cervix initiates reflexes to the body of the uterus, but the effect could also result simply from myogenic transmission of signals from the cervix to the body of the uterus.

ONSET OF LABOR—A POSITIVE FEEDBACK MECHANISM FOR ITS INITIATION

During pregnancy, the uterus undergoes periodic episodes of weak and slow rhythmic contractions called *Braxton Hicks contractions.* These contractions are usually not felt until the second or third trimester and become progressively stronger toward the end of pregnancy; then they change suddenly, within hours, to become exceptionally strong contractions that start stretching the cervix and later force the baby through the birth canal, thereby causing parturition. This process is called *labor,* and the strong contractions that result in final parturition are called *labor contractions.*

We do not know what suddenly changes the slow, weak rhythmicity of the uterus into strong labor contractions. However, the *positive feedback* theory suggests that stretching of the cervix by the fetus's head finally becomes great enough to elicit a strong reflex increase in contractility of the uterine body. This pushes the baby forward, which stretches the cervix more and initiates more positive feedback to the uterine body. Thus, the process repeats until the baby is expelled. This theory is shown in **Figure 83-10**, and the following observations support this theory.

First, labor contractions obey all the principles of positive feedback. That is, once the strength of uterine contraction becomes greater than a critical value, each contraction leads to subsequent contractions that become stronger and stronger until maximum effect is achieved. By referring to the discussion in Chapter 1 of positive feedback in control systems, one can see that this is the precise nature of all positive feedback mechanisms when the feedback gain becomes greater than a critical value.

Second, two known types of positive feedback increase uterine contractions during labor: (1) stretching of the cervix causes the entire body of the uterus to contract, and this contraction stretches the cervix even more because of the downward thrust of the baby's head, and (2) cervical stretching also causes the pituitary gland to secrete oxytocin, which is another means for increasing uterine contractility.

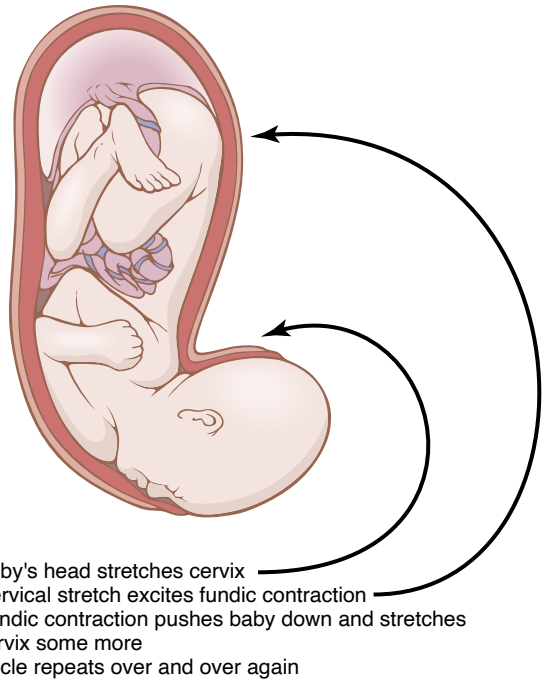

Figure 83-10. Theory for the onset of intensely strong contractions during labor.

To summarize, multiple factors increase the contractility of the uterus toward the end of pregnancy. Eventually a uterine contraction becomes strong enough to irritate the uterus, especially at the cervix, and this irritation increases uterine contractility still more because of positive feedback, resulting in a second uterine contraction stronger than the first, a third stronger than the second, and so forth. Once these contractions become strong enough to cause this type of feedback, with each succeeding contraction greater than the preceding one, the process proceeds to completion. One might ask about the many cases of false labor, in which the contractions become stronger and stronger and then fade away. Remember that for a positive feedback to continue, *each* new cycle of the positive feedback must be stronger than the previous one. If at any time after labor starts some contractions fail to re-excite the uterus sufficiently, the positive feedback could go into a retrograde decline, and the labor contractions would fade away.

ABDOMINAL MUSCLE CONTRACTIONS DURING LABOR

Once uterine contractions become strong during labor, pain signals originate both from the uterus and from the birth canal. These signals, in addition to causing suffering, elicit neurogenic reflexes in the spinal cord to the abdominal muscles, causing intense contractions of these muscles. The abdominal contractions add greatly to the force that causes expulsion of the baby.

Mechanics of Parturition

The uterine contractions during labor begin mainly at the top of the uterine fundus and spread downward over the body of the uterus. Also, the intensity of contraction is great in the top and body of the uterus but weak in the lower segment of the uterus adjacent to the cervix. Therefore, each uterine contraction tends to force the baby downward toward the cervix.

In the early part of labor, the contractions might occur only once every 30 minutes. As labor progresses, the contractions finally appear as often as once every 1 to 3 minutes and the intensity of contraction increases greatly, with only a short period of relaxation between contractions. The combined contractions of the uterine and abdominal musculature during delivery of the baby cause a downward force on the fetus of about 25 pounds during each strong contraction.

It is fortunate that the contractions of labor occur intermittently, because strong contractions impede or sometimes even stop blood flow through the placenta and would cause death of the fetus if the contractions were continuous. Indeed, overuse of various uterine stimulants, such as oxytocin, can cause uterine spasm rather than rhythmic contractions and can lead to death of the fetus.

In more than 95% of births, the head is the first part of the baby to be expelled and, in most of the remaining cases, the buttocks are presented first. Entering the birth canal with the buttocks or feet first is called a *breech* presentation.

The head acts as a wedge to open the structures of the birth canal as the fetus is forced downward. The first major obstruction to expulsion of the fetus is the uterine cervix. Toward the end of pregnancy, the cervix becomes soft, which allows it to stretch when labor contractions begin in the uterus. The so-called *first stage of labor* is a period of progressive cervical dilation, lasting until the cervical opening is as large as the head of the fetus. This stage usually lasts for 8 to 24 hours in the first pregnancy but often only a few minutes after many pregnancies.

Once the cervix has dilated fully, the fetal membranes usually rupture and the amniotic fluid is lost suddenly through the vagina. Then the head of the fetus moves rapidly into the birth canal, and with additional force from above, it continues to wedge its way through the canal until delivery occurs. This is called the *second stage of labor,* and it may last from as little as 1 minute after many pregnancies to 30 minutes or more in the first pregnancy.

Separation and Delivery of the Placenta. For 10 to 45 minutes after birth of the baby, the uterus continues to contract to a smaller and smaller size, which causes a *shearing* effect between the walls of the uterus and the placenta, thus separating the placenta from its implantation site. Separation of the placenta opens the placental sinuses and causes bleeding. The amount of bleeding is usually limited to an average of 350 ml by the following mechanism:

- The smooth muscle fibers of the uterine musculature are arranged in figures of eight around the blood vessels as the vessels pass through the uterine wall.
- Therefore, contraction of the uterus after delivery of the baby constricts the vessels that had previously supplied blood to the placenta.
- In addition, it is believed that vasoconstrictor prostaglandins formed at the placental separation site cause additional blood vessel spasm.

Labor Pains

With each uterine contraction, the mother experiences considerable pain. The cramping pain in early labor is probably caused mainly by hypoxia of the uterine muscle resulting from compression of the blood vessels in the uterus. This pain is not felt when the visceral sensory *hypogastric nerves,* which carry the visceral sensory fibers leading from the uterus, have been sectioned.

During the second stage of labor, when the fetus is being expelled through the birth canal, much more severe pain is caused by cervical stretching, perineal stretching, and stretching or tearing of structures in the vaginal canal. This pain is conducted to the mother's spinal cord and brain by somatic nerves instead of by the visceral sensory nerves.

Involution of the Uterus After Parturition

During the first 4 to 5 weeks after parturition, the uterus involutes. Its weight becomes less than half its immediate postpartum weight within 1 week, and in 4 weeks, if the mother lactates, the uterus may become as small as it was before pregnancy. This effect of lactation results from the suppression of pituitary gonadotropin and ovarian hormone secretion during the first few months of lactation, as discussed later. During early involution of the uterus, the placental site on the endometrial surface autolyzes, causing a vaginal discharge known as *lochia,* which is first bloody and then serous in nature and continues for a total of about 10 days. After this time, the endometrial surface becomes reepithelialized and ready for normal, nongravid sex life again.

LACTATION

DEVELOPMENT OF THE BREASTS

The breasts, shown in **Figure 83-11**, begin to develop at puberty. This development is stimulated by the estrogens of the monthly female sexual cycle; estrogens stimulate growth of the breasts' *mammary glands* plus the deposition of fat to give the breasts mass. In addition, far greater growth occurs during the high-estrogen state of pregnancy, and only then does the glandular tissue become completely developed for production of milk.

Estrogens Stimulate Growth of the Ductal System of the Breasts. All through pregnancy, the large quantities of estrogens secreted by the placenta cause the ductal system of the breasts to grow and branch. Simultaneously, the stroma of the breasts increases in quantity, and large quantities of fat are laid down in the stroma.

Also important for growth of the ductal system are at least four other hormones: *growth hormone, prolactin, adrenal glucocorticoids,* and *insulin.* Each of these

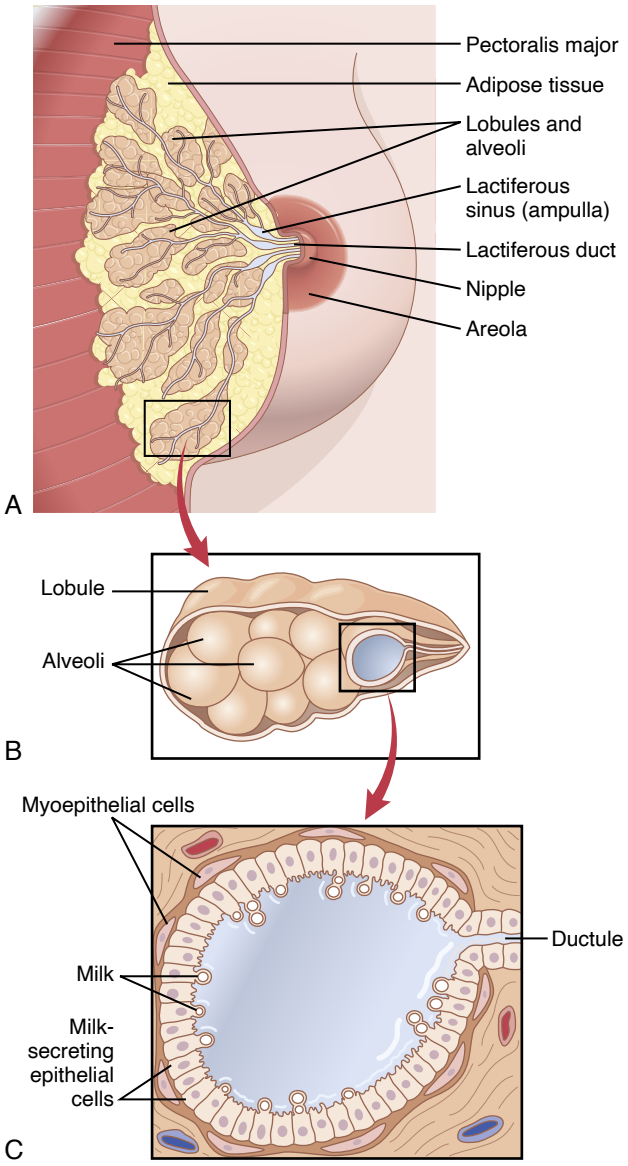

Figure 83-11. A, The breast and its secretory lobules, alveoli, and lactiferous ducts (milk ducts) that constitute its mammary gland. **B,** The enlargements show a lobule and milk-secreting cells (**C**) of an alveolus.

hormones is known to play at least some role in protein metabolism, which presumably explains their function in the development of the breasts.

Progesterone Is Required for Full Development of the Lobule-Alveolar System. Final development of the breasts into milk-secreting organs also requires *progesterone.* Once the ductal system has developed, progesterone—acting synergistically with estrogen, as well as with the other hormones just mentioned—causes additional growth of the breast lobules, with budding of alveoli and development of secretory characteristics in the cells of the alveoli. These changes are analogous to the secretory effects of progesterone on the endometrium of the uterus during the latter half of the female menstrual cycle.

PROLACTIN PROMOTES LACTATION

Although estrogen and progesterone are essential for physical development of the breasts during pregnancy, a specific effect of both these hormones is to inhibit *the actual secretion of milk.* Conversely, the hormone *prolactin* has the opposite effect and promotes milk secretion. Prolactin is secreted by the mother's anterior pituitary gland, and its concentration in her blood rises steadily from the fifth week of pregnancy until birth of the baby, at which time it has risen to 10 to 20 times the normal nonpregnant level. This high level of prolactin at the end of pregnancy is shown in **Figure 83-12**.

In addition, the placenta secretes large quantities of *human chorionic somatomammotropin,* which probably has lactogenic properties, thus supporting the prolactin from the mother's pituitary during pregnancy. Even so, because of the suppressive effects of estrogen and progesterone, no more than a few milliliters of fluid are secreted each day until after the baby is born. The fluid secreted during the last few days before and the first few days after parturition is called *colostrum;* it contains essentially the same concentrations of proteins and lactose as milk, but it has almost no fat, and its maximum rate of production is about 1/100 the subsequent rate of milk production.

Immediately after the baby is born, the sudden loss of both estrogen and progesterone secretion from the placenta allows the lactogenic effect of prolactin from the mother's pituitary gland to assume its natural milk-promoting role, and during the next 1 to 7 days, the breasts begin to secrete copious quantities of milk instead of colostrum. This secretion of milk requires an adequate background secretion of most of the mother's other hormones as well, but most important are *growth hormone, cortisol, parathyroid hormone,* and *insulin.* These hormones are necessary to provide the amino acids, fatty acids, glucose, and calcium required for the formation of milk.

After the birth of the baby, the *basal level* of prolactin secretion returns to the nonpregnant level during the next few weeks, as shown in **Figure 83-12**. However, each time the mother nurses her baby, nervous signals from the nipples to the hypothalamus cause a 10- to 20-fold surge in prolactin secretion that lasts for about 1 hour, which is also shown in **Figure 83-12**. This prolactin acts on the mother's breasts to keep the mammary glands secreting milk into the alveoli for the subsequent nursing periods. If this prolactin surge is absent or blocked as a result of hypothalamic or pituitary damage or if nursing does not continue, the breasts lose their ability to produce milk within 1 week or so. However, milk production can continue for several years if the child continues to suckle, although the rate of milk formation normally decreases considerably after 7 to 9 months.

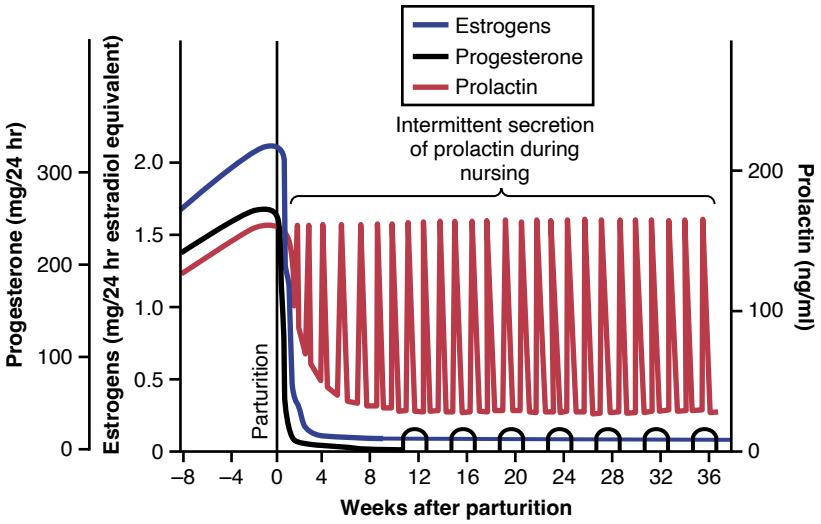

Figure 83-12. Changes in rates of secretion of estrogens, progesterone, and prolactin for 8 weeks before parturition and 36 weeks thereafter. Note especially the decrease of prolactin secretion back to basal levels within a few weeks after parturition, but also the intermittent periods of marked prolactin secretion (for about 1 hour at a time) during and after periods of nursing.

The Hypothalamus Secretes Prolactin Inhibitory Hormone. The hypothalamus plays an essential role in controlling prolactin secretion, as it does for almost all the other anterior pituitary hormones. However, this control is different in one aspect: The hypothalamus mainly *stimulates* production of all the other hormones, but it mainly *inhibits* prolactin production. Consequently, damage to the hypothalamus or blockage of the hypothalamic-hypophysial portal system often increases prolactin secretion while it depresses secretion of the other anterior pituitary hormones.

Therefore, it is believed that anterior pituitary secretion of prolactin is controlled either entirely or almost entirely by an inhibitory factor formed in the hypothalamus and transported through the hypothalamic-hypophysial portal system to the anterior pituitary gland. This factor is sometimes called *prolactin inhibitory hormone,* but it is almost certainly the same as the catecholamine *dopamine,* which is known to be secreted by the arcuate nuclei of the hypothalamus and can decrease prolactin secretion as much as 10-fold.

Suppression of the Female Ovarian Cycles in Nursing Mothers for Many Months After Delivery. In most nursing mothers, the ovarian cycle (and ovulation) does not resume until a few weeks after cessation of nursing. The reason seems to be that the same nervous signals from the breasts to the hypothalamus that cause prolactin secretion during suckling—either because of the nervous signals or because of a subsequent effect of increased prolactin—inhibit secretion of gonadotropin-releasing hormone by the hypothalamus. This inhibition, in turn, suppresses formation of the pituitary gonadotropic hormones—luteinizing hormone and follicle-stimulating hormone. However, after several months of lactation, in some mothers (especially those who nurse their babies only some of the time), the pituitary begins to secrete sufficient gonadotropic hormones to reinstate the monthly sexual cycle, even though nursing continues.

EJECTION (OR "LET-DOWN") PROCESS IN MILK SECRETION—FUNCTION OF OXYTOCIN

Milk is secreted continuously into the alveoli of the breasts, but it does not flow easily from the alveoli into the ductal system and, therefore, does not continually leak from the nipples. Instead, the milk must be *ejected* from the alveoli into the ducts before the baby can obtain it. This ejection is caused by a combined neurogenic and hormonal reflex that involves the posterior pituitary hormone *oxytocin*.

When the baby suckles, it receives virtually no milk for the first half minute or so. Sensory impulses must first be transmitted through somatic nerves from the nipples to the mother's spinal cord and then to her hypothalamus, where they cause nerve signals that promote *oxytocin* secretion at the same time that they cause prolactin secretion. The oxytocin is carried in the blood to the breasts, where it causes *myoepithelial cells* (which surround the outer walls of the alveoli) to contract, thereby expressing the milk from the alveoli into the ducts at a pressure of +10 to 20 mm Hg. Then the baby's suckling becomes effective in removing the milk. Thus, within 30 seconds to 1 minute after a baby begins to suckle, milk begins to flow. This process is called *milk ejection* or *milk let-down.*

Suckling on one breast causes milk flow not only in that breast but also in the opposite breast. It is especially interesting that fondling of the baby by the mother or hearing the baby crying often gives enough of an emotional signal to the hypothalamus to cause milk ejection.

Table 83-1 Composition of Milk

Constituent	Human Milk (%)	Cow's Milk (%)
Water	88.5	87.0
Fat	3.3	3.5
Lactose	6.8	4.8
Casein	0.9	2.7
Lactalbumin and other proteins	0.4	0.7
Ash	0.2	0.7

Inhibition of Milk Ejection. A particular problem in nursing a baby comes from the fact that many psychogenic factors or even generalized sympathetic nervous system stimulation throughout the mother's body can inhibit oxytocin secretion and consequently depress milk ejection. For this reason, many mothers must have an undisturbed period of adjustment after childbirth if they are to be successful in nursing their babies.

MILK COMPOSITION AND THE METABOLIC DRAIN ON THE MOTHER CAUSED BY LACTATION

Table 83-1 lists the approximate composition of human milk and cow's milk. The concentration of lactose in human milk is about 50% greater than in cow's milk, but the concentration of protein in cow's milk is ordinarily two or more times greater than in human milk. Finally, only one-third as much ash, which contains calcium and other minerals, is found in human milk compared with cow's milk.

At the height of lactation in the human mother, 1.5 liters of milk may be formed each day (and even more if the mother has twins). With this degree of lactation, great quantities of energy are drained from the mother; approximately 650 to 750 kilocalories per liter (or 19 to 22 kilocalories per ounce) are contained in breast milk, although the composition and caloric content of the milk depends on the mother's diet and other factors such as the fullness of the breasts.

Large amounts of metabolic substrates are also lost from the mother. For example, about 50 grams of fat enter the milk each day, as well as about 100 grams of lactose, which must be derived by conversion from the mother's glucose. Also, 2 to 3 grams of calcium phosphate may be lost each day; unless the mother is drinking large quantities of milk and has an adequate intake of vitamin D, the output of calcium and phosphate by the lactating mammae will often be much greater than the intake of these substances. To supply the needed calcium and phosphate, the parathyroid glands enlarge greatly, and the bones become progressively decalcified. The mother's bone decalcification is usually not a big problem during pregnancy, but it can become more important during lactation.

Antibodies and Other Anti-infectious Agents in Milk. Not only does milk provide the newborn baby with needed nutrients, but it also provides important protection against infection. For example, multiple types of *antibodies* and other anti-infectious agents are secreted in milk along with nutrients. Also, several different types of white blood cells are secreted, including both *neutrophils* and *macrophages,* some of which are especially lethal to bacteria that could cause deadly infections in newborn babies. Particularly important are antibodies and macrophages that destroy *Escherichia coli* bacteria, which can cause lethal diarrhea in newborns.

When cow's milk is used to supply nutrition for the baby in place of mother's milk, the protective agents in it are usually of little value because they are normally destroyed within minutes in the internal environment of the human being.

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