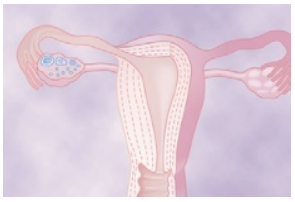
CHAPTER 81

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 82 presents the physiology of pregnancy and childbirth.

Physiologic Anatomy of the Female Sexual Organs

Figures 81-1 and 81-2 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.

During fetal life, the outer surface of the ovary is covered by a *germinal epithelium,* which embryologically is derived from the epithelium of the germinal ridges. As the female fetus develops, *primordial ova* differentiate from this germinal epithelium and migrate into the substance of the ovarian cortex. Each 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; they are then called *granulosa cells.* The ovum surrounded by a single layer of granulosa cells is called a *primordial follicle.* The ovum at this stage is still immature, requiring two more cell divisions before it can be fertilized by a sperm. At this time, the ovum is called a *primary oocyte.*

During all the reproductive years of adult life, between about 13 and 46 years of age, 400 to 500 of the primordial follicles develop enough to expel their ova—one each month; the remainder degenerate (become *atretic*). At the end of reproductive capability (at *menopause*), only a few primordial follicles remain in the ovaries and even these degenerate soon thereafter.

Female Hormonal System

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

1. A hypothalamic releasing hormone, *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 the 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

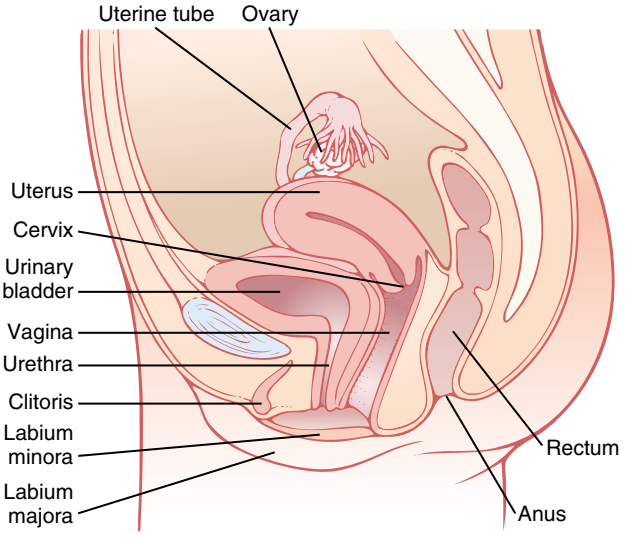


Figure 81-1 Female reproductive organs.

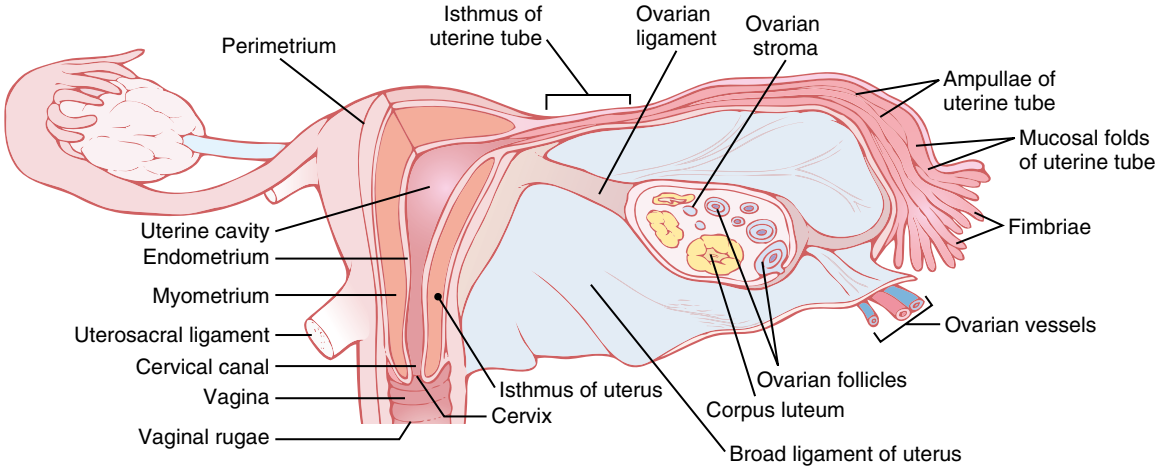


Figure 81-2 Internal structures of the uterus, ovary, and a uterine tube. (Redrawn from Guyton AC: Physiology of the Human Body, 6th ed. Philadelphia: Saunders College Publishing, 1984.)

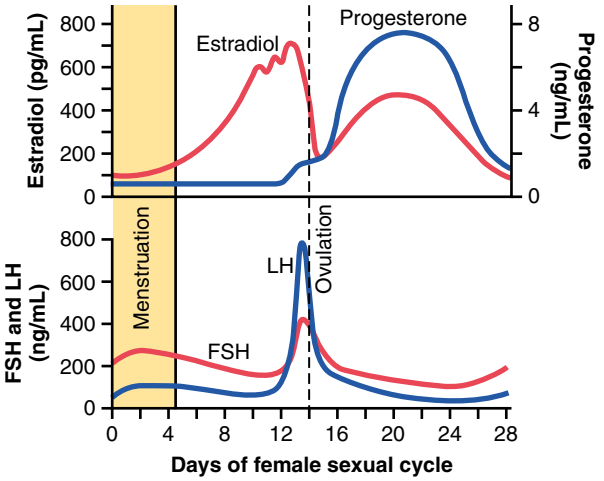


Figure 81-3 Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

These various hormones are secreted at drastically differing rates during different parts of the female monthly sexual cycle. Figure 81-3 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 the male.

Monthly Ovarian Cycle; Function of the Gonadotropic Hormones

The normal reproductive years of the female are characterized by monthly rhythmical changes in the rates of secretion of the female hormones and corresponding physical changes in the ovaries and other sexual organs. This rhythmical 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.

There are two significant results of the female sexual cycle. 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,* secreted by the anterior pituitary gland. 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 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.* Both FSH and LH are small glycoproteins having molecular weights of about 30,000.

During each month of the female sexual cycle, there is a cyclical increase and decrease of both FSH and LH, as shown in the bottom of Figure 81-3. These cyclical variations 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' rates of secretion 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*

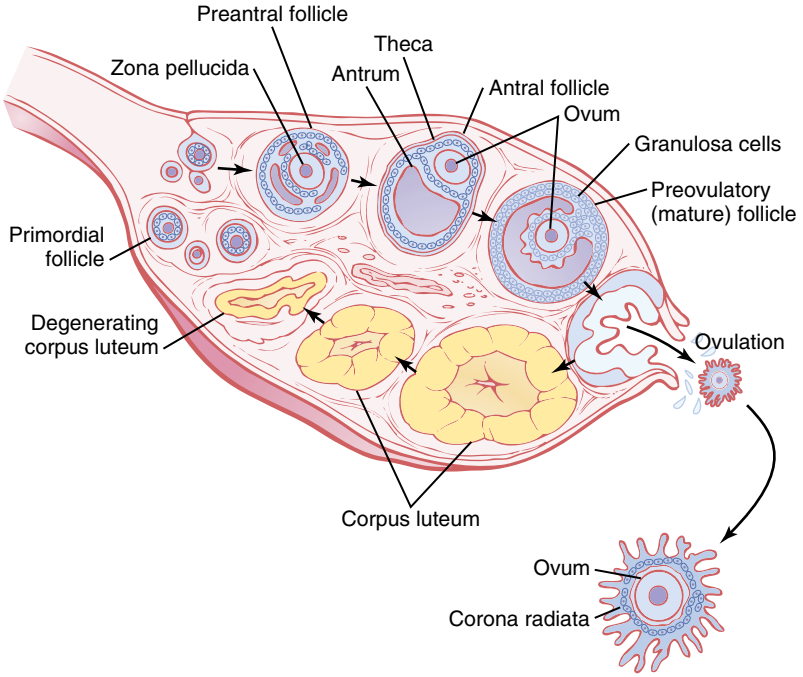


Figure 81-4 Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

system in the cell cytoplasm, which causes the formation of *protein kinase* and multiple *phosphorylations of key enzymes* that stimulate sex hormone synthesis, as explained in Chapter 74.

Ovarian Follicle Growth—"Follicular" Phase of the Ovarian Cycle

Figure 81-4 shows the progressive stages of follicular growth in the ovaries. When a female child is born, 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 itself, which increases in diameter twofold to threefold. Then follows 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 both 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.* This 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, lasting 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 81-4.

The early growth of the primary follicle up to the antral stage is stimulated mainly by FSH alone. Then greatly accelerated growth occurs, leading to still larger follicles called *vesicular follicles.* This accelerated growth is caused by the following: (1) Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors; this 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 as well.

Once the antral follicles begin to grow, their growth occurs almost explosively. The ovum itself also enlarges

in diameter another threefold to fourfold, 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; the remaining 5 to 11 developing follicles involute (a process called *atresia*), and these follicles are said to become *atretic.*

The cause of the atresia is unknown, 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; this 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.*

Surge of LH 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 stage of ovulation.

About 2 days before ovulation (for reasons that are not completely understood but are discussed in more detail later in the chapter), 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 twofold to threefold 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 secretion of estrogen 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.

Initiation of Ovulation. Figure 81-5 gives 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* (the capsule of the follicle) begins to release proteolytic enzymes from lysosomes, and these 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, and 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—"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.

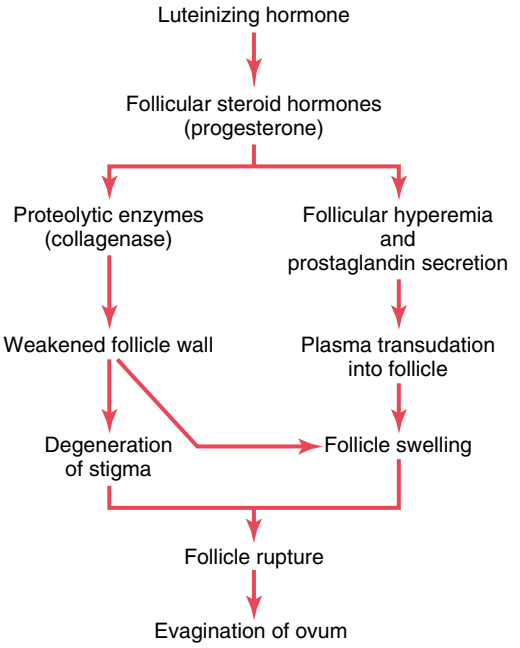


Figure 81-5 Postulated mechanism of ovulation.

This process is called *luteinization,* and the total mass of cells together is called the *corpus luteum,* which is shown in Figure 81-4. 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* (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 female hormones.

The corpus luteum normally grows to about 1.5 centimeters in diameter, reaching this stage of development 7 to 8 days after ovulation. Then it 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, this is replaced by connective tissue and over months is absorbed.

Luteinizing Function of LH. The change of granulosa and theca interna cells into lutein cells is dependent 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 local hormone 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 LH. The corpus luteum is a highly secretory organ, secreting large amounts of both *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 seem to be programmed to go through a preordained sequence of (1) proliferation, (2) enlargement, and (3) secretion, followed by (4) degeneration. All this occurs in about 12 days. We shall see in the discussion of pregnancy in Chapter 82 that 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 both 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 secretion by the anterior pituitary gland, especially FSH secretion. Low blood concentrations of both 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 secretion of estrogen, progesterone, and inhibin 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 secretion of progesterone and estrogen at this time also leads to menstruation by the uterus, as explained later.

Summary

About every 28 days, gonadotropic hormones from the anterior pituitary gland cause about 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, mainly estrogen is secreted.

After ovulation, the secretory cells of the ovulating follicle develop into a corpus luteum that secretes large quantities of both the major female hormones, 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 the 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 the hormone *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 the development of most secondary sexual characteristics of the female. 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,* tremendous quantities of estrogens are also secreted by the placenta, as discussed in Chapter 82.

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 81-6. The principal estrogen secreted by the ovaries is β-estradiol. Small amounts of estrone are also secreted,

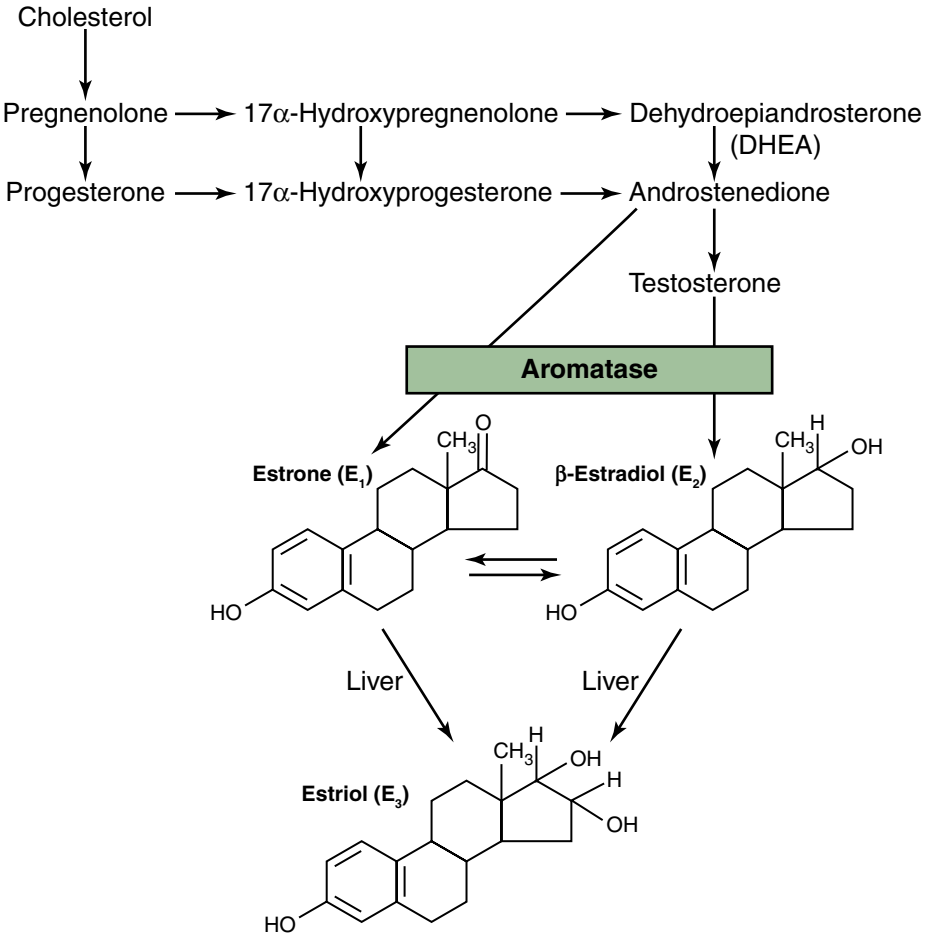


Figure 81-6 Synthesis of the principal female hormones.The chemical structures of the precursor hormones, including progesterone, are shown in Figure 77-2.

but most of this is formed in the 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, 17-α-hydroxyprogesterone, are secreted along with progesterone and have essentially the same effects. Yet for practical purposes, it is usually reasonable to consider progesterone the only important progestin.

In the normal nonpregnant female, progesterone is secreted in significant amounts only during the latter half of each ovarian cycle, when it is secreted by the corpus luteum.

As we shall see in Chapter 82, 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 81-6 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 the 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 81-7).

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.

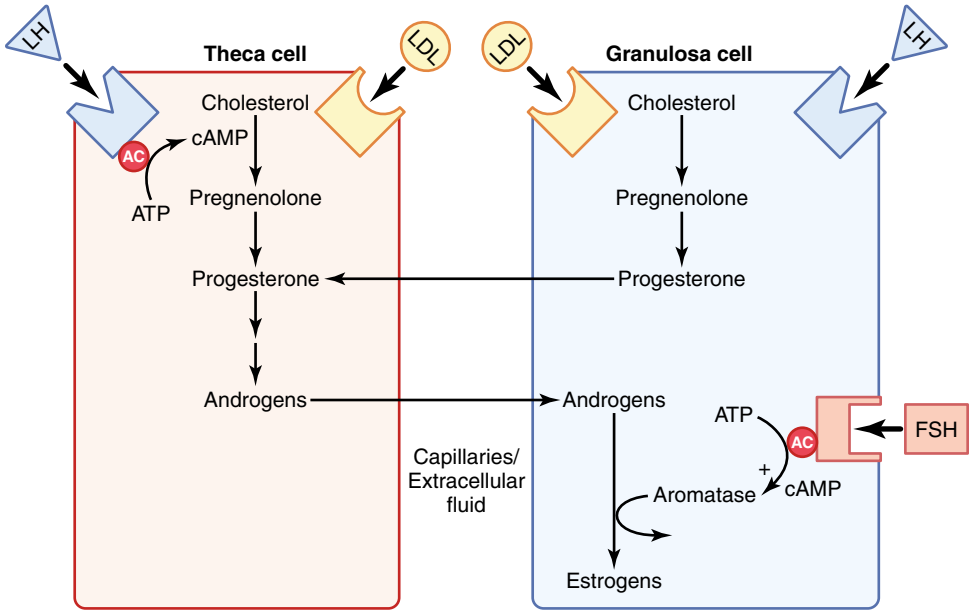


Figure 81-7 Interaction of follicular theca and granulosa cells for production of estrogens. The theca cells, under the control of luteinizing hormone (LH), produce androgens that diffuse into the granulosa cells. In mature follicles, follicle stimulating hormone (FSH) acts on granulosa cells to stimulate aromatase activity, which converts the androgens to estrogens. AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; LDL, low-density lipoproteins.

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 the 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 percent 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 twofold to threefold, 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' effect on the mucosal lining of the fallopian tubes is similar to that on the uterine endometrium. They cause the glandular tissues of this lining to proliferate; 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 cause the ultimate determinative 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 79, at least part of this effect is due to stimulation of *osteoprotegerin,* 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 have another potent effect on skeletal growth: They 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 *osteoporosis,* described in Chapter 79. Because this 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 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 the male sex hormone testosterone. They also cause deposition of increased quantities of fat in the subcutaneous tissues. As a result, the percentage of body fat in the female body is considerably greater than that in the male body, which contains more protein. In addition to deposition of fat in the breasts and subcutaneous tissues, estrogens cause the 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.

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. Also, estrogens cause the skin to become more vascular; this is often associated with increased warmth of the skin and also promotes 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 pointed out. 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 82.

Functions of Progesterone

Progesterone Promotes Secretory Changes in the Uterus. By far the most important 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.

Effect of Progesterone on 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 in nature. However, progesterone does not cause the alveoli to secrete milk; as discussed in Chapter 82, 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 81-8.

Proliferative Phase (Estrogen Phase) of the Endometrial Cycle, Occurring 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.

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 a 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.

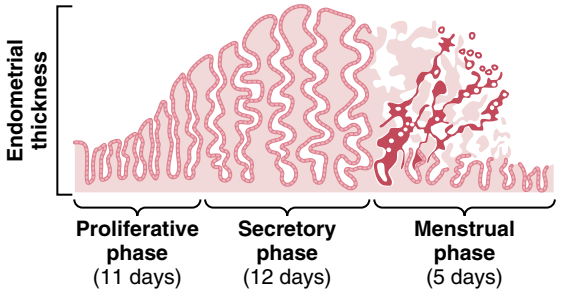


Figure 81-8 Phases of endometrial growth and menstruation during each monthly female sexual cycle.

Secretory Phase (Progestational Phase) of the Endometrial Cycle, Occurring 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; an excess of secretory substances accumulates in the glandular epithelial cells. Also, 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 whole 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 suddenly involutes and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion, as shown in Figure 81-3. 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 itself to about 65 percent 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 excessive bleeding occurs from the uterine surface, the quantity of fibrinolysin may not be sufficient to prevent clotting. The presence of clots during menstruation is often clinical evidence of uterine pathology.

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, tremendous numbers of leukocytes are released along with the necrotic material and blood. It is probable that some substance liberated by the endometrial necrosis causes this outflow of leukocytes. As a result of these leukocytes and possibly other factors, the uterus is highly resistant to infection during menstruation, even though the endometrial surfaces are denuded. This is of extreme protective value.

Regulation of the Female Monthly Rhythm—Interplay Between the Ovarian and Hypothalamic-Pituitary Hormones

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

The Hypothalamus Secretes GnRH, Which Causes the Anterior Pituitary Gland to Secrete LH and FSH

As pointed out in Chapter 74, 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 81-9 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 the release of LH and FSH by the anterior pituitary gland is lost. Therefore, for reasons unknown, the pulsatile nature of GnRH release is essential to its function.

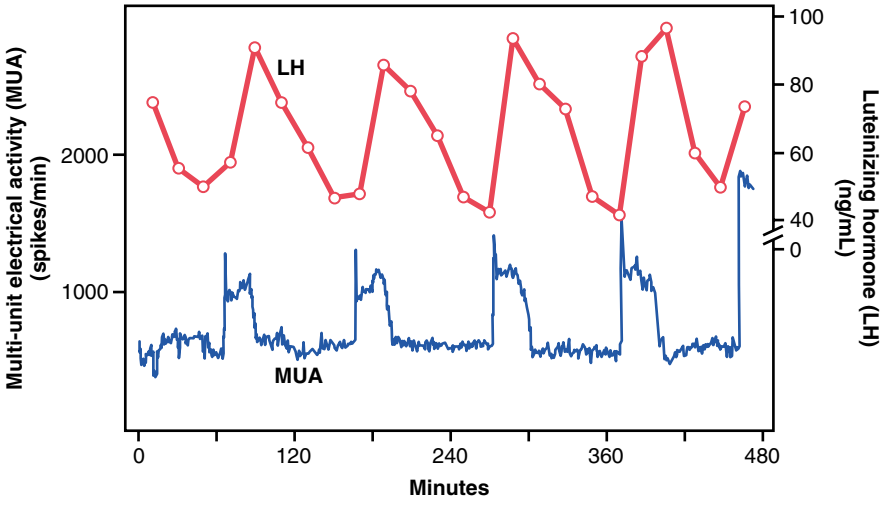


Figure 81-9 *Upper curve:* Pulsatile change in luteinizing hormone (LH) in the peripheral circulation of a pentobarbital-anesthetized ovariectomized rhesus monkey. *Lower curve:* Minute-by-minute recording of multi-unit electrical activity (MUA) in the mediobasal hypothalamus. (Data from Wilson RC, Kesner JS, Kaufman JM, et al: Central electrophysiologic correlates of pulsatile luteinizing hormone secretion. Neuroendocrinology 39:256, 1984.)

The pulsatile release of GnRH also causes intermittent output of LH secretion about every 90 minutes. This is shown by the upper curve in Figure 81-9.

Hypothalamic Centers for Release of GnRH. The neuronal activity that causes pulsatile release of GnRH occurs primarily in the mediobasal hypothalamus, especially in the arcuate nuclei of this area. Therefore, it is believed that these arcuate nuclei control most female sexual activity, although 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 arcuate nuclei to modify both 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 effect to inhibit the production of both LH and FSH. Also, when progesterone is available, the inhibitory effect of estrogen is multiplied, even though progesterone by itself has little effect (Figure 81-10).

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 seem to be 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 81-10). This hormone has the same effect in the female as in the male—inhibiting the secretion of FSH and, to a lesser extent, LH by the anterior pituitary gland. Therefore, it is believed that inhibin might 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 LH Surge

For reasons not completely understood, the anterior pituitary gland secretes greatly increased amounts of LH for 1 to 2 days beginning 24 to 48 hours before ovulation. This effect is demonstrated in Figure 81-3. The figure shows a much smaller preovulatory surge of FSH as well.

Experiments have shown that infusion of estrogen 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 both FSH and LH by the anterior pituitary gland are at first slightly suppressed. Then secretion of LH increases abruptly sixfold to eightfold, and secretion of FSH increases about twofold. The greatly increased secretion of LH causes ovulation to occur.

The cause of this abrupt surge in LH secretion is not known. However, several possible explanations are as follows: (1) It has been suggested that estrogen at this point in the cycle has a peculiar *positive feedback effect*

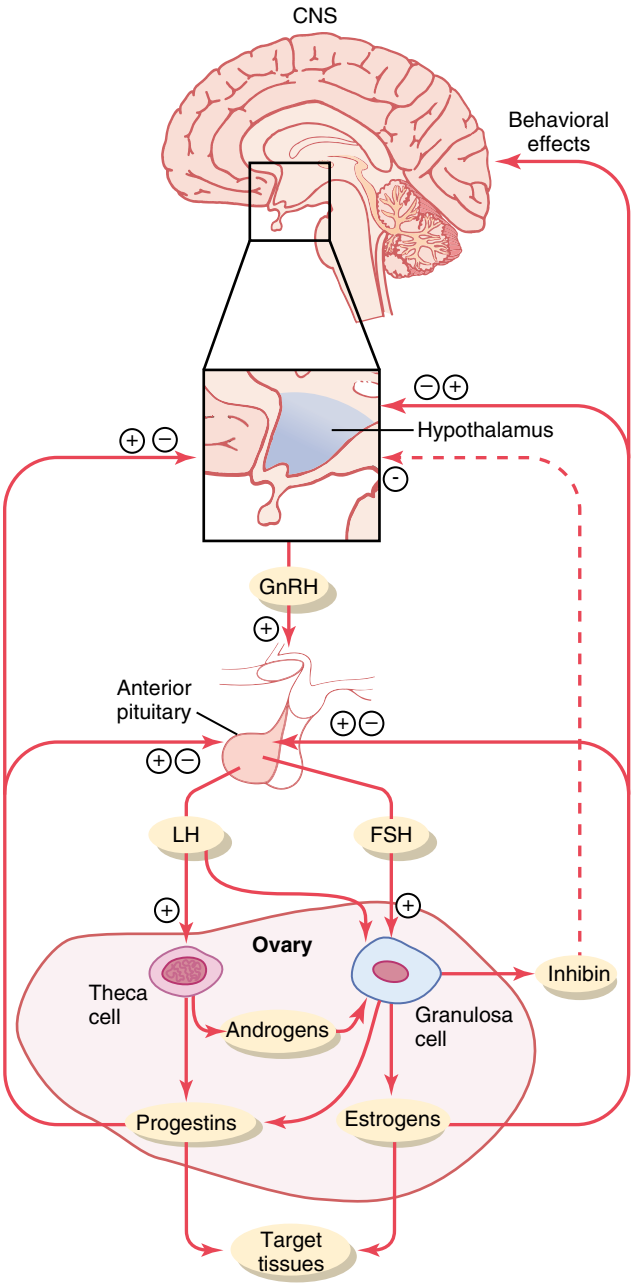


Figure 81-10 Feedback regulation of the hypothalamic-pituitary-ovarian axis in females. Stimulatory effects are shown by ⊕ and negative feedback inhibitory effects are shown by ⊖. Estrogens and progestins exert both negative and positive feedback effects on the anterior pituitary and hypothalamus depending on the stage of the ovarian cycle. Inhibin has a negative feedback effect on the anterior pituitary. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

of stimulating pituitary secretion of LH and, to a lesser extent, FSH (see Figure 81-10); this is in sharp contrast to its normal negative feedback effect 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 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, after discussing much of the known information about 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.** The easiest part of the cycle to explain is the events that occur during the postovulatory phase—between ovulation and the beginning of menstruation. During this time, the corpus luteum secretes large quantities of progesterone and estrogen, as well as the hormone inhibin. All these hormones together have a combined negative feedback effect on the anterior pituitary gland and hypothalamus, causing the suppression of both 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 81-3.
2. **Follicular Growth Phase.** Two to 3 days before menstruation, the corpus luteum has regressed to almost total involution and the secretion of estrogen, progesterone, and inhibin from the corpus luteum decreases to a low ebb. This 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 twofold; 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 is the preovulatory surge of LH and FSH, which is followed by ovulation.
3. **Preovulatory Surge of LH and FSH Causes Ovulation.** About 11½ to 12 days after the onset of the monthly cycle, the decline in secretion of FSH and LH comes to an abrupt halt. It is believed that the high level of estrogens at this time (or the beginning of progesterone secretion by the follicles) causes a positive feedback stimulatory effect on the anterior pituitary, as explained earlier, which leads to a terrific 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 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: First, 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. Second, 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 itself, although it can alter its 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 81-11,

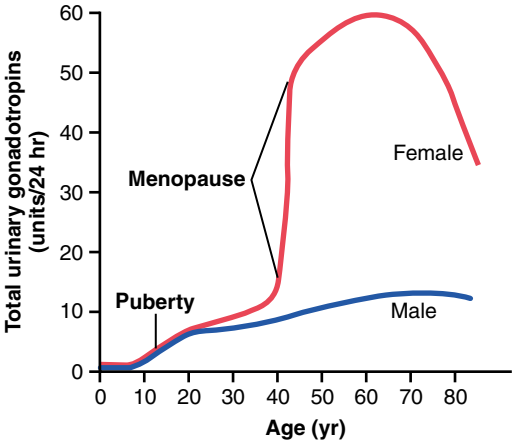


Figure 81-11 Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.

and usually culminating in the onset of puberty and menstruation between ages 11 and 16 years in girls (average, 13 years).

In the female, as in the male, the infantile pituitary gland and ovaries are capable of full function if appropriately stimulated. However, as is also true in the male, and for reasons 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 brain to cause the 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 81-12 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 81-12. 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 81-12, 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 the gonadotropins FSH and LH. Instead, as shown in Figure 81-11, the gonadotropins FSH and LH (mainly FSH) are produced after menopause in large and continuous quantities, but as the remaining primordial follicles become atretic, the production of estrogens by the ovaries falls virtually to zero.

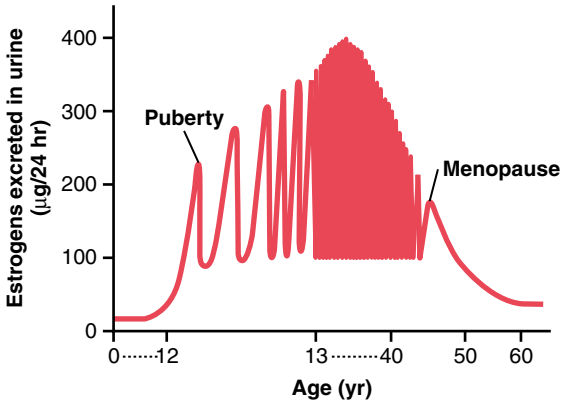


Figure 81-12 Estrogen secretion throughout the sexual life of the female human being.

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 percent of women to warrant treatment. If counseling fails, daily administration of estrogen in small quantities usually reverses the symptoms, and by gradually decreasing the dose, postmenopausal women can likely avoid severe symptoms.

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 in order to cause rhythmical 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 the production of gonadotropins by the pituitary, and this limits

the 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, occurring more often after menopause than before. 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 (VIP) at the nerve endings. This allows rapid accumulation of blood in the erectile tissue so that the introitus tightens around the penis; this aids the male greatly 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 is also provided by mucus secreted by the vaginal epithelium and a small amount 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 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 lower 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 rhythmical contractions of the uterus, which have been postulated to cause increased 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 themselves could possibly achieve. Whether this occurs in the human female is unknown.

In addition to the 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. But after culmination of the sexual act, this 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 after it is expelled from the ovary probably no longer than 24 hours. 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 of the commonly practiced methods 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. But 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 percent per year.

Hormonal Suppression of Fertility—"The Pill." It has long been known that 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.

Why the administration of estrogen or progesterone prevents the preovulatory surge of LH secretion is not fully understood. However, experimental work has suggested that immediately before the surge occurs, there is probably a sudden depression of estrogen secretion by the ovarian follicles, and this 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 instance, 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 percent per year.

Abnormal Conditions That Cause Female Sterility. About 5 to 10 percent of women are infertile. Occasionally, no abnormality can be discovered in the female genital organs, in which case it must be assumed that the infertility is due to either abnormal physiological function of the genital system or abnormal genetic development of the ova themselves.

The most common cause of female sterility is failure to ovulate. This 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 instance, 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. 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 81-13.

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 82) 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; this 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.

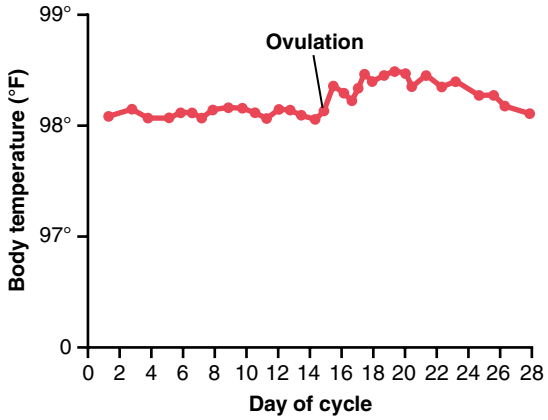


Figure 81-13 Elevation in body temperature shortly after ovulation.

Another common cause of female infertility is *salpingitis,* that is, *inflammation of the fallopian tubes;* this causes fibrosis in the tubes, thereby occluding them. In the past, such inflammation occurred mainly as a result of gonococcal infection. But with modern therapy, this 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 the 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 itself, 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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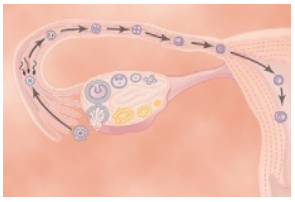
CHAPTER 82

Pregnancy and Lactation



In Chapters 80 and 81, 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 83, 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. 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, 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 percent 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 normally takes place in the ampulla of one of the fallopian tubes soon after both the sperm and the ovum enter the ampulla. But before a sperm can enter the ovum, 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 80.

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. 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 82-1*D*. Later, the 23 unpaired chromosomes of the male pronucleus and the 23 unpaired chromosomes of the female pronucleus align themselves

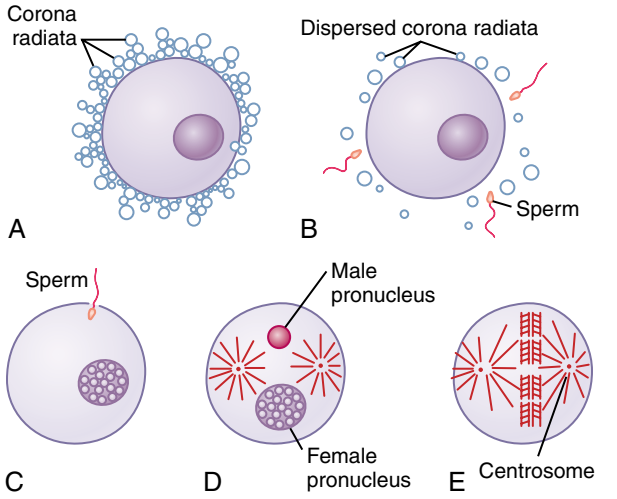


Figure 82-1 Fertilization of the ovum. *A,* The mature ovum surrounded by the corona radiata. *B,* Dispersal of the corona radiata. *C,* Entry of the sperm. *D,* Formation of the male and female pronuclei. *E,* Reorganization of a full complement of chromosomes and beginning division of the ovum. (Modified from Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, 7th ed. Philadelphia: WB Saunders, 1974.)

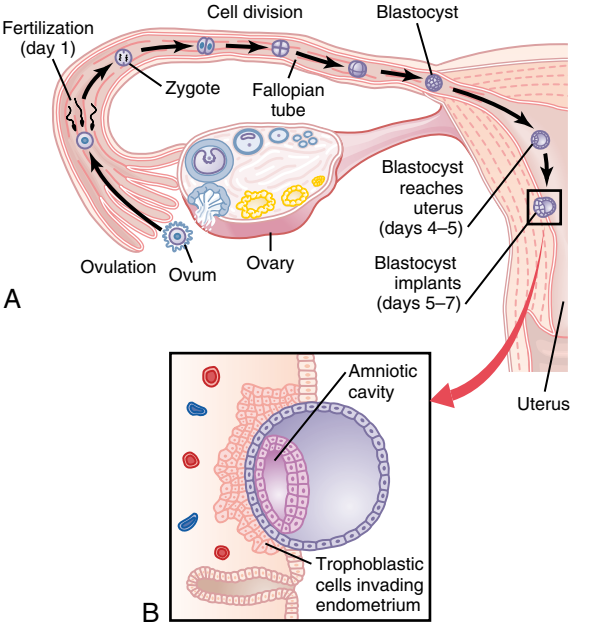


Figure 82-2 *A,* Ovulation, fertilization of the ovum in the fallopian tube, and implantation of the blastocyst in the uterus. *B,* Action of trophoblast cells in implantation of the blastocyst in the uterine endometrium.

to re-form a complete complement of 46 chromosomes (23 pairs) in the *fertilized ovum* (Figure 82-1*E*).

What Determines the Sex of the Fetus That Is Created?

After formation of the mature sperm, half of these 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 80. But 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 82-2). 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 the ovum passage.

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, exerting a tubular relaxing effect that allows 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 the 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 82-3 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 endometrium) proliferate rapidly, forming the placenta and the various membranes of pregnancy.

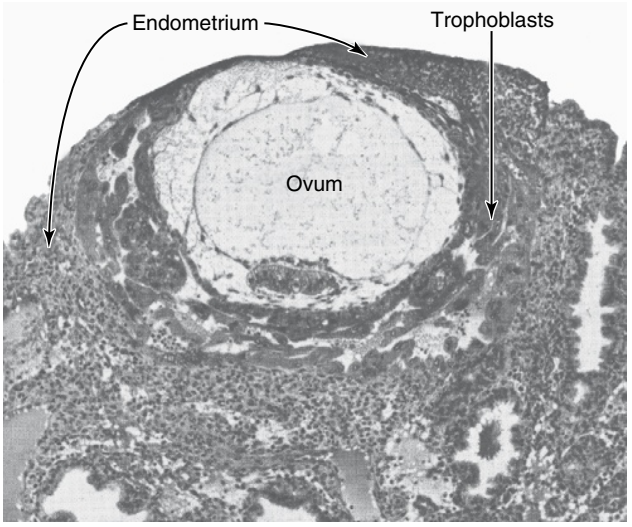


Figure 82-3 Implantation of the early human embryo, showing trophoblastic digestion and invasion of the endometrium. (Courtesy Dr. Arthur Hertig.)

Early Nutrition of the Embryo

In Chapter 81, 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, the 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 82-4 shows this trophoblastic period of nutrition, which gradually gives way to placental nutrition.

Function of the Placenta

Developmental and Physiologic Anatomy 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.

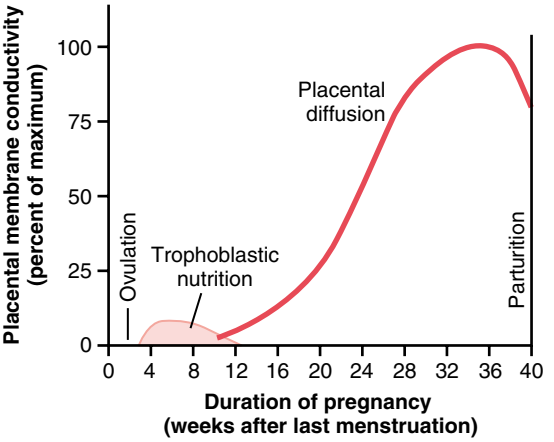


Figure 82-4 Nutrition of the fetus. Most of the early nutrition is due to trophoblastic digestion and absorption of nutrients from the endometrial decidua, and essentially all the later nutrition results from diffusion through the placental membrane.

The final structure of the placenta is shown in Figure 82-5. Note that the fetus's blood 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 82-5 shows the relation 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. Therefore, the total diffusion conductance is minuscule at first. Conversely, 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 82-4.

Rarely, "breaks" occur in the placental membrane, which allows fetal blood cells to pass into the mother or,

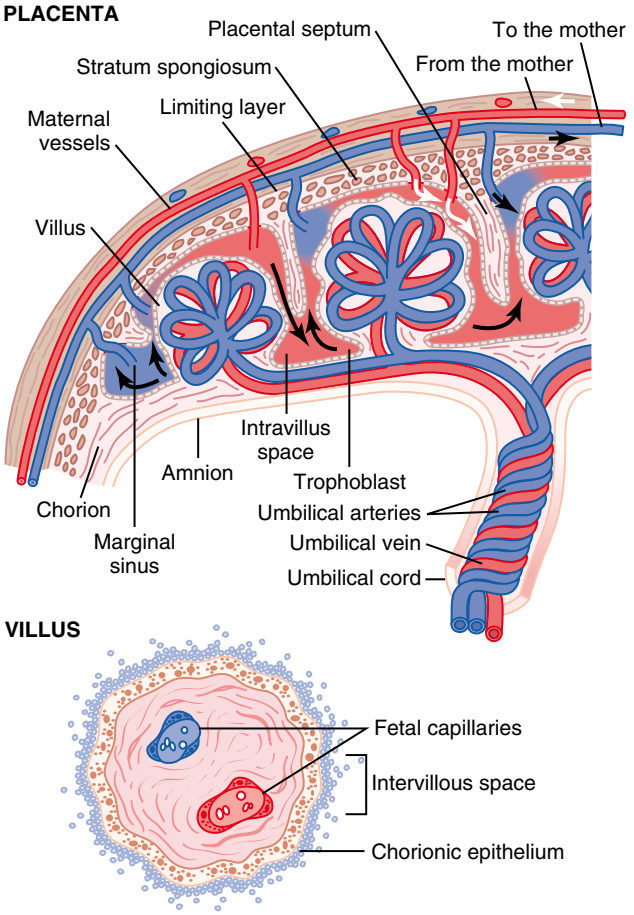


Figure 82-5 *Above,* Organization of the mature placenta. *Below,* Relation of the fetal blood in the villus capillaries to the mother's blood in the intervillous spaces. (Modified from Gray H, Goss CM: Anatomy of the Human Body, 25th ed. Philadelphia: Lea & Febiger, 1948; and from Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, 7th ed. Philadelphia: WB Saunders, 1974.)

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 39) 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 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 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,* a type of hemoglobin synthesized in the fetus before birth. Figure 82-6 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 percent more oxygen than maternal hemoglobin can.

Second, the *hemoglobin concentration of fetal blood is about 50 percent greater than that of the mother;* this 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 40, 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 cause the capacity of fetal blood to combine with oxygen to increase and that of maternal blood to decrease. This 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

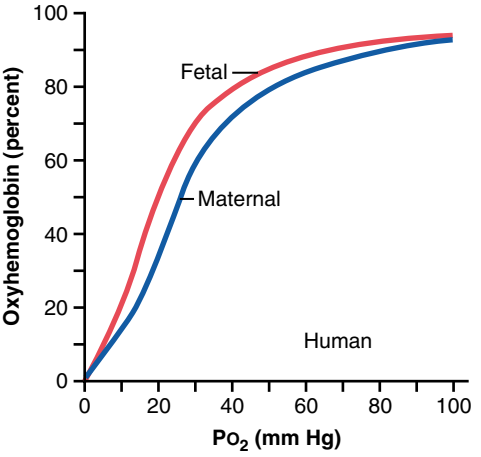


Figure 82-6 Oxygen-hemoglobin dissociation curves for maternal and fetal blood, showing that fetal blood can carry a greater quantity of oxygen than can maternal blood for a given blood P_{O_2}. (Data from Metcalfe J, Moll W, Bartels H: Gas exchange across the placenta. Fed Proc 23:775, 1964.)

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 milliliters of oxygen per minute per millimeter of mercury oxygen pressure difference across the membrane. This 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 tissues of the fetus 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 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 does. For instance, in the late stages of pregnancy, the fetus often uses as much glucose as the entire body of the mother uses. 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 percent lower than that in maternal blood.

Because of the high solubility of fatty acids in cell membranes, these also diffuse from the maternal blood into the fetal blood, but more slowly than glucose, so that 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 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. 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 should happen after an ovum has implanted, the pregnancy would terminate. However, this is prevented by the secretion of human chorionic gonadotropin by the newly developing embryonic tissues in the following manner.

Coincidental with the development of the trophoblast cells from the early fertilized ovum, the hormone *human chorionic gonadotropin* is secreted by the syncytial trophoblast cells into the fluids of the mother, as shown in Figure 82-7. The secretion of this hormone can first be

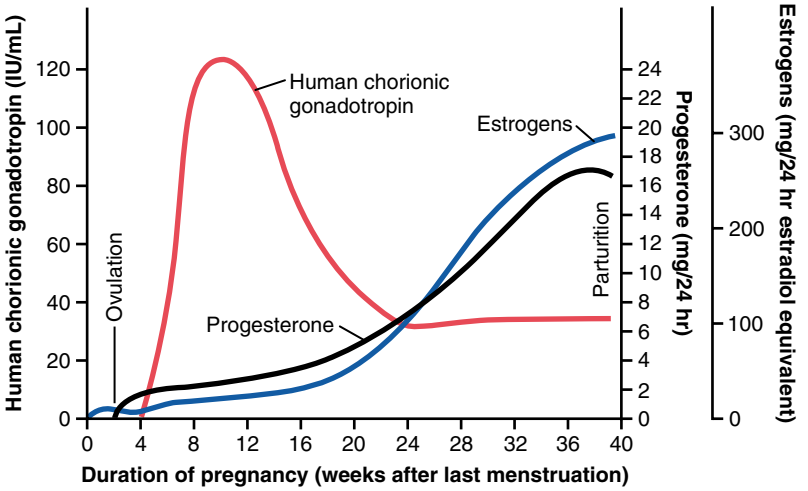


Figure 82-7 Rates of secretion of estrogens and progesterone, and concentration of human chorionic gonadotropin at different stages of pregnancy.

measured in the blood 8 to 9 days after ovulation, shortly after the blastocyst implants in the endometrium. Then the rate of secretion 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 elevated level for the remainder of 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. By far, its most important function 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 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 the 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.

Effect of Human Chorionic Gonadotropin on the Fetal Testes. Human chorionic gonadotropin also exerts an *interstitial cell*–stimulating effect on the testes of the male fetus, resulting in the 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, the 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 both 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 82-7 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, the 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-hydroxy-dehydroepiandrosterone,* which are formed both in the mother's adrenal glands and in the adrenal glands of the fetus. 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 percent 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 the discussions of estrogens in Chapter 81, we pointed out that these hormones 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 much 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 also essential for a successful pregnancy—in fact, it is just as important as estrogen. In addition to being secreted in moderate quantities by the corpus luteum at the beginning of pregnancy, it is secreted later in tremendous quantities by the placenta, averaging about a 10-fold increase during the course of pregnancy, as shown in Figure 82-7.

The special effects of progesterone that are essential for the normal progression of pregnancy are as follows:

1. Progesterone causes decidual cells to develop in the uterine endometrium, and these cells play an important role in the nutrition of the early embryo.
2. Progesterone decreases the contractility of the pregnant uterus, thus preventing uterine contractions from causing spontaneous abortion.
3. Progesterone contributes to the development of the conceptus even before implantation because it specifically increases the secretions of the mother's fallopian tubes and uterus to provide appropriate nutritive matter for the developing *morula* (the spherical mass of 16 to 32 blastomeres formed before the blastula) and *blastocyst.* There is also reason to believe that

progesterone affects cell cleavage in the early developing embryo.

4. The progesterone secreted during pregnancy helps the estrogen prepare the mother's breasts for lactation, which is discussed later in this chapter.

Human Chorionic Somatomammotropin

A more recently discovered placental hormone is called *human chorionic somatomammotropin.* It is a protein with a molecular weight of about 22,000, and it 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 all the other pregnancy hormones combined. It has several possible important effects.

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

Second, this hormone has weak actions similar to those of growth hormone, causing the formation of protein tissues 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 the 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 both 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 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. Some of the most notable effects are the following.

Pituitary Secretion. The anterior pituitary gland of the mother enlarges at least 50 percent during pregnancy and increases its production of *corticotropin, 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 the *glucocorticoids* is moderately increased throughout pregnancy. It is possible that these glucocorticoids help mobilize amino acids from the mother's tissues so that these can be used for synthesis of tissues in the fetus.

Pregnant women usually have about a twofold increase in the secretion of *aldosterone,* reaching a peak at the end of gestation. This, 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, occasionally leading to *pregnancy-induced hypertension.*

Increased Thyroid Gland Secretion. The mother's thyroid gland ordinarily enlarges up to 50 percent 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; this is especially true if the mother is on a calcium-deficient diet. 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 more intensified during lactation after the baby's birth because the growing baby requires many times more calcium than the fetus does.

Secretion of "Relaxin" by the Ovaries and Placenta. Another substance besides the estrogens and progesterone, a hormone called *relaxin,* is 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 having 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.

Response of the Mother's Body to Pregnancy

Most apparent among the many reactions of the mother to the fetus and to the excessive hormones of pregnancy is the increased size of the various sexual organs. For instance, the uterus increases from about 50 grams 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, 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 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 percent during the latter half of pregnancy. As a result, she frequently has sensations of becoming overheated. Also, owing to the extra load that 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, anticipating 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, a number of 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 usually develops *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 that the baby will have sufficient prothrombin to prevent hemorrhage, particularly brain hemorrhage, caused by the birth process.

Changes in the Maternal Circulatory System During Pregnancy

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

Maternal Blood Volume Increases During Pregnancy. The maternal blood volume shortly before term is about 30 percent above normal. This increase occurs mainly during the latter half of pregnancy, as shown by the curve of Figure 82-8. 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. Also, the bone marrow becomes increasingly active and produces extra red blood cells to go with the excess fluid volume. Therefore, at the time of 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 birth of the baby is about 20 percent 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 respiratory center's sensitivity to carbon dioxide. The net result is an increase in minute ventilation of about 50 percent and a decrease in arterial P_{CO_2} to several millimeters of mercury 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. But in addition, several special alterations of kidney function occur.

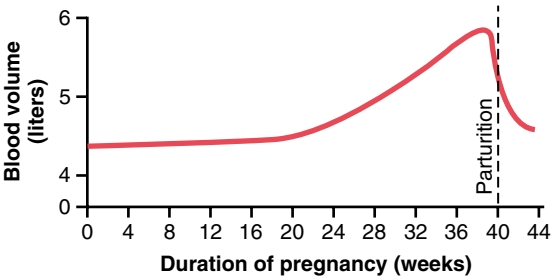


Figure 82-8 Effect of pregnancy to increase the mother's blood volume.

First, the renal tubules' reabsorptive capacity for sodium, chloride, and water is increased as much as 50 percent 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 percent during normal pregnancy due to 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 milliliters and 1 liter, but it can be only a few milliliters or as much as several liters. Isotope studies of the rate of formation of amniotic fluid show that, 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 is still present, which indicates that some of the fluid is formed and absorbed directly through the amniotic membranes.

Preeclampsia and Eclampsia

About 5 percent of all pregnant women experience a rapid rise in arterial blood pressure to hypertensive levels during the last few months of pregnancy. This is also 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, there is impaired function of the vascular endothelium and arterial spasm occurs in many parts of the mother's body, most significantly in the kidneys, brain, and liver. Both the 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.

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, the acute symptoms usually disappear within a few days after birth of the baby.

There is also evidence 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 arterioles of the uterine endometrium and completely remodel the maternal arterioles into large blood vessels with low resistance to blood flow. In patients with preeclampsia, the maternal arterioles fail to undergo these adaptive changes, for reasons that are still unclear, and there is insufficient blood supply to the placenta. This, 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 result in 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 birth of the baby. Without treatment, a high percentage of eclamptic mothers 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 eclamptic mothers has been reduced to 1 percent 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 rhythmical 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 a definite tendency 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 is a hormone secreted by the neurohypophysis that specifically causes uterine contraction (see Chapter 75). There are four reasons to believe that oxytocin might be 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) The rate of oxytocin secretion 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, too, can increase the intensity of uterine contractions.

Mechanical Factors That Increase Uterine Contractility

Stretch of the Uterine Musculature. Simply stretching smooth muscle organs usually increases their contractility. Further, intermittent stretch, as 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 instance, the obstetrician frequently induces labor by rupturing the membranes so that the head of the baby stretches the cervix more forcefully than usual or irritates it in other ways.

The mechanism by which 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 most of the months of pregnancy, the uterus undergoes periodic episodes of weak and slow rhythmical contractions called *Braxton Hicks contractions.* These contractions 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, on the basis of experience with other types of physiological control systems, a theory has been proposed for explaining the onset of labor. 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 82-9, and the observations supporting it are the following.

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. Referring to the discussion in Chapter 1 of positive

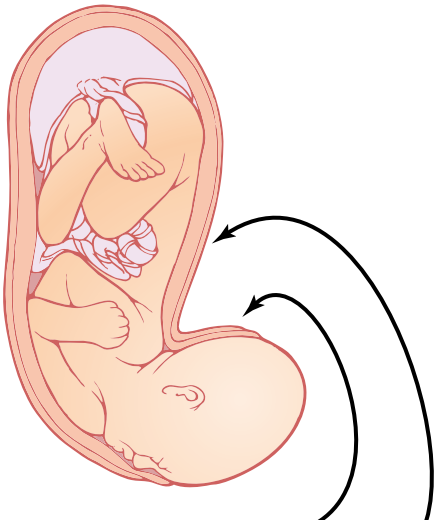


Figure 82-9 Theory for the onset of intensely strong contractions during labor.

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. (2) Cervical stretching also causes the pituitary gland to secrete oxytocin, which is another means for increasing uterine contractility.

To summarize, we can assume that 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 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—all *because positive feedback initiates a vicious circle when the gain of the feedback is greater than a critical level.*

One might ask about the many instances of false labor, in which the contractions become stronger and stronger and then fade away. Remember that for a vicious circle 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 rhythmical contractions and can lead to death of the fetus.

In more than 95 percent of births, the head is the first part of the baby to be expelled, and in most of the remaining instances, the buttocks are presented first. When the baby enters the birth canal with the buttocks or feet first, this 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 fetus's head moves rapidly into the birth canal, and with additional force from above, it continues to wedge its way through the canal until delivery is effected. 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 limited to an average of 350 milliliters 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.

However, 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 itself. 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, continuing for a total of about 10 days. After this time, the endometrial surface becomes re-epithelialized and ready for normal, nongravid sex life again.

Lactation

Development of the Breasts

The breasts, shown in Figure 82-10, 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 the production of milk.

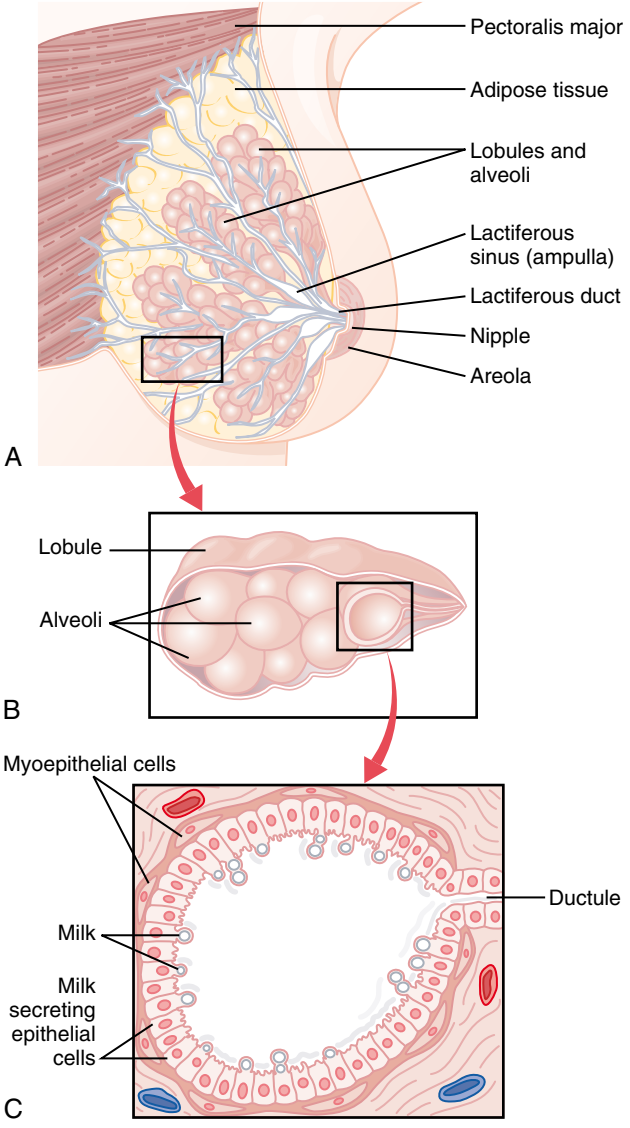


Figure 82-10 The breast and its secretory lobules, alveoli, and lactiferous ducts (milk ducts) that constitute its mammary gland (*A*). The enlargements show a lobule (*B*) and milk-secreting cells of an alveolus (*C*).

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,* the *adrenal glucocorticoids,* and *insulin.* Each of these 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 the 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 exactly the opposite effect on milk secretion—promoting it. This hormone 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 82-11.

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

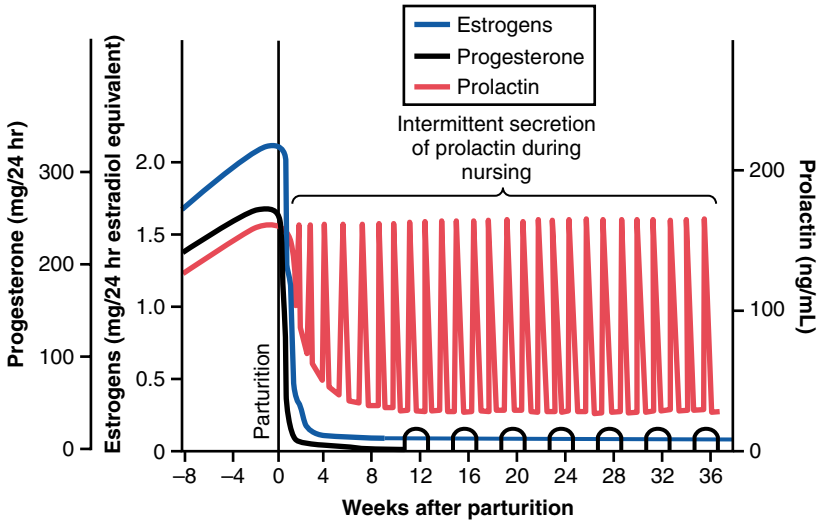


Figure 82-11 Changes in rates of secretion of estrogens, progesterone, and prolactin for 8 weeks before parturition and 36 weeks thereafter. Note especially the decrease of prolactin secretion back to basal levels within a few weeks after parturition, but also the intermittent periods of marked prolactin secretion (for about 1 hour at a time) during and after periods of nursing.

placenta allows the lactogenic effect of prolactin from the mother's pituitary gland to assume its natural milk-promoting role, and over 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 milk formation.

After birth of the baby, the *basal level* of prolactin secretion returns to the nonpregnant level over the next few weeks, as shown in Figure 82-11. 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 82-11. 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.

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 called *prolactin inhibitory hormone.* 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 themselves or because of a subsequent effect of increased prolactin—inhibit secretion of gonadotropin-releasing hormone by the hypothalamus. This, 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 in 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 breast nipples. Instead, the milk must be *ejected* from the alveoli into the ducts before the baby can obtain it. This is caused by a combined neurogenic and hormonal reflex that involves the posterior pituitary hormone *oxytocin,* as follows.

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.

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 82-1 lists the contents of human milk and cow's milk. The concentration of lactose in human milk is about 50 percent 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 instance, 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.

Table 82-1 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

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 instance, multiple types of *antibodies* and other anti-infectious agents are secreted in milk along with the 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 often 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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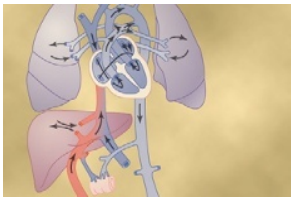
CHAPTER 83

Fetal and Neonatal Physiology



A complete discussion of fetal development, functioning of the child immediately after birth, and growth and development through the early years of life lies within the province of formal courses in obstetrics and pediatrics. However, many physiologic principles are peculiar to the infant and this chapter discusses the more important of these.

Growth and Functional Development of the Fetus

Initial development of the placenta and fetal membranes occurs far more rapidly than development of the fetus. In fact, during the first 2 to 3 weeks after implantation of the blastocyst, the fetus remains almost microscopic, but thereafter, as shown in Figure 83-1, the length of the fetus increases almost in proportion to age. At 12 weeks, the length is about 10 centimeters; at 20 weeks, 25 centimeters; and at term (40 weeks), 53 centimeters (about 21 inches). Because the weight of the fetus is approximately proportional to the cube of length, the weight increases almost in proportion to the cube of the age of the fetus.

Note in Figure 83-1 that the weight remains minuscule during the first 12 weeks and reaches 1 pound only at 23 weeks (5½ months) of gestation. Then, during the last trimester of pregnancy, the fetus gains rapidly, so 2 months before birth, the weight averages 3 pounds, 1 month before birth 4.5 pounds, and at birth 7 pounds—the final birth weight varying from as low as 4.5 pounds to as high as 11 pounds in normal infants with normal gestational periods.

Development of the Organ Systems

Within 1 month after fertilization of the ovum, the gross characteristics of all the different organs of the fetus have already begun to develop, and during the next 2 to 3 months, most of the details of the different organs are established. Beyond month 4, the organs of the fetus are grossly the same as those of the neonate. However, cellular development in each organ is usually far from complete and requires the full remaining 5 months of pregnancy for complete development. Even at birth, certain structures, particularly in the nervous system, the kidneys, and the liver, lack full development, as discussed in more detail later in the chapter.

Circulatory System. The human heart begins beating during the fourth week after fertilization, contracting at a rate of about 65 beats/min. This increases steadily to about 140 beats/min immediately before birth.

Formation of Blood Cells. Nucleated red blood cells begin to be formed in the yolk sac and mesothelial layers of the placenta at about the third week of fetal development. This is followed 1 week later (at 4 to 5 weeks) by formation of non-nucleated red blood cells by the fetal mesenchyme and also by the endothelium of the fetal blood vessels. Then, at 6 weeks, the liver begins to form blood cells, and in the third month, the spleen and other lymphoid tissues of the body begin forming blood cells. Finally, from the third month on, the bone marrow gradually becomes the principal source of the red blood cells, as well as most of the white blood cells, except for continued lymphocyte and plasma cell production in lymphoid tissue.

Respiratory System. Respiration cannot occur during fetal life because there is no air to breathe in the amniotic cavity. However, attempted respiratory movements do take place beginning at the end of the first trimester of pregnancy. Tactile stimuli and fetal asphyxia especially cause these attempted respiratory movements.

During the last 3 to 4 months of pregnancy, the respiratory movements of the fetus are mainly inhibited, for reasons unknown, and the lungs remain almost completely deflated. The inhibition of respiration during the later months of fetal life prevents filling of the lungs with fluid and debris from the

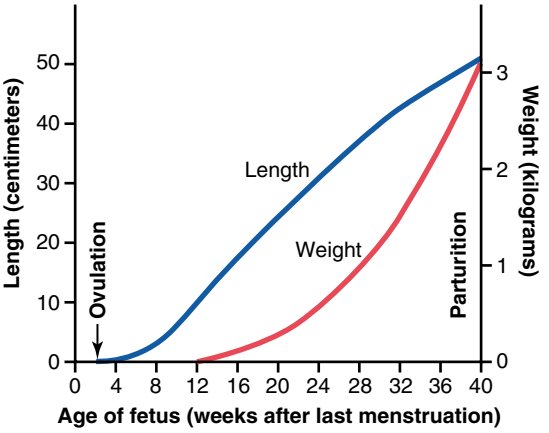


Figure 83-1 Growth of the fetus.

meconium excreted by the fetus's gastrointestinal tract into the amniotic fluid. Also, small amounts of fluid are secreted into the lungs by the alveolar epithelium up until the moment of birth, thus keeping only clean fluid in the lungs.

Nervous System. Most of the reflexes of the fetus that involve the spinal cord and even the brain stem are present by the third to fourth months of pregnancy. However, those nervous system functions that involve the cerebral cortex are still only in the early stages of development even at birth. Indeed, myelinization of some major tracts of the brain becomes complete only after about 1 year of postnatal life.

Gastrointestinal Tract. By midpregnancy the fetus begins to ingest and absorb large quantities of amniotic fluid, and during the last 2 to 3 months, gastrointestinal function approaches that of the normal neonate. By that time, small quantities of *meconium* are continually formed in the gastrointestinal tract and excreted from the anus into the amniotic fluid. Meconium is composed partly of residue from swallowed amniotic fluid and partly of *mucus,* epithelial cells, and other residues of excretory products from the gastrointestinal mucosa and glands.

Kidneys. The fetal kidneys begin to excrete urine during the second trimester pregnancy, and fetal urine accounts for about 70 to 80 percent of the amniotic fluid. Abnormal kidney development or severe impairment of kidney function in the fetus greatly reduces the formation of amniotic fluid *(oligohydramnios)* and can lead to fetal death.

Although the fetal kidneys form urine, the renal control systems for regulating fetal extracellular fluid volume and electrolyte balances, and especially acid-base balance, are almost nonexistent until late fetal life and do not reach full development until a few months after birth.

Fetal Metabolism. The fetus uses mainly glucose for energy, and the fetus has a high capability to store fat and protein, much if not most of the fat being synthesized from glucose rather than being absorbed directly from the mother's blood. In addition to these generalities, there are special problems of fetal metabolism in relation to calcium, phosphate, iron, and some vitamins.

Metabolism of Calcium and Phosphate. Figure 83-2 shows the rates of calcium and phosphate accumulation in the fetus, demonstrating that about 22.5 grams of calcium and 13.5 grams of phosphorus are accumulated in the average fetus during gestation. About one half of these accumulate during the last 4 weeks of gestation, which is coincident with the period of rapid ossification of the fetal bones and with the period of rapid weight gain of the fetus.

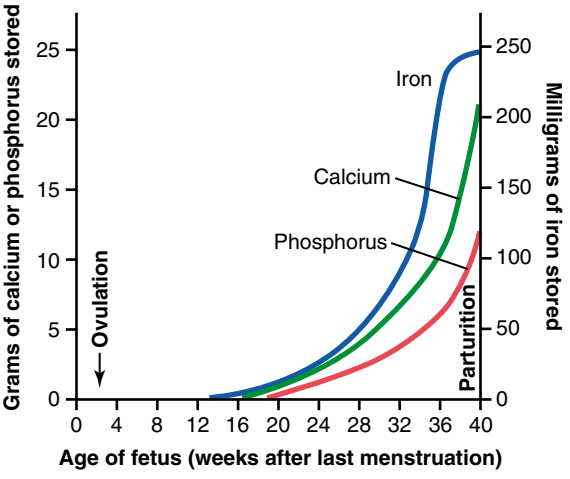


Figure 83-2 Iron, calcium, and phosphorus storage in the fetus at different stages of gestation.

During the earlier part of fetal life, the bones are relatively unossified and have mainly a cartilaginous matrix. Indeed, x-ray films ordinarily do not show any ossification until after the fourth month of pregnancy.

Note especially that the total amounts of calcium and phosphate needed by the fetus during gestation represent only about 2 percent of the quantities of these substances in the mother's bones. Therefore, this is a minimal drain from the mother. Much greater drain occurs after birth during lactation.

Accumulation of Iron. Figure 83-2 also shows that iron accumulates in the fetus even more rapidly than calcium and phosphate. Most of the iron is in the form of hemoglobin, which begins to be formed as early as the third week after fertilization of the ovum.

Small amounts of iron are concentrated in the mother's uterine progestational endometrium even before implantation of the ovum; this iron is ingested into the embryo by the trophoblastic cells and is used to form the very early red blood cells. About one third of the iron in a fully developed fetus is normally stored in the liver. This iron can then be used for several months after birth by the neonate for formation of additional hemoglobin.

Utilization and Storage of Vitamins. The fetus needs vitamins equally as much as the adult and in some instances to a far greater extent. In general, the vitamins function the same in the fetus as in the adult, as discussed in Chapter 71. Special functions of several vitamins should be mentioned, however.

The B vitamins, especially vitamin B_{12} and folic acid, are necessary for formation of red blood cells and nervous tissue, as well as for overall growth of the fetus.

Vitamin C is necessary for appropriate formation of intercellular substances, especially the bone matrix and fibers of connective tissue.

Vitamin D is necessary for normal bone growth in the fetus, but even more important, the mother needs it for adequate absorption of calcium from her gastrointestinal tract. If the mother has plenty of vitamin D in her body fluids, large quantities of the vitamin will be stored by the fetal liver to be used by the neonate for several months after birth.

Vitamin E, although the mechanisms of its functions are not entirely clear, is necessary for normal development of the early embryo. In its absence in laboratory animals, spontaneous abortion usually occurs at an early stage of pregnancy.

Vitamin K is used by the fetal liver for formation of Factor VII, prothrombin, and several other blood coagulation factors. When vitamin K is insufficient in the mother, Factor VII and prothrombin become deficient in the fetus and the mother. Because most vitamin K is formed by bacterial action in the mother's colon, the neonate has no adequate source of vitamin K for the first week or so of life after birth until normal colonic bacterial flora become established in the newborn infant. Therefore, prenatal storage in the fetal liver of at least small amounts of vitamin K derived from the mother is helpful in preventing fetal hemorrhage, particularly hemorrhage in the brain when the head is traumatized by squeezing through the birth canal.

Adjustments of the Infant to Extrauterine Life

Onset of Breathing

The most obvious effect of birth on the baby is loss of the placental connection with the mother and, therefore, loss of this means of metabolic support. One of the most important immediate adjustments required of the infant is to begin breathing.

Cause of Breathing at Birth. After normal delivery from a mother who has not been depressed by anesthetics, the child ordinarily begins to breathe within seconds and has a normal respiratory rhythm within less than 1 minute after birth. The promptness with which the fetus begins to breathe indicates that breathing is initiated by sudden exposure to the exterior world, probably resulting from (1) a slightly asphyxiated state incident to the birth process, but also from (2) sensory impulses that originate in the suddenly cooled skin. In an infant who does not breathe immediately, the body becomes progressively more hypoxic and hypercapnic, which provides additional stimulus to the respiratory center and usually causes breathing within an additional minute after birth.

Delayed or Abnormal Breathing at Birth—Danger of Hypoxia. If the mother has been depressed by a general anesthetic during delivery, which at least partially anesthetizes the fetus as well, the onset of respiration is likely to be delayed for several minutes, thus demonstrating the importance of using as little anesthesia as feasible. Also, many infants who have had head trauma during delivery or who undergo prolonged delivery are slow to breathe or sometimes do not breathe at all. This can result from two possible effects: First, in a few infants, intracranial hemorrhage or brain contusion causes a concussion syndrome with a greatly depressed respiratory center. Second, and probably much more important, prolonged fetal hypoxia during delivery can cause serious depression of the respiratory center.

Hypoxia frequently occurs during delivery because of (1) compression of the umbilical cord; (2) premature separation of the placenta; (3) excessive contraction of the uterus, which can cut off the mother's blood flow to the placenta; or (4) excessive anesthesia of the mother, which depresses oxygenation even of her blood.

Degree of Hypoxia That an Infant Can Tolerate. In an adult, failure to breathe for only 4 minutes often causes death, but a neonate often survives as long as 10 minutes of failure to breathe after birth. Permanent and serious brain impairment often ensues if breathing is delayed more than 8 to 10 minutes. Indeed, actual lesions develop mainly in the thalamus, in the inferior colliculi, and in other brain stem areas, thus permanently affecting many of the motor functions of the body.

Expansion of the Lungs at Birth. At birth, the walls of the alveoli are at first collapsed because of the surface tension of the viscid fluid that fills them. More than 25 mm Hg of negative inspiratory pressure in the lungs is usually required to oppose the effects of this surface tension and to open the alveoli for the first time. But once the alveoli do open, further respiration can be effected with relatively weak respiratory movements. Fortunately, the first inspirations of the normal neonate are extremely powerful, usually capable of creating as much as 60 mm Hg negative pressure in the intrapleural space.

Figure 83-3 shows the tremendous negative intrapleural pressures required to open the lungs at the onset of breathing. At the top is shown the pressure-volume curve ("compliance" curve) for the first breath after birth. Observe, first, the lower part of the curve *beginning at the zero pressure point* and moving to the right. The curve shows that the volume of air in the lungs remains almost exactly zero until the negative pressure has reached −40 centimeters water (−30 mm Hg). Then, as the negative pressure increases to −60 centimeters of water, about 40 milliliters of air enters the lungs. To deflate the lungs, considerable positive pressure, about +40 centimeters of water, is required because of viscous resistance offered by the fluid in the bronchioles.

Note that the second breath is much easier, with far less negative and positive pressures required. Breathing does not become completely normal until about 40 minutes after birth, as shown by the third compliance curve, the shape of which compares favorably with that for the normal adult, as shown in Chapter 38.

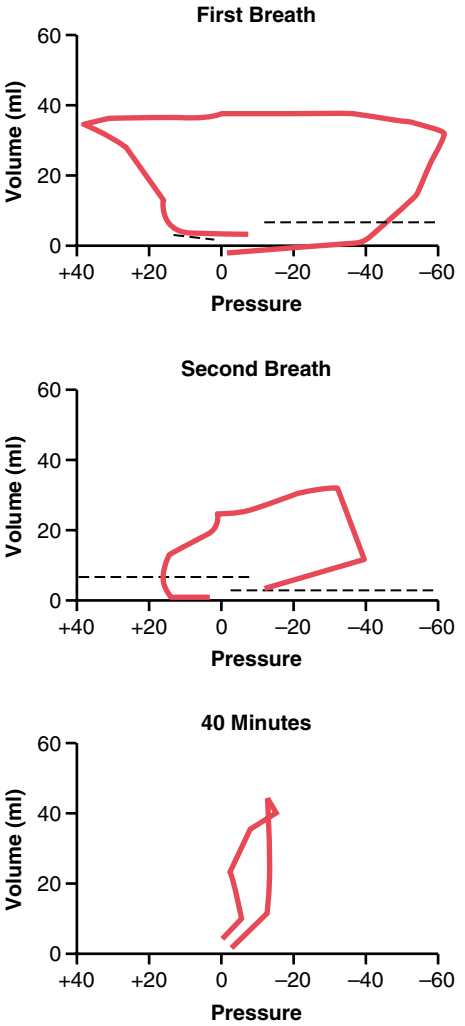


Figure 83-3 Pressure-volume curves of the lungs ("compliance" curves) of a neonate immediately after birth, showing the extreme forces required for breathing during the first two breaths of life and development of a nearly normal compliance curve within 40 minutes after birth. (Redrawn from Smith CA: The first breath. Sci Am 209:32, 1963, © 1963 by Scientific American, Inc. All rights reserved.)

Respiratory Distress Syndrome Caused When Surfactant Secretion Is Deficient. A small number of infants, especially premature infants and infants born of diabetic mothers, develop severe respiratory distress in the early hours to the first several days after birth, and some die within the next day or so. The alveoli of these infants at death contain large quantities of proteinaceous fluid, almost as if pure plasma had leaked out of the capillaries into the alveoli. The fluid also contains desquamated alveolar epithelial cells. This condition is called *hyaline membrane disease* because microscopic slides of the lung show the material filling the alveoli to look like a hyaline membrane.

A characteristic finding in respiratory distress syndrome is failure of the respiratory epithelium to secrete adequate quantities of *surfactant,* a substance normally secreted into the alveoli that decreases the surface tension of the alveolar fluid, therefore allowing the alveoli to open easily during inspiration. The surfactant-secreting cells (type II alveolar epithelial cells) do not begin to secrete surfactant until the last 1 to 3 months of gestation. Therefore, many premature babies and a few full-term babies are born without the capability to secrete sufficient surfactant, which causes both a collapse tendency of the alveoli and development of pulmonary edema. The role of surfactant in preventing these effects is discussed in Chapter 37.

Circulatory Readjustments at Birth

Equally as essential as the onset of breathing at birth are immediate circulatory adjustments that allow adequate blood flow through the lungs. Also, circulatory adjustments during the first few hours of life cause more and more blood flow through the baby's liver, which up to this point has had little blood flow. To describe these readjustments, we must first consider the anatomical structure of the fetal circulation.

Specific Anatomical Structure of the Fetal Circulation. Because the lungs are mainly nonfunctional during fetal life and because the liver is only partially functional, it is not necessary for the fetal heart to pump much blood through either the lungs or the liver. However, the fetal heart must pump large quantities of blood through the placenta. Therefore, special anatomical arrangements cause the fetal circulatory system to operate much differently from that of the newborn baby.

First, as shown in Figure 83-4, blood returning from the placenta through the umbilical vein passes through the *ductus venosus,* mainly bypassing the liver. Then most of the blood entering the right atrium from the inferior vena cava is directed in a straight pathway across the posterior aspect of the right atrium and through the *foramen ovale* directly into the left atrium. Thus, the well-oxygenated blood from the placenta enters mainly the left side of the heart, rather than the right side, and is pumped by the left ventricle mainly into the arteries of the head and forelimbs.

The blood entering the right atrium from the superior vena cava is directed downward through the tricuspid valve into the right ventricle. This blood is mainly deoxygenated blood from the head region of the fetus. It is pumped by the right ventricle into the pulmonary artery and then mainly through the *ductus arteriosus* into the descending aorta, then through the two umbilical arteries into the placenta, where the deoxygenated blood becomes oxygenated.

Figure 83-5 gives the relative percentages of the total blood pumped by the heart that pass through the different vascular

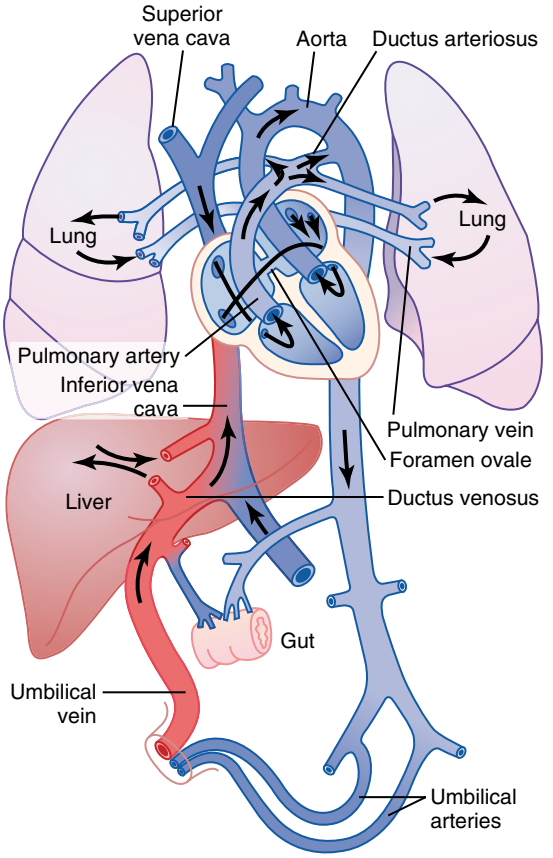


Figure 83-4 Organization of the fetal circulation. (Modified from Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, 7th ed. Philadelphia: WB Saunders, 1974.)

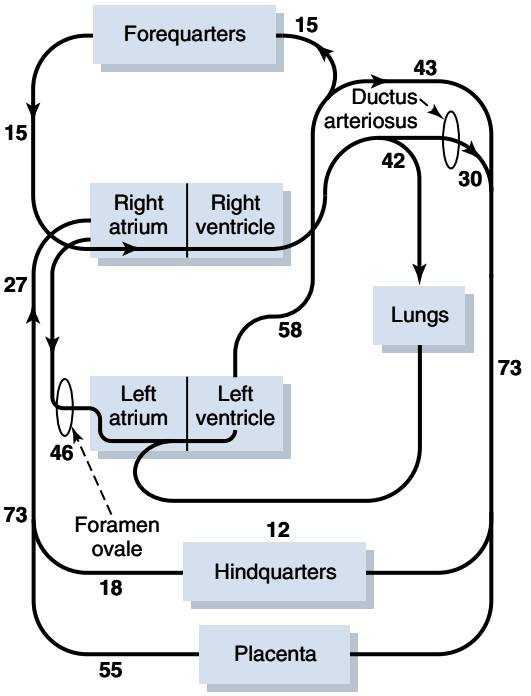


Figure 83-5 Diagram of the fetal circulatory system, showing relative distribution of blood flow to the different vascular areas. The numerals represent the percentage of the total output from both sides of the heart flowing through each particular area.

circuits of the fetus. This figure shows that 55 percent of all the blood goes through the placenta, leaving only 45 percent to pass through all the tissues of the fetus. Furthermore, during fetal life, only 12 percent of the blood flows through the lungs; immediately after birth, virtually all the blood flows through the lungs.

Changes in the Fetal Circulation at Birth. The basic changes in the fetal circulation at birth are discussed in Chapter 23 in relation to congenital anomalies of the ductus arteriosus and foramen ovale that persist throughout life in a few persons. Briefly, these changes are the following.

Decreased Pulmonary and Increased Systemic Vascular Resistances at Birth. The primary changes in the circulation at birth are, first, loss of the tremendous blood flow through the placenta, which approximately doubles the systemic vascular resistance at birth. This increases the aortic pressure, as well as the pressures in the left ventricle and left atrium.

Second, the *pulmonary vascular resistance greatly decreases* as a result of expansion of the lungs. In the unexpanded fetal lungs, the blood vessels are compressed because of the small volume of the lungs. Immediately on expansion, these vessels are no longer compressed and the resistance to blood flow decreases severalfold. Also, in fetal life, the hypoxia of the lungs causes considerable tonic vasoconstriction of the lung blood vessels, but vasodilation takes place when aeration of the lungs eliminates the hypoxia. All these changes together reduce the resistance to blood flow through the lungs as much as fivefold, which *reduces the pulmonary arterial pressure, right ventricular pressure,* and *right atrial pressure.*

Closure of the Foramen Ovale. The *low right atrial pressure* and the *high left atrial pressure* that occur secondarily to the changes in pulmonary and systemic resistances at birth cause blood now to attempt to flow backward through the foramen ovale; that is, from the left atrium into the right atrium, rather than in the other direction, as occurred during fetal life. Consequently, the small valve that lies over the foramen ovale on the left side of the atrial septum closes over this opening, thereby preventing further flow through the foramen ovale.

In two thirds of all people, the valve becomes adherent over the foramen ovale within a few months to a few years and forms a permanent closure. But even if permanent closure does not occur, the left atrial pressure throughout life normally remains 2 to 4 mm Hg greater than the right atrial pressure and the backpressure keeps the valve closed.

Closure of the Ductus Arteriosus. The ductus arteriosus also closes, but for different reasons. First, the increased systemic resistance elevates the aortic pressure while the decreased pulmonary resistance reduces the pulmonary arterial pressure. As a consequence, after birth, blood begins to flow backward from the aorta into the pulmonary artery through the ductus arteriosus, rather than in the other direction, as in fetal life. However, after only a few hours, the muscle wall of the ductus arteriosus constricts markedly and within 1 to 8 days, the constriction is usually sufficient to stop all blood flow. This is called *functional closure* of the ductus arteriosus. Then, during the next 1 to 4 months, the ductus arteriosus ordinarily becomes anatomically occluded by growth of fibrous tissue into its lumen.

The cause of ductus arteriosus closure relates to the increased oxygenation of the blood flowing through the ductus. In fetal life the P_{O_2} of the ductus blood is only 15 to 20 mm Hg, but it increases to about 100 mm Hg within a few hours after birth. Furthermore, many experiments have shown that the degree of contraction of the smooth muscle in the ductus wall is highly related to this availability of oxygen.

In one of several thousand infants, the ductus fails to close, resulting in a *patent ductus arteriosus,* the consequences of which are discussed in Chapter 23. The failure of closure has been postulated to result from excessive ductus dilation caused by vasodilating prostaglandins in the ductus wall. In fact, administration of the drug *indomethacin,* which blocks synthesis of prostaglandins, often leads to closure.

Closure of the Ductus Venosus. In fetal life the portal blood from the fetus's abdomen joins the blood from the umbilical vein, and these together pass by way of the *ductus venosus* directly into the vena cava immediately below the heart but above the liver, thus bypassing the liver.

Immediately after birth, blood flow through the umbilical vein ceases, but most of the portal blood still flows through the ductus venosus, with only a small amount passing through the channels of the liver. However, within 1 to 3 hours the muscle wall of the ductus venosus contracts strongly and closes this avenue of flow. As a consequence, the portal venous pressure rises from near 0 to 6 to 10 mm Hg, which is enough to force portal venous blood flow through the liver sinuses. Although the ductus venosus rarely fails to close, we know almost nothing about what causes the closure.

Nutrition of the Neonate

Before birth, the fetus derives almost all its energy from glucose obtained from the mother's blood. After birth, the amount of glucose stored in the infant's body in the form of liver and muscle glycogen is sufficient to supply the infant's needs for only a few hours. The liver of the neonate is still far from functionally adequate at birth, which prevents significant gluconeogenesis. Therefore, the infant's blood glucose concentration frequently falls the first day to as low as 30 to 40 mg/dl of plasma, less than half the normal value. Fortunately, however, appropriate mechanisms are available for the infant to use its stored fats and proteins for metabolism until mother's milk can be provided 2 to 3 days later.

Special problems are also frequently associated with getting an adequate fluid supply to the neonate because the infant's rate of body fluid turnover averages seven times that of an adult, and the mother's milk supply requires several days to develop. Ordinarily, the infant's weight decreases 5 to 10 percent and sometimes as much as 20 percent within the first 2 to 3 days of life. Most of this weight loss is loss of fluid rather than of body solids.

Special Functional Problems in the Neonate

An important characteristic of the neonate is instability of the various hormonal and neurogenic control systems. This results partly from immature development of the different organs of the body and partly from the fact that the control systems simply have not become adjusted to the new way of life.

Respiratory System

The normal rate of respiration in a neonate is about 40 breaths per minute, and tidal air with each breath averages 16 milliliters. This gives a total minute respiratory volume of 640 ml/min, which is about twice as great in relation to the body weight as that of an adult. *The functional residual capacity of the infant's lungs is only one-half that of an adult in relation to body weight.* This difference causes excessive cyclical increases and decreases in the newborn baby's blood gas concentrations if the respiratory rate becomes slowed because it is the residual air in the lungs that smoothes out the blood gas variations.

Circulation

Blood Volume. The blood volume of a neonate immediately after birth averages about 300 milliliters, but if the infant is left attached to the placenta for a few minutes after birth or if the umbilical cord is stripped to force blood out of its vessels into the baby, an additional 75 milliliters of blood enters the infant, to make a total of 375 milliliters. Then, during the ensuing few hours, fluid is lost into the neonate's tissue spaces from this blood, which increases the hematocrit but returns the blood volume once again to the normal value of about 300 milliliters. Some pediatricians believe that this extra blood volume caused by stripping the umbilical cord can lead to mild pulmonary edema with some degree of respiratory distress, but the extra red blood cells are often valuable to the infant.

Cardiac Output. The cardiac output of the neonate averages 500 ml/min, which, like respiration and body metabolism, is about twice as much in relation to body weight as in the adult. Occasionally a child is born with an especially low cardiac output caused by hemorrhage of much of its blood volume from the placenta at birth.

Arterial Pressure. The arterial pressure during the first day after birth averages about 70 mm Hg systolic and 50 mm Hg diastolic; this increases slowly during the next several months to about 90/60. Then there is a much slower rise during the subsequent years until the adult pressure of 115/70 is attained at adolescence.

Blood Characteristics. The red blood cell count in the neonate averages about 4 million per cubic millimeter. If blood is stripped from the cord into the infant, the red blood cell count rises an additional 0.5 to 0.75 million during the first few hours of life, giving a red blood cell count of about 4.75 million per cubic millimeter, as shown in Figure 83-6. Subsequent to this, however, few new red blood cells are formed in the infant during the first few weeks of life, presumably because the hypoxic stimulus of fetal life is no longer present to stimulate red cell production. Thus, as shown in Figure 83-6, the average red blood cell count falls to less than 4 million per cubic millimeter by about 6 to 8 weeks of age. From that time on, increasing activity by the baby provides the appropriate stimulus for returning the red blood cell count to normal within another 2 to 3 months. Immediately after birth, the white blood cell count of the neonate is about 45,000 per cubic millimeter, which is about five times as great as that of the normal adult.

Neonatal Jaundice and Erythroblastosis Fetalis. Bilirubin formed in the fetus can cross the placenta into the mother and be excreted through the liver of the mother, but immediately after birth, the only means for ridding the neonate of bilirubin is through the neonate's own liver, which

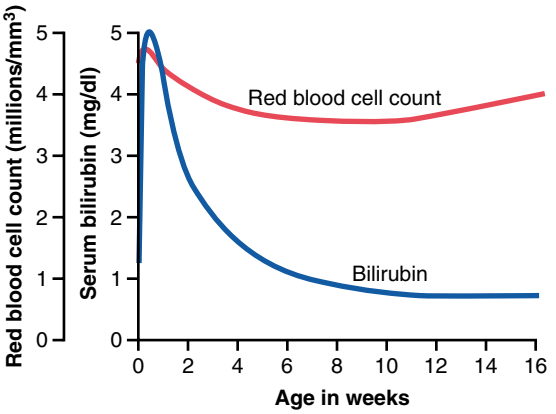


Figure 83-6 Changes in the red blood cell count and in serum bilirubin concentration during the first 16 weeks of life, showing physiological anemia at 6 to 12 weeks of life and physiological hyperbilirubinemia during the first 2 weeks of life.

for the first week or so of life functions poorly and is incapable of conjugating significant quantities of bilirubin with glucuronic acid for excretion into the bile. Consequently, the plasma bilirubin concentration rises from a normal value of less than 1 mg/dl to an average of 5 mg/dl during the first 3 days of life and then gradually falls back to normal as the liver becomes functional. This effect, called *physiological hyperbilirubinemia,* is shown in Figure 83-6, and it is associated with mild *jaundice* (yellowness) of the infant's skin and especially of the sclerae of its eyes for a week or two.

However, by far the most important abnormal cause of serious neonatal jaundice is *erythroblastosis fetalis,* which is discussed in detail in Chapter 32 in relation to Rh factor incompatibility between the fetus and mother. Briefly, the *erythroblastotic baby* inherits Rh-positive red cells from the father, while the mother is Rh negative. The mother then becomes immunized against the Rh-positive factor (a protein) in the fetus's blood cells, and her antibodies destroy fetal red cells, releasing extreme quantities of bilirubin into the fetus's plasma and often causing fetal death for lack of adequate red cells. Before the advent of modern obstetrical therapeutics, this condition occurred either mildly or seriously in 1 of every 50 to 100 neonates.

Fluid Balance, Acid-Base Balance, and Renal Function

The rate of fluid intake and fluid excretion in the newborn infant is seven times as great in relation to weight as in the adult, which means that even a slight percentage alteration of fluid intake or fluid output can cause rapidly developing abnormalities.

The rate of metabolism in the infant is also twice as great in relation to body mass as in the adult, which means that twice as much acid is normally formed, creating a tendency toward acidosis in the infant. Functional development of the kidneys is not complete until the end of about the first month of life. For instance, the kidneys of the neonate can concentrate urine to only 1.5 times the osmolality of the plasma, whereas the adult can concentrate the urine to three to four times the plasma osmolarity. Therefore, considering the immaturity of the kidneys, together with the marked fluid turnover in the infant and rapid formation of acid, one can readily understand that among the most important problems of infancy are acidosis, dehydration, and, more rarely, overhydration.

Liver Function

During the first few days of life, liver function in the neonate may be quite deficient, as evidenced by the following effects:

1. The liver of the neonate conjugates bilirubin with glucuronic acid poorly and therefore excretes bilirubin only slightly during the first few days of life.
2. The liver of the neonate is deficient in forming plasma proteins, so the plasma protein concentration falls during the first weeks of life to 15 to 20 percent less than that for older children. Occasionally the protein concentration falls so low that the infant develops hypoproteinemic edema.
3. The gluconeogenesis function of the liver is particularly deficient. As a result, the blood glucose level of the unfed neonate falls to about 30 to 40 mg/dl (about 40 percent of normal) and the infant must depend mainly on its stored fats for energy until sufficient feeding can occur.
4. The liver of the neonate usually also forms too little of the blood factors needed for normal blood coagulation.

Digestion, Absorption, and Metabolism of Energy Foods; and Nutrition

In general, the ability of the neonate to digest, absorb, and metabolize foods is no different from that of the older child, with the following three exceptions.

First, *secretion of pancreatic amylase in the neonate is deficient*, so the neonate uses starches less adequately than do older children.

Second, *absorption of fats from the gastrointestinal tract is somewhat less than that in the older child.* Consequently, milk with a high fat content, such as cow's milk, is frequently inadequately absorbed.

Third, because the liver functions imperfectly during at least the first week of life, *the glucose concentration in the blood is unstable and low.*

The neonate is especially capable of synthesizing and storing proteins. Indeed, with an adequate diet, up to 90 percent of the ingested amino acids is used for formation of body proteins. This is a much higher percentage than in adults.

Increased Metabolic Rate and Poor Body Temperature Regulation. The normal metabolic rate of the neonate in relation to body weight is about twice that of the adult, which accounts also for the twice as great cardiac output and twice as great minute respiratory volume in relation to body weight in the infant.

Because the body surface area is large in relation to body mass, heat is readily lost from the body. As a result, the body temperature of the neonate, particularly of premature infants, falls easily. Figure 83-7 shows that the body temperature of even a normal infant often falls several degrees during the first few hours after birth but returns to normal in 7 to 10 hours. Still, the body temperature regulatory mechanisms remain poor during the early days of life, allowing marked deviations in temperature, which are also shown in Figure 83-7.

Nutritional Needs During the Early Weeks of Life. At birth, a neonate is usually in complete nutritional balance, provided the mother has had an adequate diet. Furthermore, function of the gastrointestinal system is usually more than adequate to digest and assimilate all the nutritional needs of the infant if appropriate nutrients are provided in the diet.

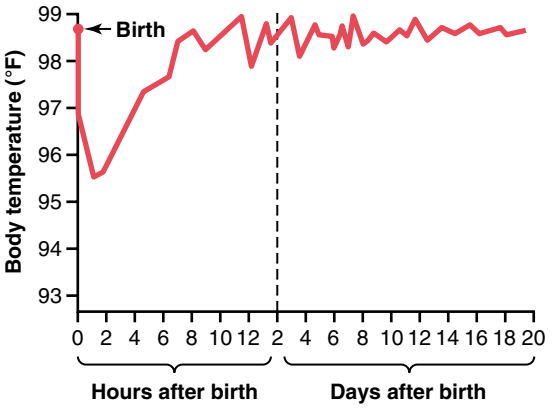


Figure 83-7 Fall in body temperature of the neonate immediately after birth, and instability of body temperature during the first few days of life.

However, three specific problems do occur in the early nutrition of the infant.

Need for Calcium and Vitamin D. The neonate is in a stage of rapid ossification of its bones at birth, so a ready supply of calcium throughout infancy is necessary. This is ordinarily supplied adequately by the usual diet of milk. Yet absorption of calcium by the gastrointestinal tract is poor in the absence of vitamin D. Therefore, the vitamin D–deficient infant can develop severe rickets in only a few weeks. This is particularly true in premature babies because their gastrointestinal tracts absorb calcium even less effectively than those of normal infants.

Necessity for Iron in the Diet. If the mother has had adequate amounts of iron in her diet, the liver of the infant usually has stored enough iron to keep forming blood cells for 4 to 6 months after birth. But if the mother has had insufficient iron in her diet, severe anemia is likely to occur in the infant after about 3 months of life. To prevent this possibility, early feeding of the infant with egg yolk, which contains reasonably large quantities of iron, or the administration of iron in some other form is desirable by the second or third month of life.

Vitamin C Deficiency in Infants. Ascorbic acid (vitamin C) is not stored in significant quantities in the fetal tissues, yet it is required for proper formation of cartilage, bone, and other intercellular structures of the infant. Furthermore, milk provides only small supplies of ascorbic acid, especially cow's milk, which has only one fourth as much as human milk. For this reason, orange juice or other sources of ascorbic acid are often prescribed by the third week of life.

Immunity

The neonate inherits much immunity from the mother because many protein antibodies diffuse from the mother's blood through the placenta into the fetus. However, the neonate does not form antibodies of its own to a significant extent. By the end of the first month, the baby's gamma globulins, which contain the antibodies, have decreased to less than half the original level, with a corresponding decrease in immunity. Thereafter, the baby's own immunity system begins to form antibodies and the gamma globulin concentration returns essentially to normal by the age of 12 to 20 months.

Despite the decrease in gamma globulins soon after birth, the antibodies inherited from the mother protect the infant for about 6 months against most major childhood infectious diseases, including diphtheria, measles, and polio. Therefore, immunization against these diseases before 6 months is usually unnecessary. Conversely, the inherited antibodies against whooping cough are normally insufficient to protect the neonate; therefore, for full safety, the infant requires immunization against this disease within the first month or so of life.

Allergy. The newborn infant is seldom subject to allergy. Several months later, however, when the infant's own antibodies first begin to form, extreme allergic states can develop, often resulting in serious eczema, gastrointestinal abnormalities, and even anaphylaxis. As the child grows older and still higher degrees of immunity develop, these allergic manifestations usually disappear. This relation of immunity to allergy is discussed in Chapter 34.

Endocrine Problems

Ordinarily, the endocrine system of the infant is highly developed at birth, and the infant seldom exhibits any immediate endocrine abnormalities. However, there are special instances in which the endocrinology of infancy is important:

1. If a pregnant mother bearing a female child is treated with an androgenic hormone or if an androgenic tumor develops during pregnancy, the child will be born with a high degree of masculinization of her sexual organs, thus resulting in a type of *hermaphroditism.*
2. The sex hormones secreted by the placenta and by the mother's glands during pregnancy occasionally cause the neonate's breasts to form milk during the first days of life. Sometimes the breasts then become inflamed, or infectious mastitis develops.
3. An infant born of an untreated diabetic mother will have considerable hypertrophy and hyperfunction of the islets of Langerhans in the pancreas. As a consequence, the infant's blood glucose concentration may fall to lower than 20 mg/dl shortly after birth. Fortunately, however, in the neonate, unlike in the adult, insulin shock or coma from this low level of blood glucose concentration only rarely develops.

   Maternal type II diabetes is the most common cause of large babies. Type II diabetes in the mother is associated with resistance to the metabolic effects of insulin and compensatory increases in plasma insulin concentration. The high levels of insulin are believed to stimulate fetal growth and contribute to increased birth weight. Increased supply of glucose and other nutrients to the fetus may also contribute to increased fetal growth. However, most of the increased fetal weight is due to increased body fat; there is usually little increase in body length, although the size of some organs may be increased *(organomegaly).*

   In the mother with uncontrolled type I diabetes (caused by lack of insulin secretion), fetal growth may be stunted because of metabolic deficits in the mother and growth and tissue maturation of the neonate are often impaired. Also, there is a high rate of intrauterine mortality. Among the fetuses that do come to term, there is still a high mortality rate. Two thirds of the infants who die succumb to *respiratory distress syndrome,* described earlier in the chapter.
4. Occasionally a child is born with hypofunctional adrenal cortices, often resulting from *agenesis* of the adrenal glands or *exhaustion atrophy*, which can occur when the adrenal glands have been vastly overstimulated.
5. If a pregnant woman has hyperthyroidism or is treated with excess thyroid hormone, the infant is likely to be born with a temporarily hyposecreting thyroid gland. Conversely, if before pregnancy a woman had had her thyroid gland removed, her pituitary gland may secrete great quantities of thyrotropin during gestation and the child might be born with temporary hyperthyroidism.
6. In a fetus lacking thyroid hormone secretion, the bones grow poorly and there is mental retardation. This causes the condition called *cretin dwarfism,* discussed in Chapter 76.

Special Problems of Prematurity

All the problems in neonatal life just noted are severely exacerbated in prematurity. They can be categorized under the following two headings: (1) immaturity of certain organ systems and (2) instability of the different homeostatic control systems. Because of these effects, a premature baby seldom lives if it is born more than 3 months before term.

Immature Development of the Premature Infant

Almost all the organ systems of the body are immature in the premature infant and require particular attention if the life of the premature baby is to be saved.

Respiration. The respiratory system is especially likely to be underdeveloped in the premature infant. The vital capacity and the functional residual capacity of the lungs are especially small in relation to the size of the infant. Also, surfactant secretion is depressed or absent. As a consequence, *respiratory distress syndrome* is a common cause of death. Also, the low functional residual capacity in the premature infant is often associated with periodic breathing of the Cheyne-Stokes type.

Gastrointestinal Function. Another major problem of the premature infant is to ingest and absorb adequate food. If the infant is more than 2 months premature, the digestive and absorptive systems are almost always inadequate. The absorption of fat is so poor that the premature infant must have a low-fat diet. Furthermore, the premature infant has unusual difficulty in absorbing calcium and, therefore, can develop severe rickets before the difficulty is recognized. For this reason, special attention must be paid to adequate calcium and vitamin D intake.

Function of Other Organs. Immaturity of other organ systems that frequently causes serious difficulties in the premature infant includes (1) immaturity of the liver, which results in poor intermediary metabolism and often a bleeding tendency as a result of poor formation of coagulation factors; (2) immaturity of the kidneys, which are particularly deficient in their ability to rid the body of acids, thereby predisposing to acidosis and to serious fluid balance abnormalities; (3) immaturity of the blood-forming mechanism of the bone marrow, which allows rapid development of anemia; and (4) depressed formation of gamma globulin by the lymphoid system, which often leads to serious infection.

Instability of the Homeostatic Control Systems in the Premature Infant

Immaturity of the different organ systems in the premature infant creates a high degree of instability in the homeostatic mechanisms of the body. For instance, the acid-base balance can vary tremendously, particularly when the rate of food intake varies from time to time. Likewise, the blood protein concentration is usually low because of immature liver development, often leading to *hypoproteinemic edema.* And inability of the infant to regulate its calcium ion concentration may bring on hypocalcemic tetany. Also, the blood glucose concentration can vary between the extremely wide limits of 20 to more than 100 mg/dl, depending principally on the regularity of feeding. It is no wonder, then, with these extreme variations in the internal environment of the premature infant, that mortality is high if a baby is born 3 or more months prematurely.

Instability of Body Temperature. One of the particular problems of the premature infant is inability to maintain normal body temperature. Its temperature tends to approach that of its surroundings. At normal room temperature, the infant's temperature may stabilize in the low 90°s or even in the 80°sF. Statistical studies show that a body temperature maintained below 96°F (35.5°C) is associated with a particularly high incidence of death, which explains the almost mandatory use of the incubator in treatment of prematurity.

Danger of Blindness Caused by Excess Oxygen Therapy in the Premature Infant

Because premature infants frequently develop respiratory distress, oxygen therapy has often been used in treating prematurity. However, it has been discovered that use of excess oxygen in treating premature infants, especially in early prematurity, can lead to blindness. The reason is that too much oxygen stops the growth of new blood vessels in the retina. Then when oxygen therapy is stopped, the blood vessels try to make up for lost time and burst forth with a great mass of vessels growing all through the vitreous humor, blocking light from the pupil to the retina. And later, the vessels are replaced with a mass of fibrous tissue where the eye's clear vitreous humor should be.

This condition is known as *retrolental fibroplasias* and causes permanent blindness. For this reason, it is particularly important to avoid treatment of premature infants with high concentrations of respiratory oxygen. Physiologic studies indicate that the premature infant is usually safe with up to 40 percent oxygen in the air breathed, but some child physiologists believe that complete safety can be achieved only at normal oxygen concentration in the air that is breathed.

Growth and Development of the Child

The major physiologic problems of the child beyond the neonatal period are related to special metabolic needs for growth, which have been fully covered in the sections of this book on metabolism and endocrinology.

Figure 83-8 shows the changes in heights of boys and girls from the time of birth until the age of 20 years. Note especially that these parallel each other almost exactly until the end of the first decade of life. Between the ages of 11 and 13 years, the female estrogens begin to be formed and cause rapid growth in height but early uniting of the epiphyses

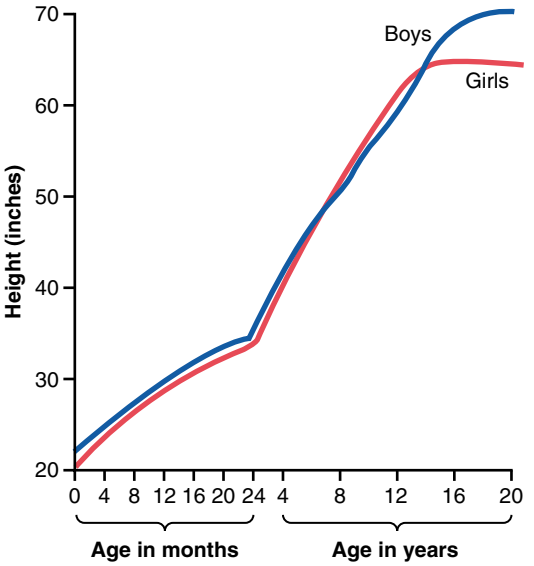


Figure 83-8 Average height of boys and girls from infancy to 20 years of age.

of the long bones at about the 14th to 16th year of life, so growth in height then ceases. This contrasts with the effect of testosterone in the male, which causes extra growth at a slightly later age—mainly between ages 13 and 17 years. The male, however, undergoes more prolonged growth because of delayed uniting of the epiphyses, so his final height is considerably greater than that of the female.

Behavioral Growth

Behavioral growth is principally a problem of maturity of the nervous system. It is difficult to dissociate maturity of the anatomical structures of the nervous system from maturity caused by training. Anatomical studies show that certain major tracts in the central nervous system are not completely myelinated until the end of the first year of life. For this reason, it is frequently stated that the nervous system is not

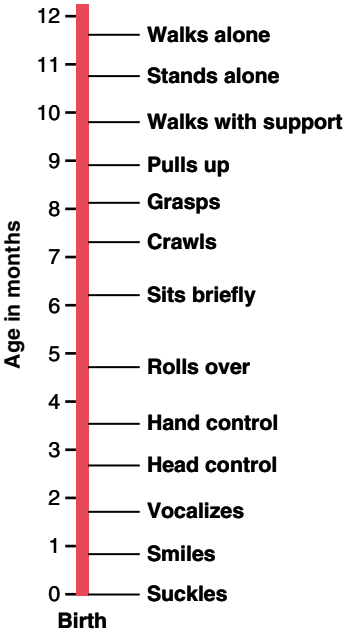


Figure 83-9 Behavioral development of the infant during the first year of life.

fully functional at birth. The brain cortex and its associated functions, such as vision, seem to require several months after birth for final functional development to occur.

At birth, the infant brain mass is only 26 percent of the adult brain mass and 55 percent at 1 year, but it reaches almost adult proportions by the end of the second year. This is also associated with closure of the fontanels and sutures of the skull, which allows only 20 percent additional growth of the brain beyond the first 2 years of life. Figure 83-9 shows a normal progress chart for the infant during the first year of life. Comparison of this chart with the baby's actual development is used for clinical assessment of mental and behavioral growth.

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CHAPTER 84

Sports Physiology

There are few stresses to which the body is exposed that approach the extreme stresses of heavy exercise. In fact, if some of the extremes of exercise were continued for even moderately prolonged periods, they might be lethal. Therefore, sports physiology is mainly a discussion of the ultimate limits to which several of the bodily mechanisms can be stressed. To give one simple example: In a person who has extremely high fever approaching the level of lethality, the body metabolism increases to about 100 percent above normal. By comparison, the metabolism of the body during a marathon race may increase to 2000 percent above normal.

Female and Male Athletes

Most of the quantitative data that are given in this chapter are for the young male athlete, not because it is desirable to know only these values but because it is only in male athletes that relatively complete measurements have been made. However, for those measurements that have been made in the female athlete, similar basic physiologic principles apply, except for quantitative differences caused by differences in body size, body composition, and the presence or absence of the male sex hormone testosterone.

In general, most quantitative values for women—such as muscle strength, pulmonary ventilation, and cardiac output, all of which are related mainly to the muscle mass—vary between two thirds and three quarters of the values recorded in men. When measured in terms of strength per square centimeter of cross-sectional area, the female muscle can achieve almost exactly the same maximal force of contraction as that of the male—between 3 and 4 kg/cm^2. Therefore, most of the difference in total muscle performance lies in the extra percentage of the male body that is muscle, caused by endocrine differences that we discuss later.

The performance capabilities of the female versus male athlete are illustrated by the relative running speeds for a marathon race. In a comparison, the top female performer had a running speed that was 11 percent less than that of the top male performer. For other events, however, women have at times held records faster than men—for instance, for the two-way swim across the English Channel, where the availability of extra fat seems to be an advantage for heat insulation, buoyancy, and extra long-term energy.

Testosterone secreted by the male testes has a powerful *anabolic effect* in causing greatly increased deposition of protein everywhere in the body, but especially in the muscles. In fact, even a male who participates in very little sports activity but who nevertheless has a normal level of testosterone will have muscles that grow about 40 percent larger than those of a comparable female without the testosterone.

The female sex hormone *estrogen* probably also accounts for some of the difference between female and male performance, although not nearly so much as testosterone. Estrogen increases the deposition of fat in the female, especially in the breasts, hips, and subcutaneous tissue. At least partly for this reason, the average nonathletic female has about 27 percent body fat composition, in contrast to the nonathletic male, who has about 15 percent. This is a detriment to the highest levels of athletic performance in those events in which performance depends on speed or on ratio of total body muscle strength to body weight.

Muscles in Exercise

Strength, Power, and Endurance of Muscles

The final common determinant of success in athletic events is what the muscles can do for you—what strength they can give when it is needed, what power they can achieve in the performance of work, and how long they can continue their activity.

The strength of a muscle is determined mainly by its size, with a *maximal contractile force between 3 and 4 kg/cm*^{2} of muscle cross-sectional area. Thus, a man who is well supplied with testosterone or who has enlarged his muscles through an exercise training program will have correspondingly increased muscle strength.

To give an example of muscle strength, a world-class weight lifter might have a quadriceps muscle with a cross-sectional area as great as 150 square centimeters. This would translate into a maximal contractile strength of 525 kilograms (or 1155 pounds), with all this force applied to the patellar tendon. Therefore, one can readily understand how it is possible for this tendon at times to be ruptured or actually to be avulsed from its insertion into the tibia below the knee. Also, when such forces occur in tendons that span a joint, similar forces are applied to the surfaces of the joint or sometimes to ligaments spanning the joints, thus accounting for such happenings as displaced cartilages, compression fractures about the joint, and torn ligaments.

The *holding strength* of muscles is about 40 percent greater than the contractile strength. That is, if a muscle is already contracted and a force then attempts to stretch out the muscle, as occurs when landing after a jump, this requires about 40 percent more force than can be achieved by a shortening contraction. Therefore, the force of 525 kilograms calculated above for the patellar tendon during muscle contraction becomes 735 kilograms (1617 pounds) during holding contractions. This further compounds the problems of the tendons, joints, and ligaments. It can also lead to internal tearing in the muscle itself. In fact, forceful stretching of a maximally contracted muscle is one of the surest ways to create the highest degree of muscle soreness.

Mechanical work performed by a muscle is the amount of force applied by the muscle multiplied by the distance over which the force is applied. The *power* of muscle contraction is different from muscle strength because power is a measure of the total amount of work that the muscle performs in a unit period of time. Power is therefore determined not only by the strength of muscle contraction but also by its *distance of contraction* and the *number of times that it contracts each minute.* Muscle power is generally measured in *kilogram meters (kg-m) per minute.* That is, a muscle that can lift 1 kilogram weight to a height of 1 meter or that can move some object laterally against a force of 1 kilogram for a distance of 1 meter in 1 minute is said to have a power of 1 kg-m/min. The maximal power achievable by all the muscles in the body of a highly trained athlete with all the muscles working together is approximately the following:

	kg-m/min
First 8 to 10 seconds	7000
Next 1 minute	4000
Next 30 minutes	1700

Thus, it is clear that a person has the capability of extreme power surges for short periods of time, such as during a 100-meter dash that is completed entirely within 10 seconds, whereas for long-term endurance events, the power output of the muscles is only one fourth as great as during the initial power surge.

This does not mean that one's athletic performance is four times as great during the initial power surge as it is for the next 30 minutes, because the *efficiency* for translation of muscle power output into athletic performance is often much less during rapid activity than during less rapid but sustained activity. Thus, the velocity of the 100-meter dash is only 1.75 times as great as the velocity of a 30-minute race, despite the fourfold difference in short-term versus long-term muscle power capability.

Another measure of muscle performance is *endurance.* This, to a great extent, depends on the nutritive support for the muscle—more than anything else on the amount of glycogen that has been stored in the muscle before the period of exercise. A person on a high-carbohydrate diet stores far more glycogen in muscles than a person on either a mixed diet or a high-fat diet. Therefore, endurance is greatly enhanced by a high-carbohydrate diet. When athletes run at speeds typical for the marathon race, their endurance (as measured by the time that they can sustain the race until complete exhaustion) is approximately the following:

	Minutes
High-carbohydrate diet	240
Mixed diet	120
High-fat diet	85

The corresponding amounts of glycogen stored in the muscle before the race started explain these differences. The amounts stored are approximately the following:

	g/kg Muscle
High-carbohydrate diet	40
Mixed diet	20
High-fat diet	6

Muscle Metabolic Systems in Exercise

The same basic metabolic systems are present in muscle as in other parts of the body; these are discussed in detail in Chapters 67 through 73. However, special quantitative measures of the activities of three metabolic systems are exceedingly important in understanding the limits of physical activity. These systems are (1) *the phosphocreatine-creatine system,* (2) *the glycogen-lactic acid system,* and (3) *the aerobic system.*

Adenosine Triphosphate. The source of energy actually used to cause muscle contraction is adenosine triphosphate (ATP), which has the following basic formula:

$$\text{Adenosine-PO}_3 \sim \text{PO}_3 \sim \text{PO}_3^-$$

The bonds attaching the last two phosphate radicals to the molecule, designated by the symbol ~, are *high-energy phosphate bonds.* Each of these bonds stores 7300 calories of energy per mole of ATP under standard conditions (and even slightly more than this under the physical conditions in the body, which is discussed in detail in Chapter 67). Therefore, when one phosphate radical is removed, more than 7300 calories of energy are released to energize the muscle contractile process. Then, when the second phosphate radical is removed, still another 7300 calories become available. Removal of the first phosphate converts the ATP into *adenosine diphosphate* (ADP), and removal of the second converts this ADP into *adenosine monophosphate* (AMP).

The amount of ATP present in the muscles, even in a well-trained athlete, is sufficient to sustain maximal muscle power for only about 3 seconds, maybe enough for one half of a 50-meter dash. Therefore, except for a few seconds at a time, it is essential that new ATP be formed continuously, even during the performance of short athletic events. Figure 84-1 shows the overall metabolic system, demonstrating the breakdown of ATP first to ADP and then to AMP, with the release of energy to the muscles for contraction. The left-hand side of the figure shows the three metabolic systems that provide a continuous supply of ATP in the muscle fibers.

Phosphocreatine-Creatine System

Phosphocreatine (also called *creatine phosphate*) is another chemical compound that has a high-energy phosphate bond, with the following formula:

$$\text{Creatine} \sim \text{PO}_3^-$$

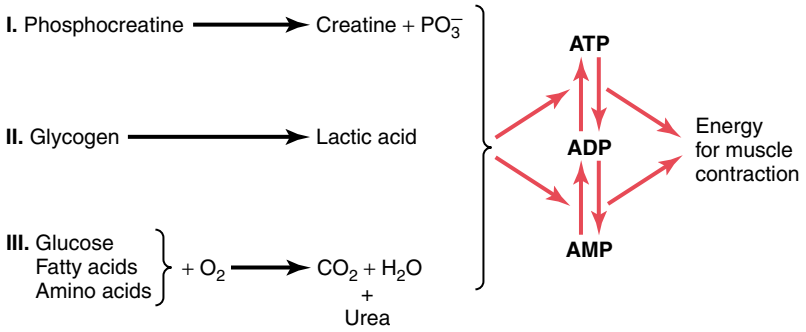

Figure 84-1 Important metabolic systems that supply energy for muscle contraction.

This can decompose to *creatine* and *phosphate ion,* as shown in Figure 84-1, and in doing so releases large amounts of energy. In fact, the high-energy phosphate bond of phosphocreatine has more energy than the bond of ATP, 10,300 calories per mole compared with 7300 for the ATP bond. Therefore, phosphocreatine can easily provide enough energy to reconstitute the high-energy bond of ATP. Furthermore, most muscle cells have two to four times as much phosphocreatine as ATP.

A special characteristic of energy transfer from phosphocreatine to ATP is that it occurs within a small fraction of a second. Therefore, all the energy stored in the muscle phosphocreatine is almost instantaneously available for muscle contraction, just as is the energy stored in ATP.

The combined amounts of cell ATP and cell phosphocreatine are called the *phosphagen energy system.* These together can provide maximal muscle power for 8 to 10 seconds, almost enough for the 100-meter run. *Thus, the energy from the phosphagen system is used for maximal short bursts of muscle power.*

Glycogen-Lactic Acid System. The stored glycogen in muscle can be split into glucose and the glucose then used for energy. The initial stage of this process, called *glycolysis,* occurs without use of oxygen and, therefore, is said to be *anaerobic metabolism* (see Chapter 67). During glycolysis, each glucose molecule is split into two *pyruvic acid molecules,* and energy is released to form four ATP molecules for each original glucose molecule, as explained in Chapter 67. Ordinarily, the pyruvic acid then enters the mitochondria of the muscle cells and reacts with oxygen to form still many more ATP molecules. However, when there is insufficient oxygen for this second stage (the oxidative stage) of glucose metabolism to occur, most of the pyruvic acid then is converted into *lactic acid,* which diffuses out of the muscle cells into the interstitial fluid and blood. Therefore, much of the muscle glycogen is transformed to lactic acid, but in doing so, considerable amounts of ATP are formed entirely without the consumption of oxygen.

Another characteristic of the glycogen-lactic acid system is that it can form ATP molecules about 2.5 times as rapidly as can the oxidative mechanism of the mitochondria. Therefore, when large amounts of ATP are required for short to moderate periods of muscle contraction, this anaerobic glycolysis mechanism can be used as a rapid source of energy. It is, however, only about one half as rapid as the phosphagen system. Under optimal conditions, the glycogen-lactic acid system can provide 1.3 to 1.6 minutes of maximal muscle activity in addition to the 8 to 10 seconds provided by the phosphagen system, although at somewhat reduced muscle power.

Aerobic System. The aerobic system is the oxidation of foodstuffs in the mitochondria to provide energy. That is, as shown to the left in Figure 84-1, glucose, fatty acids, and amino acids from the foodstuffs—after some intermediate processing—combine with oxygen to release tremendous amounts of energy that are used to convert AMP and ADP into ATP, as discussed in Chapter 67.

In comparing this aerobic mechanism of energy supply with the glycogen-lactic acid system and the phosphagen system, the relative *maximal rates of power generation* in terms of moles of ATP generation per minute are the following:

	Moles of ATP/min
Phosphagen system	4
Glycogen-lactic acid system	2.5
Aerobic system	1

When comparing the same systems for endurance, the relative values are the following:

	Time
Phosphagen system	8-10 seconds
Glycogen-lactic acid system	1.3-1.6 minutes
Aerobic system	Unlimited time (as long as nutrients last)

Thus, one can readily see that the phosphagen system is the one used by the muscle for power surges of a few seconds, and the aerobic system is required for prolonged athletic activity. In between is the glycogen-lactic acid system, which is especially important for giving extra power during such intermediate races as the 200- to 800-meter runs.

What Types of Sports Use Which Energy Systems? By considering the vigor of a sports activity and its duration, one can estimate closely which of the energy systems is used for each activity. Various approximations are presented in Table 84-1.

Recovery of the Muscle Metabolic Systems After Exercise. In the same way that the energy from phosphocreatine can be used to reconstitute ATP, energy from the glycogen-lactic acid system can be used to reconstitute both phosphocreatine and ATP. And then energy from the oxidative metabolism of the aerobic system can be used to reconstitute all the other systems—the ATP, the phosphocreatine, and the glycogen-lactic acid system.

Table 84-1 Energy Systems Used in Various Sports

Phosphagen System, Almost Entirely
100-meter dash
Jumping
Weight lifting
Diving
Football dashes
Baseball triple
Phosphagen and Glycogen-Lactic Acid Systems
200-meter dash
Basketball
Ice hockey dashes
Glycogen-Lactic Acid System, Mainly
400-meter dash
100-meter swim
Tennis
Soccer
Glycogen-Lactic Acid and Aerobic Systems
800-meter dash
200-meter swim
1500-meter skating
Boxing
2000-meter rowing
1500-meter run
1-mile run
400-meter swim
Aerobic System
10,000-meter skating
Cross-country skiing
Marathon run (26.2 miles, 42.2km)
Jogging

Reconstitution of the lactic acid system means mainly the removal of the excess lactic acid that has accumulated in all the fluids of the body. This is especially important because *lactic acid causes extreme fatigue.* When adequate amounts of energy are available from oxidative metabolism, removal of lactic acid is achieved in two ways: (1) A small portion of it is converted back into pyruvic acid and then metabolized oxidatively by all the body tissues. (2) The remaining lactic acid is reconverted into glucose mainly in the liver, and the glucose in turn is used to replenish the glycogen stores of the muscles.

Recovery of the Aerobic System After Exercise. Even during the early stages of heavy exercise, a portion of one's aerobic energy capability is depleted. This results from two effects: (1) the so-called *oxygen debt* and (2) *depletion of the glycogen stores* of the muscles.

Oxygen Debt. The body normally contains about 2 liters of stored oxygen that can be used for aerobic metabolism even without breathing any new oxygen. This stored oxygen consists of the following: (1) 0.5 liter in the air of the lungs, (2) 0.25 liter dissolved in the body fluids, (3) 1 liter combined with the hemoglobin of the blood, and (4) 0.3 liter stored in the muscle fibers themselves, combined mainly with myoglobin, an oxygen-binding chemical similar to hemoglobin.

In heavy exercise, almost all this stored oxygen is used within a minute or so for aerobic metabolism. Then, after the exercise is over, this stored oxygen must be replenished by breathing extra amounts of oxygen over and above the normal requirements. In addition, about 9 liters more oxygen must be consumed to provide for reconstituting both the phosphagen system and the lactic acid system. All this extra oxygen that must be "repaid," about 11.5 liters, is called the oxygen debt.

Figure 84-2 shows this principle of oxygen debt. During the first 4 minutes of the figure, the person exercises heavily, and the rate of oxygen uptake increases more than 15-fold. Then, even after the exercise is over, the oxygen uptake still remains above normal, at first very high while the body is reconstituting the phosphagen system and repaying the stored oxygen portion of the oxygen debt, and then for another 40 minutes at a lower level while the lactic acid is removed. The early portion of the oxygen debt is called the *alactacid oxygen debt* and amounts to about 3.5 liters. The latter portion is called the *lactic acid oxygen debt* and amounts to about 8 liters.

Recovery of Muscle Glycogen. Recovery from exhaustive muscle glycogen depletion is not a simple matter. This often requires days, rather than the seconds, minutes, or hours required for recovery of the phosphagen and lactic acid metabolic systems. Figure 84-3 shows this recovery process under three conditions: first, in people on a high-carbohydrate diet; second, in people on a high-fat, high-protein diet; and third, in people with no food. Note that on a high-carbohydrate diet, full recovery occurs in about 2 days. Conversely, people on a high-fat, high-protein diet or on no food at all show very little recovery even after as long as 5 days. The messages of this comparison are (1) that it is important for an athlete to have a high-carbohydrate diet before a grueling athletic event and (2) not to participate in exhaustive exercise during the 48 hours preceding the event.

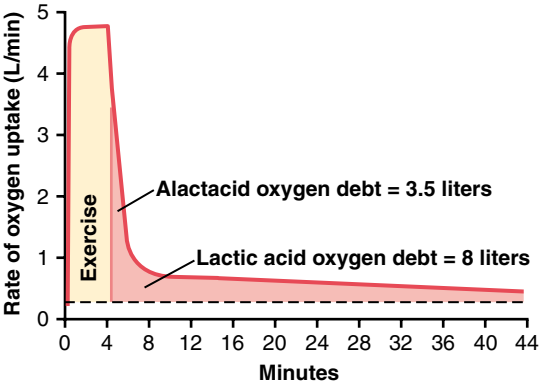

Figure 84-2 Rate of oxygen uptake by the lungs during maximal exercise for 4 minutes and then for about 40 minutes after the exercise is over. This figure demonstrates the principle of *oxygen debt*.

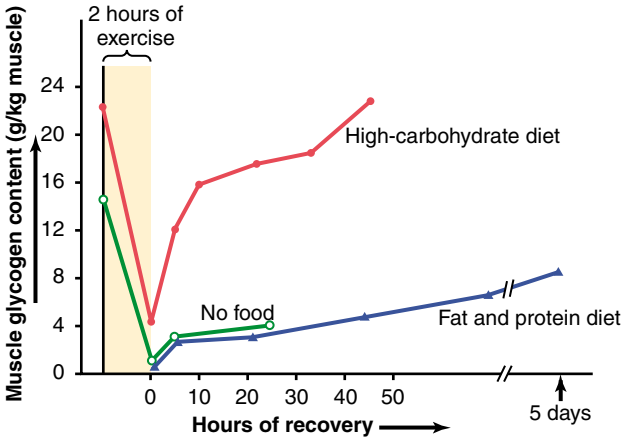

Figure 84-3 Effect of diet on the rate of muscle glycogen replenishment after prolonged exercise. (Redrawn from Fox EL: Sports Physiology. Philadelphia: Saunders College Publishing, 1979.)

Nutrients Used During Muscle Activity

In addition to the large usage of carbohydrates by the muscles during exercise, especially during the early stages of exercise, muscles use large amounts of fat for energy in the form of *fatty acids* and *acetoacetic acid* (see Chapter 68), and they use to a much less extent proteins in the form of *amino acids.* In fact, even under the best conditions, in endurance athletic events that last longer than 4 to 5 hours, the glycogen stores of the muscle become almost totally depleted and are of little further use for energizing muscle contraction. Instead, the muscle now depends on energy from other sources, mainly from fats.

Figure 84-4 shows the approximate relative usage of carbohydrates and fat for energy during prolonged exhaustive exercise under three dietary conditions: high-carbohydrate diet, mixed diet, and high-fat diet. Note that most of the energy is derived from carbohydrates during the first few seconds or minutes of the exercise, but at the time of exhaustion, as much as 60 to 85 percent of the energy is being derived from fats, rather than carbohydrates.

Not all the energy from carbohydrates comes from the stored *muscle* glycogen. In fact, almost as much glycogen is stored in the *liver* as in the muscles, and this can be released into the blood in the form of glucose and then taken up by the muscles as an energy source. In addition, glucose solutions given to an athlete to drink during the course of an athletic event can provide as much as 30 to 40 percent of the energy required during prolonged events such as marathon races.

Therefore, if muscle glycogen and blood glucose are available, they are the energy nutrients of choice for intense muscle activity. Even so, for a long-term endurance event, one can expect fat to supply more than 50 percent of the required energy after about the first 3 to 4 hours.

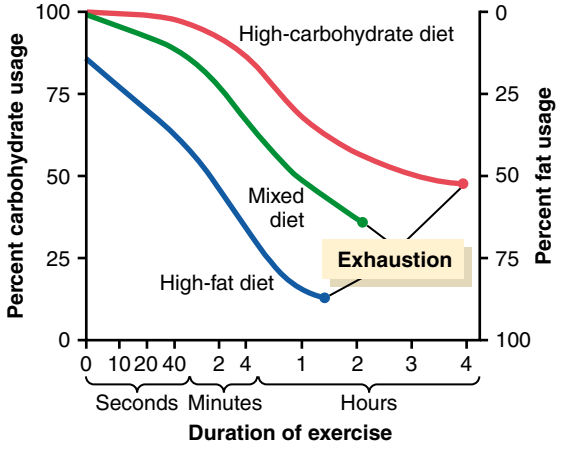

Figure 84-4 Effect of duration of exercise, as well as type of diet on relative percentages of carbohydrate or fat used for energy by muscles. (Based partly on data in Fox EL: Sports Physiology. Philadelphia: Saunders College Publishing, 1979.)

Effect of Athletic Training on Muscles and Muscle Performance

Importance of Maximal Resistance Training. One of the cardinal principles of muscle development during athletic training is the following: Muscles that function under no load, even if they are exercised for hours on end, increase little in strength. At the other extreme, muscles that contract at more than 50 percent maximal force of contraction will develop strength rapidly even if the contractions are performed only a few times each day. Using this principle, experiments on muscle building have shown that *six nearly maximal muscle contractions performed in three sets 3 days a week give approximately optimal increase in muscle strength, without producing chronic muscle fatigue.*

The upper curve in Figure 84-5 shows the approximate percentage increase in strength that can be achieved in a previously untrained young person by this resistive training program, demonstrating that the muscle strength increases about 30 percent during the first 6 to 8 weeks but almost plateaus after that time. Along with this increase in strength is an approximately equal percentage increase in muscle mass, which is called *muscle hypertrophy.*

In old age, many people become so sedentary that their muscles atrophy tremendously. In these instances, muscle training often increases muscle strength more than 100 percent.

Muscle Hypertrophy. The average size of a person's muscles is determined to a great extent by heredity plus the level of testosterone secretion, which, in men, causes considerably larger muscles than in women. With training, however, the muscles can become hypertrophied perhaps an additional 30 to 60 percent. Most of this hypertrophy results from

Figure 84-5 Approximate effect of optimal resistive exercise training on increase in muscle strength over a training period of 10 weeks.

increased diameter of the muscle fibers rather than increased numbers of fibers. However, a very few greatly enlarged muscle fibers are believed to split down the middle along their entire length to form entirely new fibers, thus increasing the number of fibers slightly.

The changes that occur inside the hypertrophied muscle fibers themselves include (1) increased numbers of myofibrils, proportionate to the degree of hypertrophy; (2) up to 120 percent increase in mitochondrial enzymes; (3) as much as 60 to 80 percent increase in the components of the phosphagen metabolic system, including both ATP and phosphocreatine; (4) as much as 50 percent increase in stored glycogen; and (5) as much as 75 to 100 percent increase in stored triglyceride (fat). Because of all these changes, the capabilities of both the anaerobic and the aerobic metabolic systems are increased, increasing especially the maximum oxidation rate and efficiency of the oxidative metabolic system as much as 45 percent.

Fast-Twitch and Slow-Twitch Muscle Fibers. In the human being, all muscles have varying percentages of *fast-twitch* and *slow-twitch muscle fibers.* For instance, the gastrocnemius muscle has a higher preponderance of fast-twitch fibers, which gives it the capability of forceful and rapid contraction of the type used in jumping. In contrast, the soleus muscle has a higher preponderance of slow-twitch muscle fibers and therefore is used to a greater extent for prolonged lower leg muscle activity.

The basic differences between the fast-twitch and the slow-twitch fibers are the following:

1. Fast-twitch fibers are about twice as large in diameter.
2. The enzymes that promote rapid release of energy from the phosphagen and glycogen-lactic acid energy systems are two to three times as active in fast-twitch fibers as in slow-twitch fibers, thus making the maximal power that can be achieved for very short periods of time by fast-twitch fibers about twice as great as that of slow-twitch fibers.
3. Slow-twitch fibers are mainly organized for endurance, especially for generation of aerobic energy. They have far more mitochondria than the fast-twitch fibers. In addition, they contain considerably more myoglobin, a hemoglobin-like protein that combines with oxygen within the muscle fiber; the extra myoglobin increases the rate of diffusion of oxygen throughout the fiber by shuttling oxygen from one molecule of myoglobin to the next. In addition, the enzymes of the aerobic metabolic system are considerably more active in slow-twitch fibers than in fast-twitch fibers.
4. The number of capillaries is greater in the vicinity of slow-twitch fibers than in the vicinity of fast-twitch fibers.

In summary, fast-twitch fibers can deliver extreme amounts of power for a few seconds to a minute or so. Conversely, slow-twitch fibers provide endurance, delivering prolonged strength of contraction over many minutes to hours.

Hereditary Differences Among Athletes for Fast-Twitch Versus Slow-Twitch Muscle Fibers. Some people have considerably more fast-twitch than slow-twitch fibers, and others have more slow-twitch fibers; this could determine to some extent the athletic capabilities of different individuals. Athletic training has not been shown to change the relative proportions of fast-twitch and slow-twitch fibers however much an athlete might want to develop one type of athletic prowess over another. Instead, this seems to be determined almost entirely by genetic inheritance, and this in turn helps determine which area of athletics is most suited to each person: some people appear to be born to be marathoners; others are born to be sprinters and jumpers. For example, the following are recorded percentages of fast-twitch versus slow-twitch fiber in the quadriceps muscles of different types of athletes:

	Fast-Twitch	Slow-Twitch
Marathoners	18	82
Swimmers	26	74
Average male	55	45
Weight lifters	55	45
Sprinters	63	37
Jumpers	63	37

Respiration in Exercise

Although one's respiratory ability is of relatively little concern in the performance of sprint types of athletics, it is critical for maximal performance in endurance athletics.

Oxygen Consumption and Pulmonary Ventilation in Exercise. Normal oxygen consumption for a young man at rest is about 250 ml/min. However, under maximal conditions, this can be increased to approximately the following average levels:

	ml/min
Untrained average male	3600
Athletically trained average male	4000
Male marathon runner	5100

Figure 84-6 shows the relation between *oxygen consumption* and *total pulmonary ventilation* at different levels of exercise. It is clear from this figure, as would be expected, that there is a linear relation. Both oxygen consumption and total pulmonary ventilation increase about 20-fold between the resting state and maximal intensity of exercise *in the well-trained athlete.*

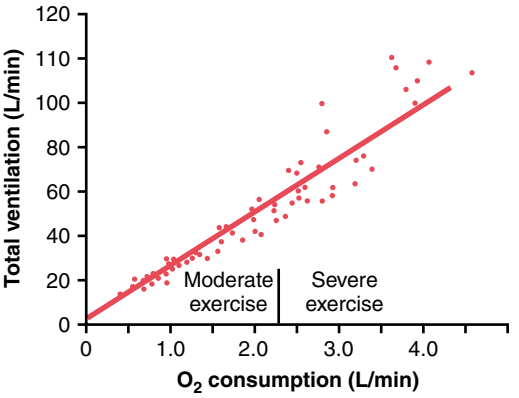

Figure 84-6 Effect of exercise on oxygen consumption and ventilatory rate. (Redrawn from Gray JS: Pulmonary Ventilation and Its Physiological Regulation. Springfield, Ill: Charles C Thomas, 1950.)

Limits of Pulmonary Ventilation. How severely do we stress our respiratory systems during exercise? This can be answered by the following comparison for a normal young man:

	L/min
Pulmonary ventilation at maximal exercise	100-110
Maximal breathing capacity	150-170

Thus, the maximal breathing capacity is about 50 percent greater than the actual pulmonary ventilation during maximal exercise. This provides an element of safety for athletes, giving them extra ventilation that can be called on in such conditions as (1) exercise at high altitudes, (2) exercise under very hot conditions, and (3) abnormalities in the respiratory system.

The important point is that the respiratory system is not normally the most limiting factor in the delivery of oxygen to the muscles during maximal muscle aerobic metabolism. We shall see shortly that the ability of the heart to pump blood to the muscles is usually a greater limiting factor.

Effect of Training on $\dot{V}o_2$ Max. The abbreviation for the rate of oxygen usage under maximal aerobic metabolism is $\dot{V}o_2$ Max. Figure 84-7 shows the progressive effect of athletic training on $\dot{V}o_2$ Max recorded in a group of subjects beginning at the level of no training and then pursuing the training program for 7 to 13 weeks. In this study, it is surprising that the $\dot{V}o_2$ Max increased only about 10 percent. Furthermore, the frequency of training, whether two times or five times per week, had little effect on the increase in $\dot{V}o_2$ Max. Yet, as pointed out earlier, the $\dot{V}o_2$ Max of a marathoner is about 45 percent greater than that of an untrained person. Part of this greater $\dot{V}o_2$ Max of the marathoner probably is genetically determined; that is, those people who have greater chest sizes in relation to body size and stronger respiratory muscles select themselves to become marathoners. However, it is also likely that many years of training increase the marathoner's $\dot{V}o_2$ Max by values considerably greater than the 10 percent that has been recorded in short-term experiments such as that in Figure 84-7.

Oxygen-Diffusing Capacity of Athletes. The *oxygen-diffusing capacity* is a measure of the rate at which oxygen can diffuse from the pulmonary alveoli into the blood. This is expressed in terms of *milliliters of oxygen that will diffuse each minute for each millimeter of mercury difference between alveolar partial pressure of oxygen and pulmonary blood oxygen pressure.* That is, if the partial pressure of oxygen in the alveoli is 91 mm Hg and the oxygen pressure in the blood is 90 mm Hg, the amount of oxygen that diffuses through the respiratory membrane each minute is equal to the diffusing capacity. The following are measured values for different diffusing capacities:

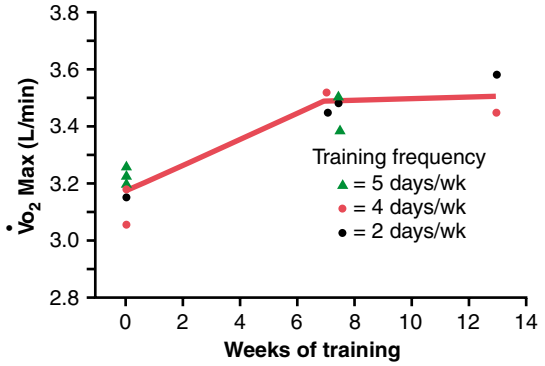

Figure 84-7 Increase in $\dot{V}o_2$ Max over a period of 7 to 13 weeks of athletic training. (Redrawn from Fox EL: Sports Physiology. Philadelphia: Saunders College Publishing, 1979.)

	ml/min
Nonathlete at rest	23
Nonathlete during maximal exercise	48
Speed skaters during maximal exercise	64
Swimmers during maximal exercise	71
Oarsman during maximal exercise	80

The most startling fact about these results is the severalfold increase in diffusing capacity between the resting state and the state of maximal exercise. This results mainly from the fact that blood flow through many of the pulmonary capillaries is sluggish or even dormant in the resting state, whereas in maximal exercise, increased blood flow through the lungs causes all the pulmonary capillaries to be perfused at their maximal rates, thus providing a far greater surface area through which oxygen can diffuse into the pulmonary capillary blood.

It is also clear from these values that those athletes who require greater amounts of oxygen per minute have higher diffusing capacities. Is this because people with naturally greater diffusing capacities choose these types of sports, or is it because something about the training procedures increases the diffusing capacity? The answer is not known, but it is very likely that training, particularly endurance training, does play an important role.

Blood Gases During Exercise. Because of the great usage of oxygen by the muscles in exercise, one would expect the oxygen pressure of the arterial blood to decrease markedly during strenuous athletics and the carbon dioxide pressure of the venous blood to increase far above normal. However, this normally is not the case. Both of these values remain nearly normal, demonstrating the extreme ability of the respiratory system to provide adequate aeration of the blood even during heavy exercise.

This demonstrates another important point: *The blood gases do not always have to become abnormal for respiration to be stimulated in exercise.* Instead, respiration is stimulated mainly by neurogenic mechanisms during exercise, as discussed in Chapter 41. Part of this stimulation results from direct stimulation of the respiratory center by the same nervous signals that are transmitted from the brain to the muscles to cause the exercise. An additional part is believed to result from sensory signals transmitted into the respiratory center from the contracting muscles and moving joints. All this extra nervous stimulation of respiration is normally sufficient to provide almost exactly the necessary increase in pulmonary ventilation required to keep the blood respiratory gases—the oxygen and the carbon dioxide—very near to normal.

Effect of Smoking on Pulmonary Ventilation in Exercise. It is widely known that smoking can decrease an athlete's "wind." This is true for many reasons. First, one effect of nicotine is constriction of the terminal bronchioles of the lungs, which increases the resistance of airflow into and out of the lungs. Second, the irritating effects of the smoke itself

cause increased fluid secretion into the bronchial tree, as well as some swelling of the epithelial linings. Third, nicotine paralyzes the cilia on the surfaces of the respiratory epithelial cells that normally beat continuously to remove excess fluids and foreign particles from the respiratory passageways. As a result, much debris accumulates in the passageways and adds further to the difficulty of breathing. Putting all these factors together, even a light smoker often feels respiratory strain during maximal exercise, and the level of performance may be reduced.

Much more severe are the effects of chronic smoking. There are few chronic smokers in whom some degree of emphysema does not develop. In this disease, the following occur: (1) chronic bronchitis, (2) obstruction of many of the terminal bronchioles, and (3) destruction of many alveolar walls. In severe emphysema, as much as four fifths of the respiratory membrane can be destroyed; then even the slightest exercise can cause respiratory distress. In fact, many such patients cannot even perform the simple feat of walking across the floor of a single room without gasping for breath.

Cardiovascular System in Exercise

Muscle Blood Flow. A key requirement of cardiovascular function in exercise is to deliver the required oxygen and other nutrients to the exercising muscles. For this purpose, the muscle blood flow increases drastically during exercise. Figure 84-8 shows a recording of muscle blood flow in the calf of a person for a period of 6 minutes during moderately strong intermittent contractions. Note not only the great increase in flow—about 13-fold—but also the flow decrease during each muscle contraction. Two points can be made from this study: (1) The actual contractile process itself temporarily decreases muscle blood flow because the contracting skeletal muscle compresses the intramuscular blood vessels; therefore, strong *tonic* muscle contractions can cause rapid muscle fatigue because of lack of delivery of enough oxygen and other nutrients during the continuous contraction. (2) The blood flow to muscles during exercise increases markedly. The following comparison shows the maximal increase in blood flow that can occur in a well-trained athlete.

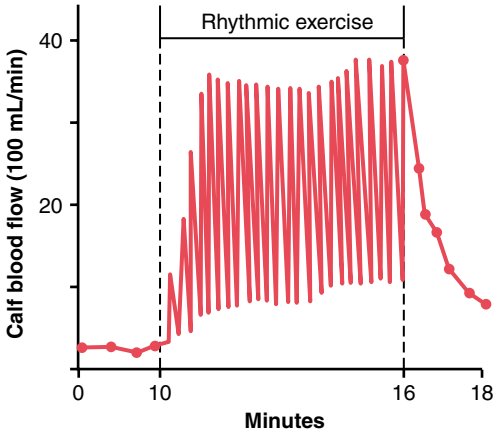

Figure 84-8 Effects of muscle exercise on blood flow in the calf of a leg during strong rhythmical contraction. The blood flow was much less during contraction than between contractions. (Redrawn from Barcroft H, Dornhors AC: Blood flow through human calf during rhythmic exercise. J Physiol 109:402, 1949.)

	ml/100 g Muscle/min
Resting blood flow	3.6
Blood flow during maximal exercise	90

Thus, muscle blood flow can increase a maximum of about 25-fold during the most strenuous exercise. Almost one-half this increase in flow results from intramuscular vasodilation caused by the direct effects of increased muscle metabolism, as explained in Chapter 21. The remaining increase results from multiple factors, the most important of which is probably the moderate increase in arterial blood pressure that occurs in exercise, usually about a 30 percent increase. The increase in pressure not only forces more blood through the blood vessels but also stretches the walls of the arterioles and further reduces the vascular resistance. Therefore, a 30 percent increase in blood pressure can often more than double the blood flow; this multiplies the great increase in flow already caused by the metabolic vasodilation at least another twofold.

Work Output, Oxygen Consumption, and Cardiac Output During Exercise. Figure 84-9 shows the interrelations among work output, oxygen consumption, and cardiac output during exercise. It is not surprising that all these are directly related to one another, as shown by the linear functions, because the muscle work output increases oxygen consumption, and increased oxygen consumption in turn dilates the muscle blood vessels, thus increasing venous return and cardiac output. Typical cardiac outputs at several levels of exercise are the following:

	L/min
Cardiac output in young man at rest	5.5
Maximal cardiac output during exercise in young untrained man	23
Maximal cardiac output during exercise in average male marathoner	30

Thus, the normal untrained person can increase cardiac output a little over fourfold, and the well-trained athlete can increase output about sixfold. (Individual marathoners have been clocked at cardiac outputs as great as 35 to 40 L/min, seven to eight times normal resting output.)

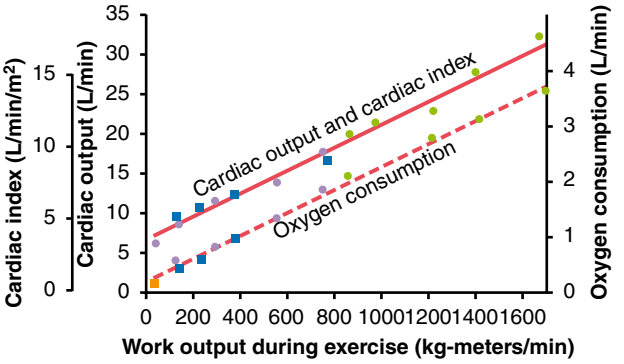

Figure 84-9 Relation between cardiac output and work output (*solid line*) and between oxygen consumption and work output (*dashed line*) during different levels of exercise. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation. Philadelphia: WB Saunders, 1973.)

Effect of Training on Heart Hypertrophy and on Cardiac Output. From the foregoing data, it is clear that marathoners can achieve maximal cardiac outputs about 40 percent greater than those achieved by untrained persons. This results mainly from the fact that the heart chambers of marathoners enlarge about 40 percent; along with this enlargement of the chambers, the heart mass also increases 40 percent or more. Therefore, not only do the skeletal muscles hypertrophy during athletic training, but so does the heart. However, heart enlargement and increased pumping capacity occur almost entirely in the endurance types, not in the sprint types, of athletic training.

Even though the heart of the marathoner is considerably larger than that of the normal person, resting cardiac output is almost exactly the same as that in the normal person. However, this normal cardiac output is achieved by a large stroke volume at a reduced heart rate. Table 84-2 compares stroke volume and heart rate in the untrained person and the marathoner.

Thus, the heart-pumping effectiveness of each heartbeat is 40 to 50 percent greater in the highly trained athlete than in the untrained person, but there is a corresponding decrease in heart rate at rest.

Role of Stroke Volume and Heart Rate in Increasing the Cardiac Output. Figure 84-10 shows the approximate changes in stroke volume and heart rate as the cardiac output increases from its resting level of about 5.5 L/min to 30 L/min in the marathon runner. The *stroke volume* increases from 105 to 162 milliliters, an increase of about 50 percent, whereas the heart rate increases from 50 to 185 beats/min, an increase of 270 percent. Therefore, the heart rate increase accounts by far for a greater proportion of the increase in cardiac output than does the increase in stroke volume during strenuous exercise. The stroke volume normally reaches its maximum by the time the cardiac output has increased only halfway to its maximum. Any further increase in cardiac output must occur by increasing the heart rate.

Table 84-2 Comparison of Cardiac Function Between Marathoner and Nonathlete

	Stroke Volume (ml)	Heart Rate (beats/min)
Resting		
Nonathlete	75	75
Marathoner	105	50
Maximum		
Nonathlete	110	195
Marathoner	162	185

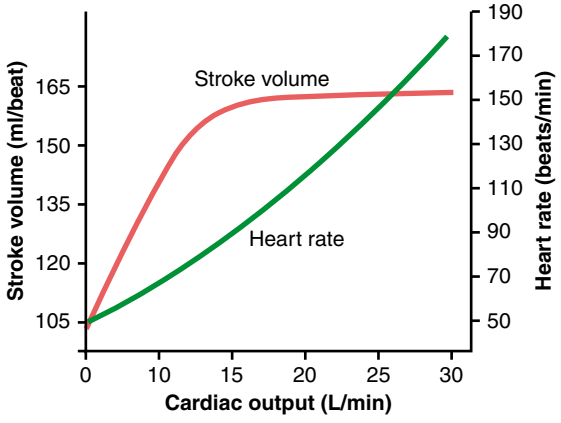

Figure 84-10 Approximate stroke volume output and heart rate at different levels of cardiac output in a marathon athlete.

Relation of Cardiovascular Performance to $\dot{V}O_2$ Max. During maximal exercise, both the heart rate and stroke volume are increased to about 95 percent of their maximal levels. Because the cardiac output is equal to stroke volume *times* heart rate, one finds that the cardiac output is about 90 percent of the maximum that the person can achieve. This is in contrast to about 65 percent of maximum for pulmonary ventilation. Therefore, one can readily see that the cardiovascular system is normally much more limiting on $\dot{V}O_2$ Max than is the respiratory system, because oxygen utilization by the body can never be more than the rate at which the cardiovascular system can transport oxygen to the tissues.

For this reason, it is frequently stated that the level of athletic performance that can be achieved by the marathoner mainly depends on the performance capability of his or her heart, because this is the most limiting link in the delivery of adequate oxygen to the exercising muscles. Therefore, the 40 percent greater cardiac output that the marathoner can achieve over the average untrained male is probably the single most important physiologic benefit of the marathoner's training program.

Effect of Heart Disease and Old Age on Athletic Performance. Because of the critical limitation that the cardiovascular system places on maximal performance in endurance athletics, one can readily understand that any type of heart disease that reduces maximal cardiac output will cause an almost corresponding decrease in achievable total body muscle power. Therefore, a person with congestive heart failure frequently has difficulty achieving even the muscle power required to climb out of bed, much less to walk across the floor.

The maximal cardiac output of older people also decreases considerably—there is as much as a 50 percent decrease between ages 18 and 80. Also, there is even more decrease in maximal breathing capacity. For these reasons, as well as reduced skeletal muscle mass, the maximal achievable muscle power is greatly reduced in old age.

Body Heat in Exercise

Almost all the energy released by the body's metabolism of nutrients is eventually converted into body heat. This applies even to the energy that causes muscle contraction for the following reasons: First, the maximal efficiency for conversion of nutrient energy into muscle work, even under the best of conditions, is only 20 to 25 percent; the remainder of the nutrient energy is converted into heat during the course of the intracellular chemical reactions. Second, almost all the energy that does go into creating muscle work still becomes body heat because all but a small portion of this energy is used for (1) overcoming viscous resistance to the movement of the muscles and joints, (2) overcoming the friction of the blood flowing through the blood vessels, and (3) other, similar effects—all of which convert the muscle contractile energy into heat.

Now, recognizing that the oxygen consumption by the body can increase as much as 20-fold in the well-trained athlete and that the amount of heat liberated in the body is almost exactly proportional to the oxygen consumption (as discussed in Chapter 72), one quickly realizes that tremendous amounts of heat are injected into the internal body tissues when performing endurance athletic events. Next, with a vast rate of heat flow into the body, on a very hot and humid day so that the sweating mechanism cannot eliminate the heat, an intolerable and even lethal condition called *heatstroke* can easily develop in the athlete.

Heatstroke. During endurance athletics, even under normal environmental conditions, the body temperature often rises from its normal level of 98.6° to 102° or 103°F (37° to 40°C). With very hot and humid conditions or excess clothing, the body temperature can easily rise to 106° to 108°F (41° to 42°C). At this level, the elevated temperature itself becomes destructive to tissue cells, especially the brain cells. When this happens, multiple symptoms begin to appear, including extreme weakness, exhaustion, headache, dizziness, nausea, profuse sweating, confusion, staggering gait, collapse, and unconsciousness.

This whole complex is called *heatstroke,* and failure to treat it immediately can lead to death. In fact, even though the person has stopped exercising, the temperature does not easily decrease by itself. One of the reasons for this is that at these high temperatures, the temperature-regulating mechanism itself often fails (see Chapter 73). A second reason is that in heatstroke, the very high body temperature approximately doubles the rates of all intracellular chemical reactions, thus liberating still more heat.

The treatment of heatstroke is to reduce the body temperature as rapidly as possible. The most practical way to do this is to remove all clothing, maintain a spray of cool water on all surfaces of the body or continually sponge the body, and blow air over the body with a fan. Experiments have shown that this treatment can reduce the temperature either as rapidly or almost as rapidly as any other procedure, although some physicians prefer total immersion of the body in water containing a mush of crushed ice if available.

Body Fluids and Salt in Exercise

As much as a 5- to 10-pound weight loss has been recorded in athletes in a period of 1 hour during endurance athletic events under hot and humid conditions. Essentially all this weight loss results from loss of sweat. Loss of enough sweat to decrease body weight only 3 percent can significantly diminish a person's performance, and a 5 to 10 percent rapid decrease in weight can often be serious, leading to muscle cramps, nausea, and other effects. Therefore, it is essential to replace fluid as it is lost.

Replacement of Sodium Chloride and Potassium. Sweat contains a large amount of sodium chloride, for which reason it has long been stated that all athletes should take salt (sodium chloride) tablets when performing exercise on hot and humid days. However, overuse of salt tablets has often done as much harm as good. Furthermore, if an athlete becomes acclimatized to the heat by progressive increase in athletic exposure over a period of 1 to 2 weeks rather than performing maximal athletic feats on the first day, the sweat glands also become acclimatized, so the amount of salt lost in the sweat becomes only a small fraction of that lost before acclimatization. This sweat gland acclimatization results mainly from increased aldosterone secretion by the adrenal cortex. The aldosterone in turn has a direct effect on the sweat glands, increasing reabsorption of sodium chloride from the sweat before the sweat itself issues forth from the sweat gland tubules onto the surface of the skin. Once the athlete is acclimatized, only rarely do salt supplements need to be considered during athletic events.

Experience by military units exposed to heavy exercise in the desert has demonstrated still another electrolyte problem—the loss of potassium. Potassium loss results partly from the increased secretion of aldosterone during heat acclimatization, which increases the loss of potassium in the urine, as well as in the sweat. As a consequence of these findings, some of the supplemental fluids for athletics contain properly proportioned amounts of potassium along with sodium, usually in the form of fruit juices.

Drugs and Athletes

Without belaboring this issue, let us list some of the effects of drugs in athletics.

First, *caffeine* is believed by some to increase athletic performance. In one experiment on a marathon runner, running time for the marathon was improved by 7 percent by judicious use of caffeine in amounts similar to those found in one to three cups of coffee. Yet experiments by others have failed to confirm any advantage, thus leaving this issue in doubt.

Second, use of *male sex hormones (androgens)* or other anabolic steroids to increase muscle strength undoubtedly can increase athletic performance under some conditions, especially in women and even in men. However, anabolic steroids also greatly increase the risk of cardiovascular damage because they often cause hypertension, decreased high-density blood lipoproteins, and increased low-density lipoproteins, all of which promote heart attacks and strokes.

In men, any type of male sex hormone preparation also leads to decreased testicular function, including both decreased formation of sperm and decreased secretion of the person's own natural testosterone, with residual effects sometimes lasting at least for many months and perhaps indefinitely. In a woman, even more dire effects can occur because she is not normally adapted to the male sex hormone—hair on the face, a bass voice, ruddy skin, and cessation of menses.

Other drugs, such as *amphetamines* and *cocaine,* have been reputed to increase one's athletic performance. It is equally true that overuse of these drugs can lead to deterioration of performance. Furthermore, experiments have failed to prove the value of these drugs except as a psychic stimulant. Some athletes have been known to die during athletic events because of interaction between such drugs and the norepinephrine and epinephrine released by the sympathetic nervous system during exercise. One of the possible causes of death under these conditions is overexcitability of the heart, leading to ventricular fibrillation, which is lethal within seconds.

Body Fitness Prolongs Life

Multiple studies have now shown that people who maintain appropriate body fitness, using judicious regimens of exercise and weight control, have the additional benefit of prolonged life. Especially between the ages of 50 and 70, studies have shown mortality to be three times less in the most fit people than in the least fit.

But why does body fitness prolong life? The following are some of the most important reasons.

Body fitness and weight control greatly reduce cardiovascular disease. This results from (1) maintenance of moderately lower blood pressure and (2) reduced blood cholesterol and low-density lipoprotein along with increased high-density lipoprotein. As pointed out earlier, these changes all work together to reduce the number of heart attacks, brain strokes, and kidney disease.

The athletically fit person has more bodily reserves to call on when he or she does become sick. For instance, an 80-year-old nonfit person may have a respiratory system that limits oxygen delivery to the tissues to no more than 1 L/min; this means a *respiratory reserve of no more than threefold to fourfold.* However, an athletically fit old person may have twice as much reserve. This is especially important in preserving life when the older person develops conditions such as pneumonia that can rapidly require all available respiratory reserve. In addition, the ability to increase cardiac output in times of need (the "cardiac reserve") is often 50 percent greater in the athletically fit old person than in the nonfit person.

Exercise and overall body fitness also reduce the risk for several chronic metabolic disorders associated with obesity such as insulin resistance and type II diabetes. Moderate exercise, even in the absence of significant weight loss, has been shown to improve insulin sensitivity and reduce, or in some cases eliminate, the need for insulin treatment in patients with type II diabetes.

Improved body fitness also reduces the risk for several types of cancers, including breast, prostate, and colon cancer. Much of the beneficial effects of exercise may be related to reduction in obesity. However, studies in experimental animals and in humans have also shown that regular exercise reduces the risk for many chronic diseases through mechanisms that are incompletely understood but are, at least to some extent, independent of weight loss or decreased adiposity.

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