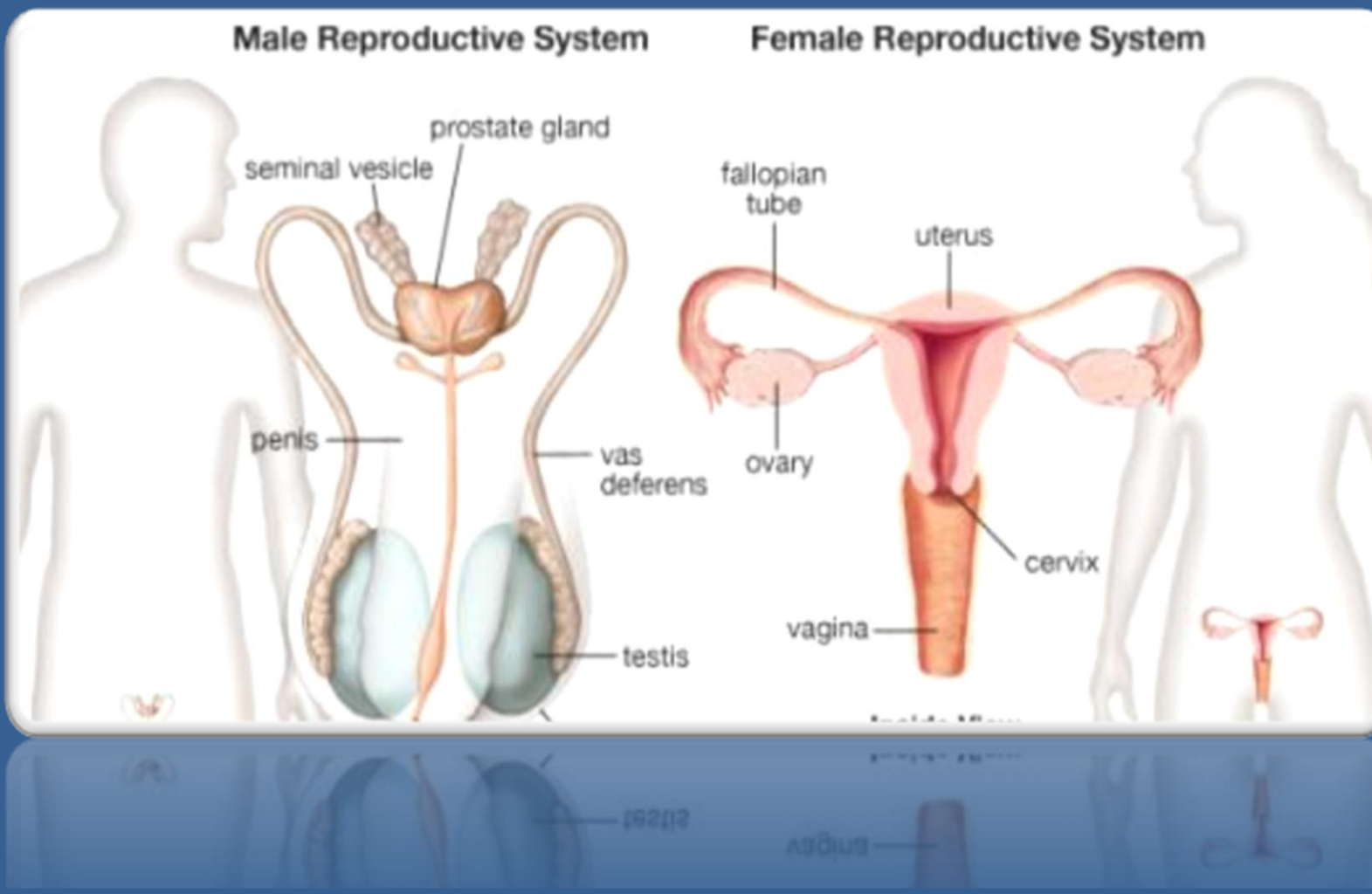
Physiology and pathology of reproductive system



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اهداء

نهدى لكم نسخه من الكتاب المرسوم وعنوانه

Physiology and pathology of Reproductive system

رقم الايداع فى دار الكتب والوثائق ببغداد ٤٢٥٣ لسنه ٢٠١٧ والذى تم باشراف الجامعه المستنصريه

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شاكرا لهم تعاونهم معنا فى هذا الجهد العلمى خدمه لطلبتنا الاعزاء ككتاب مساعد لهم فى فسلجه التناسل .

الحمد لله رب العالمين الذى وفقنا فى كتابه واصدار هذا الكتاب ندعو من الله ان يكون بصيصا من النور فى علم المعرفه وان يفتح للقارىء الكريم افاق من العلم والاستمتاع وان يثرى مكتبته المعرفيه واستثمارا فى وقته بما ينفع البشريه.

و الى روح والدي و والدتي وجدتي رحمهم الله

المؤلفون

CONTENTS

REPRODUCTIVE SYSTEM

Chapter1: Development of the Male and Female Reproductive Systems

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but there is little change in the reproductive system between infancy and puberty.

Development of the Sexual Organs in the Embryo and Fetus

Females are considered the “fundamental” sex—that is, without much chemical prompting, all fertilized eggs would develop into females. To become a male, an individual must be exposed to the cascade of factors initiated by a single gene on the male Y chromosome. This is called the SRY (*S*ex-determining *R*egion of the *Y* chromosome). Because females do not have a Y chromosome, they do not have the *SRY* gene. Without a functional *SRY* gene, an individual will be female.

In both male and female embryos, the same group of cells has the potential to develop into either the male or female gonads; this tissue is considered bipotential. The *SRY* gene actively recruits other genes that begin to develop the testes, and suppresses genes that are important in female development. As part of this *SRY*-prompted cascade, germ cells

in the bipotential gonads differentiate into spermatogonia. Without *SRY*, different genes are expressed, oogonia form, and primordial follicles develop in the primitive ovary.

Soon after the formation of the testis, the Leydig cells begin to secrete testosterone. Testosterone can influence tissues that are bipotential to become male reproductive structures. For example, with exposure to testosterone, cells that could become either the glans penis or the glans clitoris form the glans penis. Without testosterone, these same cells differentiate into the clitoris.

Not all tissues in the reproductive tract are bipotential. The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, ductus deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. For proper reproductive function in the adult, one set of these

ducts must develop properly, and the other must degrade. In males, secretions from sustentacular cells trigger a degradation of the female duct, called the **Mullerian duct**. At the same time, testosterone secretion stimulates growth of the male tract, the **Wolffian duct**. Without such sustentacular cell secretion, the Mullerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be female. For more information and a figure of differentiation of the gonads, seek additional content on fetal development.

Further Sexual Development Occurs at Puberty

Puberty is the stage of development at which individuals become sexually mature. Though the outcomes of puberty for boys and girls are very different, the hormonal control of the process is very similar. In addition, though the timing of these events varies between individuals, the sequence of changes that occur is predictable for male and female adolescents. Asshown in **Figure 1**, a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of **secondary sex characteristics**, which are physical changes that serve auxiliary roles in reproduction.

The first changes begin around the age of eight or nine when the production of LH becomes detectable. The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low concentrations of androgens or estrogens will negatively feed back onto the hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase

and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in girls in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in girls, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In girls who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

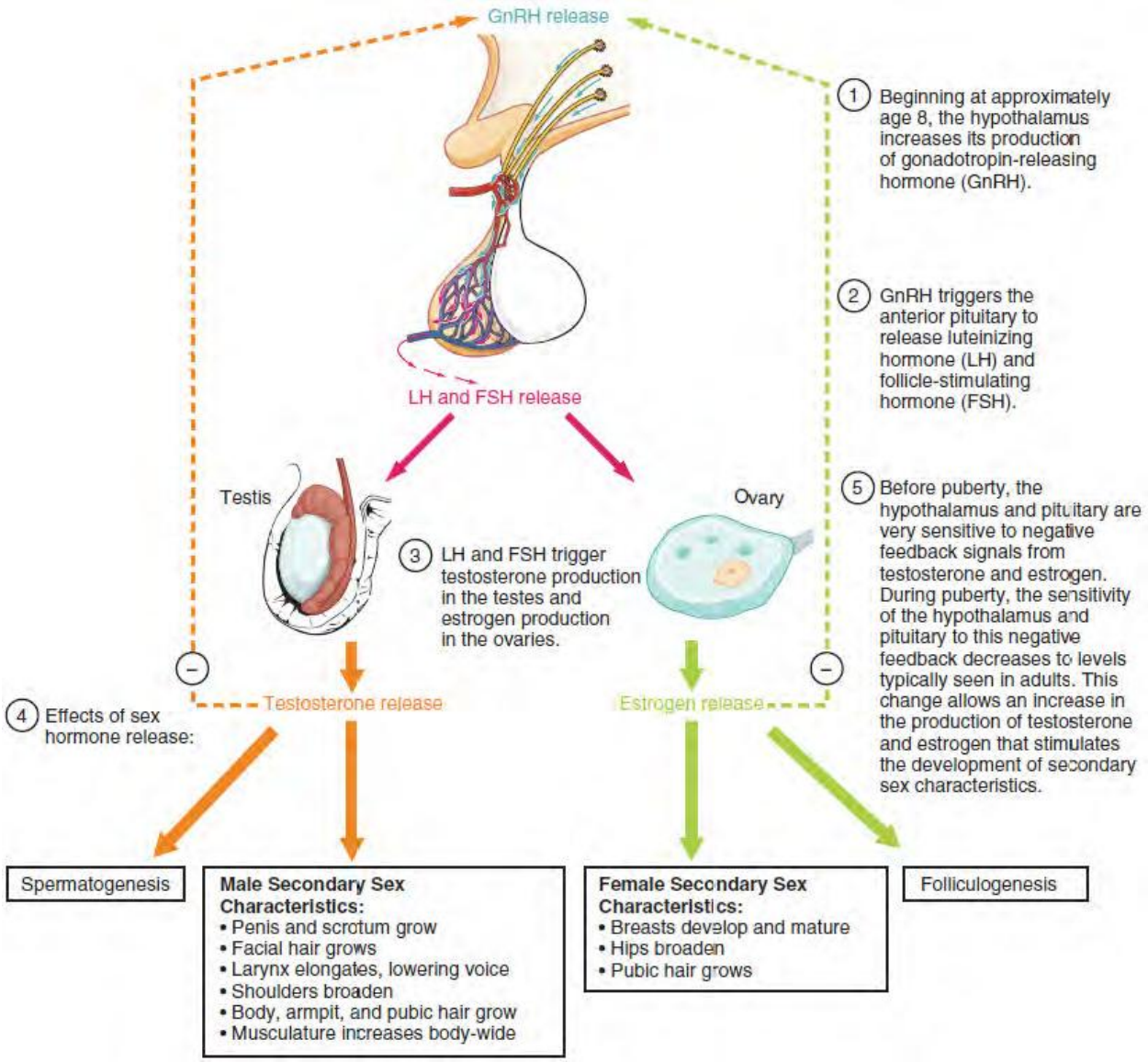


Figure 1 Hormones of Puberty During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones in both male and female adolescents.

Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in the table.

Development of the Secondary Sexual Characteristics

Male	Female
Increased larynx size and deepening of the voice	Deposition of fat, predominantly in breasts and hips
Increased muscular development	Breast development
Growth of facial, axillary, and pubic hair, and increased growth of body hair	Broadening of the pelvis and growth of axillary and pubic hair

As a girl reaches puberty, typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, a girl's height can
increase 3 inches a year. The next step in puberty is menarche, the start of menstruation. In boys, the growth of the testes is typically the first physical sign of the beginning of puberty, which is followed by growth and pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the larynx and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individual boys. Unlike the early

growth spurt observed in females, the male growth spurt occurs toward the end of puberty, at approximately age 11 to 13, and a boy’s height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

Chapter 2: Anatomy and Physiology of the Male Reproductive System

Unique for its role in human reproduction, a **gamete** is a specialized sex cell carrying 23 chromosomes—one half the number in body cells. At fertilization, the chromosomes in one male gamete, called a **sperm** (or spermatozoon), combine with the chromosomes in one female gamete, called an oocyte. The function of the male reproductive system (Figure 2) is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In humans, the most important male androgen is testosterone. Several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which delivers sperm to the female reproductive tract

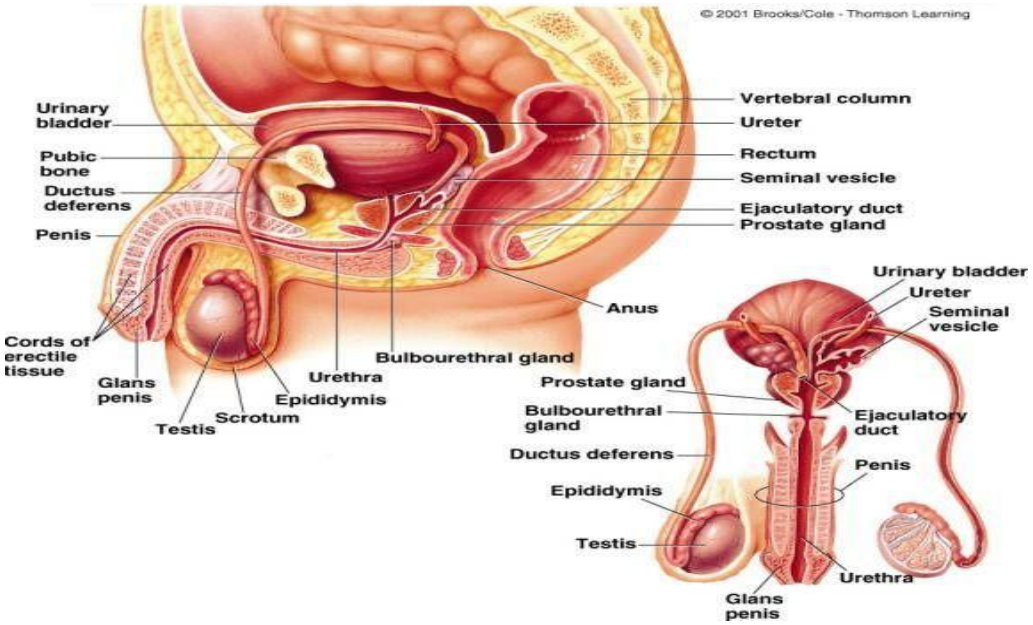


Figure 2 Male Reproductive System The structures of the male reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.

Male reproductive system consists of:

Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the **scrotum** that extends from the body behind the penis (see Figure2)This location is important in sperm production, which occurs within the testes and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

By contracting simultaneously, the dartos and cremaster muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss.

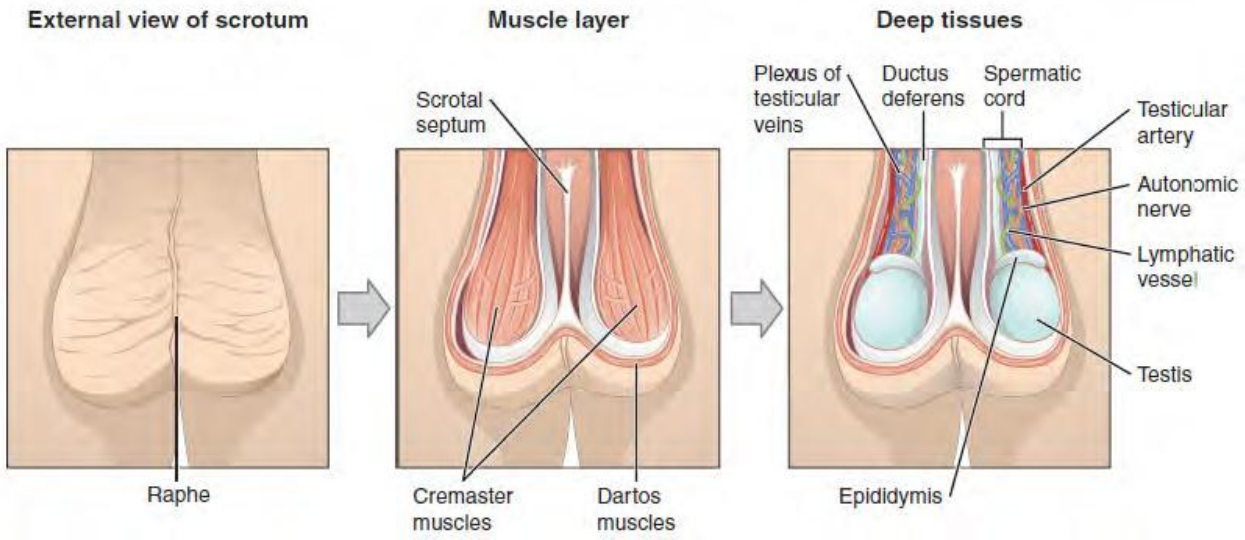


Figure 3 The Scrotum and Testes This anterior view shows the structures of the scrotum and testes.

Testes

The **testes** (singular = testis) are the male **gonads**—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the

male. Paired ovals, the testes are housed within the scrotum (see Figure3). They are surrounded by two distinct layers of protective connective tissue: the outer tunica vaginalis and inner tunica albuginea. The tunica albuginea cover the outside of the testis, and also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the " descent of the testis." Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

Seminiferous tubules

The tightly coiled **seminiferous tubules** form the bulk of each testis. They are composed of developing sperm cells and then released into the duct system (the straight tubules (or tubuli recti) and rete testes) of the testis. Inside the seminiferous tubules are different cell types of developing sperm cells called germ cells. Germ cell development progresses from the basement membrane toward the lumen. Let's look more closely at these cell types.(figure 4)

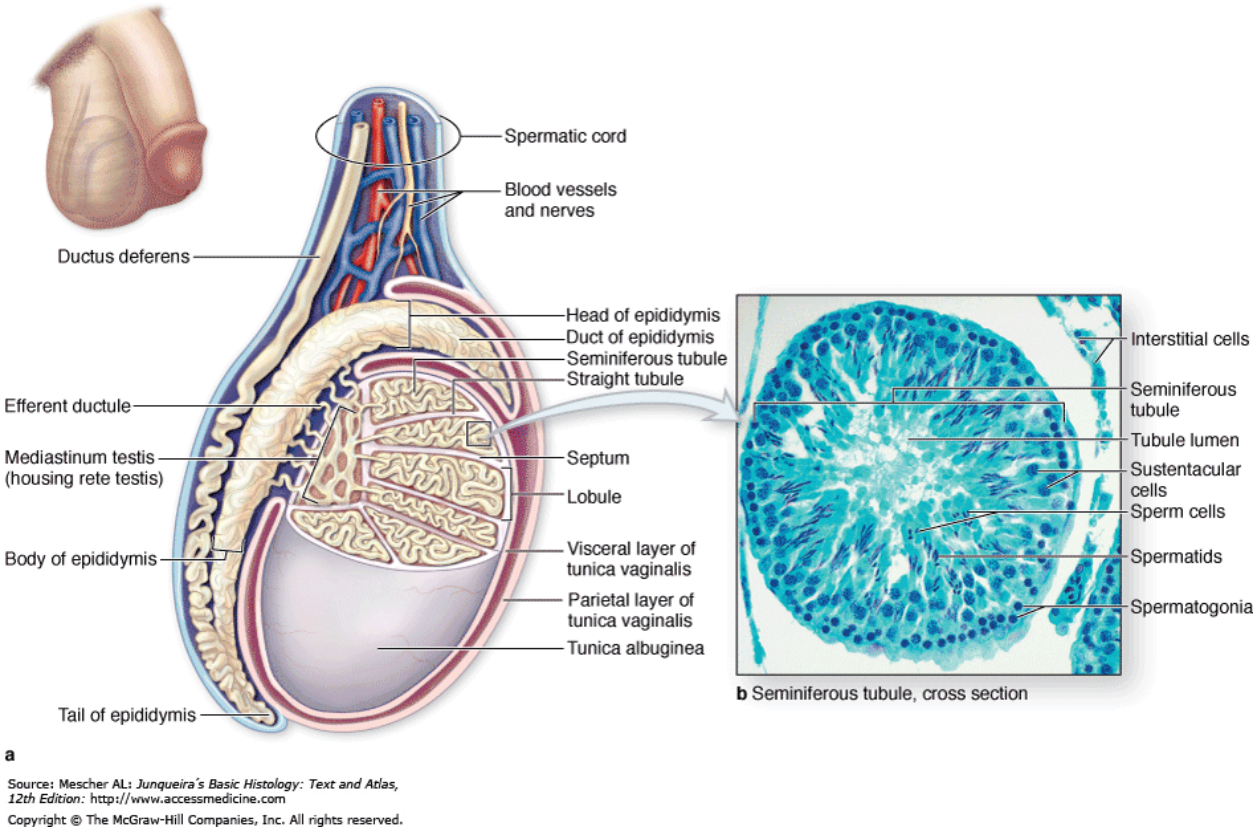


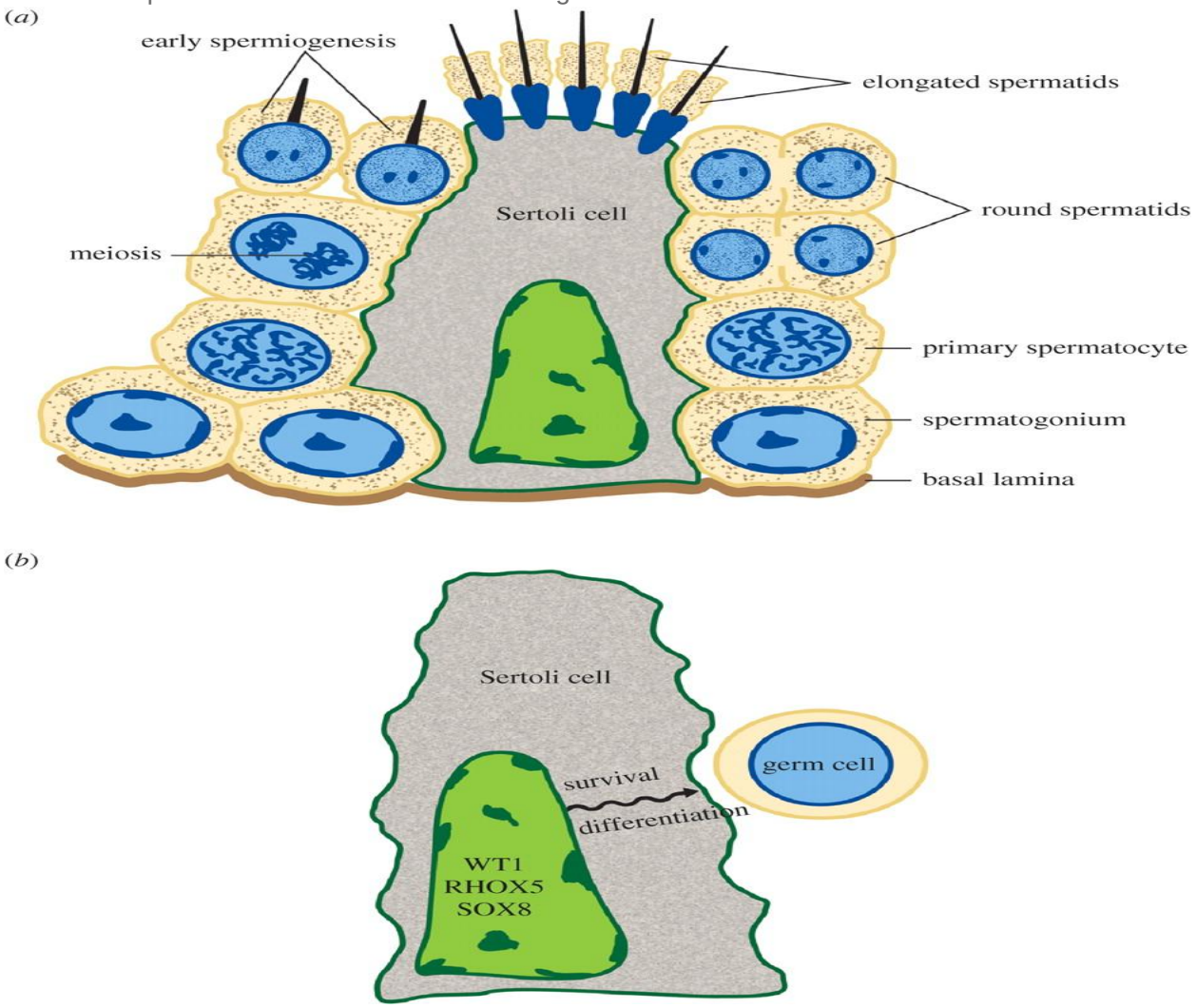
Figure 4 Anatomy of the Testis and seminiferous tubule This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens.

Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching **Sertoli cells**.

Sertoli cells secrete signaling molecules that promote sperm production and can control whether germ cells live or die. They extend physically around the germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these cells create the **blood–testis barrier**, which keeps blood borne substances from reaching the germ cells.(Figure 5)

Figure 5:sertoli cells(*a*) Schematic representation of developing germ cells imbedded in a Sertoli cell in the seminiferous tubule. Spermatogonia undergo mitotic divisions, ultimately giving rise to meiotic spermatocytes. Meiosis causes reductive divisions, leading to the generation of haploid round spermatids. These latter cells undergo a series of differentiation events to become



elongated spermatids, which detach from the Sertoli cell and travel down the seminiferous tubule lumen to reach the epididymis (not shown). (*b*) Recently defined Sertoli-cell-expressed transcription factors that guide the survival and differentiation of the adjacent germ cells.

Germ Cells

The least mature cells, the **spermatogonia** (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes,

then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with the production of sperm is called **spermatogenesis**.

Spermatogenesis

During formation of the embryo, the primordial germ cells migrate into the testes and become immature germ cells called spermatogonia, which lie in two or three layers of the inner surfaces of the seminiferous tubules

At puberty the spermatogonia begin to undergo mitotic division and continually proliferate and differentiate through definite stages of development to form sperm.(Figure6)

STEPS OF SPERMATOGENESIS

Spermatogenesis occurs in the seminiferous tubules during active sexual life as the result of stimulation by anterior pituitary gonadotropic hormones. Spermatogenesis begins at an average age of 13 years and continues

throughout most of the remainder of life but decreases markedly in old age.

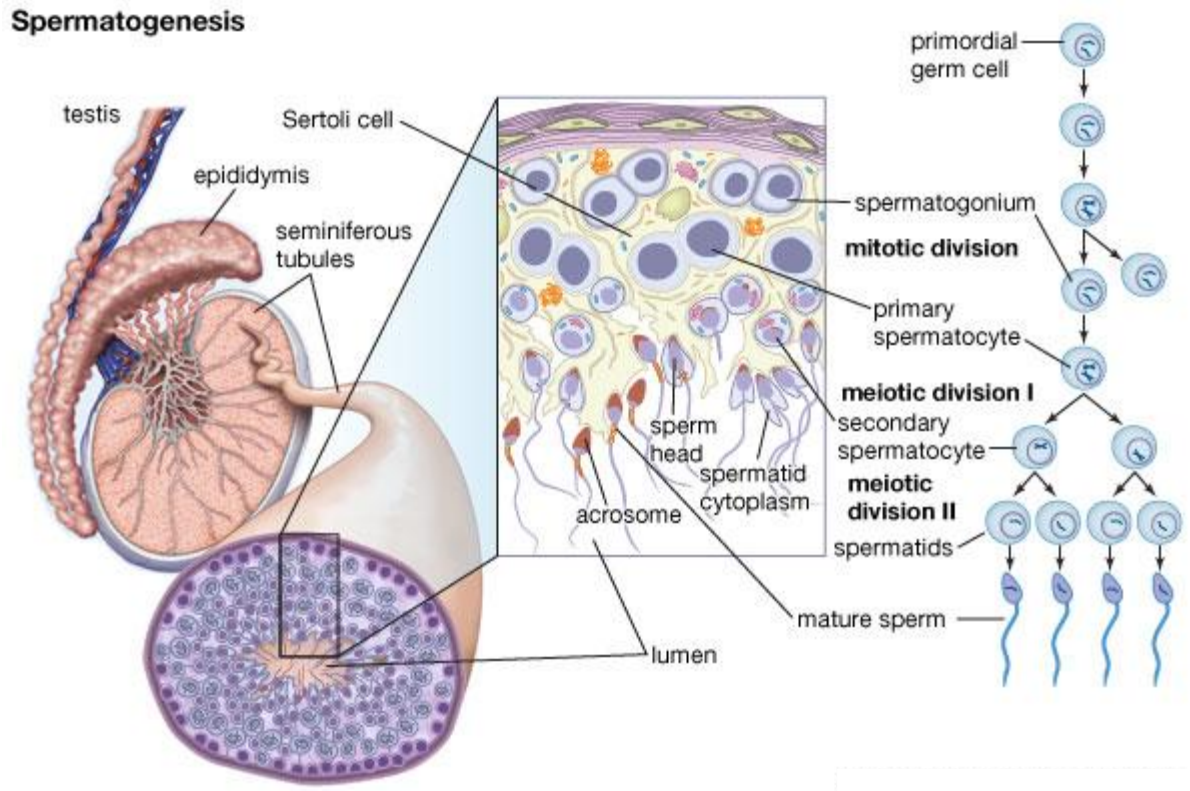
In the first stage of spermatogenesis, the spermatogonia migrate among Sertoli cells toward the central lumen of the seminiferous tubule. The Sertoli cells are large, with overflowing cytoplasmic envelopes that surround the developing spermatogonia all the way to the central lumen of the tubule.

Meiosis. Spermatogonia that cross the barrier into the Sertoli cell layer become progressively modified and enlarged to form large primary spermatocytes . Each of these primary spermatocytes, in turn, undergoes meiotic division to form two secondary spermatocytes. After another few days, these secondary spermatocytes also divide to form

spermatids that are eventually modified to become spermatozoa (sperm).

During the change from the spermatocyte stage to the spermatid stage, the 46 chromosomes (23 pairs of chromosomes) of the spermatocyte are divided, and thus 23 chromosomes go to one spermatid and the other 23 go to the second spermatid. The chromosomal genes are also divided so that only one half of the genetic characteristics of the eventual fetus are provided by the father, with the other half being derived from the oocyte provided by the mother. The entire period of spermatogenesis, from spermatogonia to spermatozoa, takes about 74 days.

Sex Chromosomes. In each spermatogonium, one of the 23 pairs of chromosomes carries the genetic information that determines the sex of each eventual offspring. This pair is composed of one X chromosome, which iscalled the female chromosome, and one Y chromosome, the male chromosome. During meiotic division, the male Y chromosome goes to one spermatid that then becomes a male sperm, and the female X chromosome goes to another spermatid that becomes a female sperm. The sex of the eventual offspring is determined by which of these two types of sperm fertilizes the ovum.



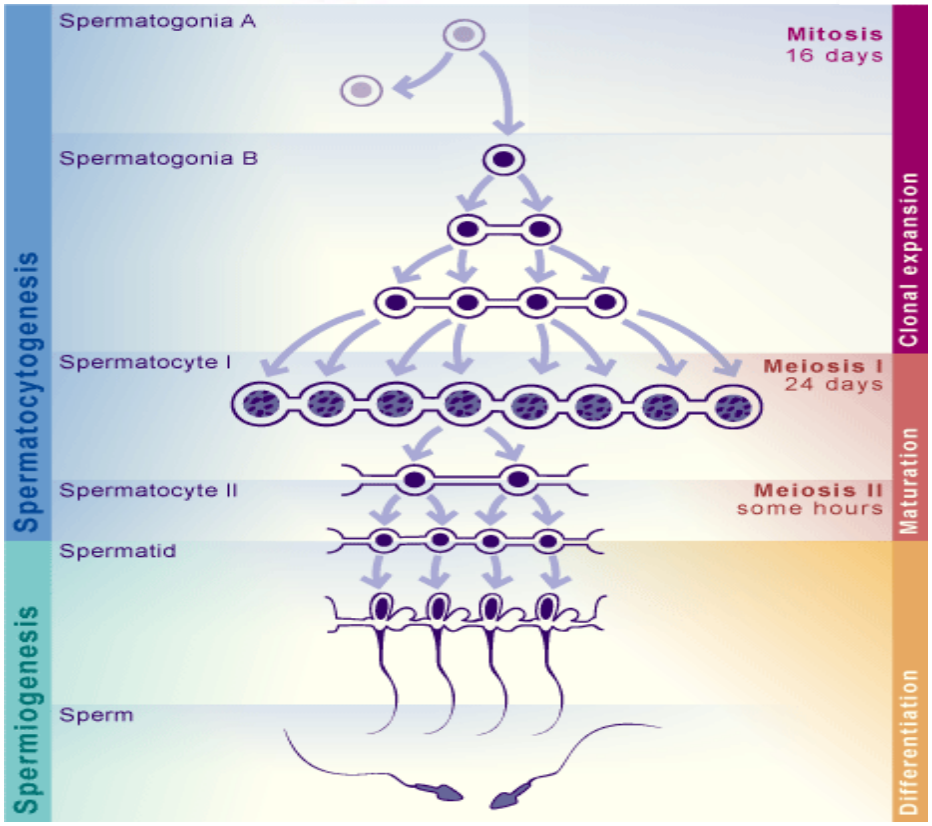


Figure 6:spermatognesis

Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas women typically ovulate only one oocyte per month as is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region (**Figure 8**). The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm. A structure called the acrosome covers most of the head of the sperm cell as a “cap” that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.(Figure7)

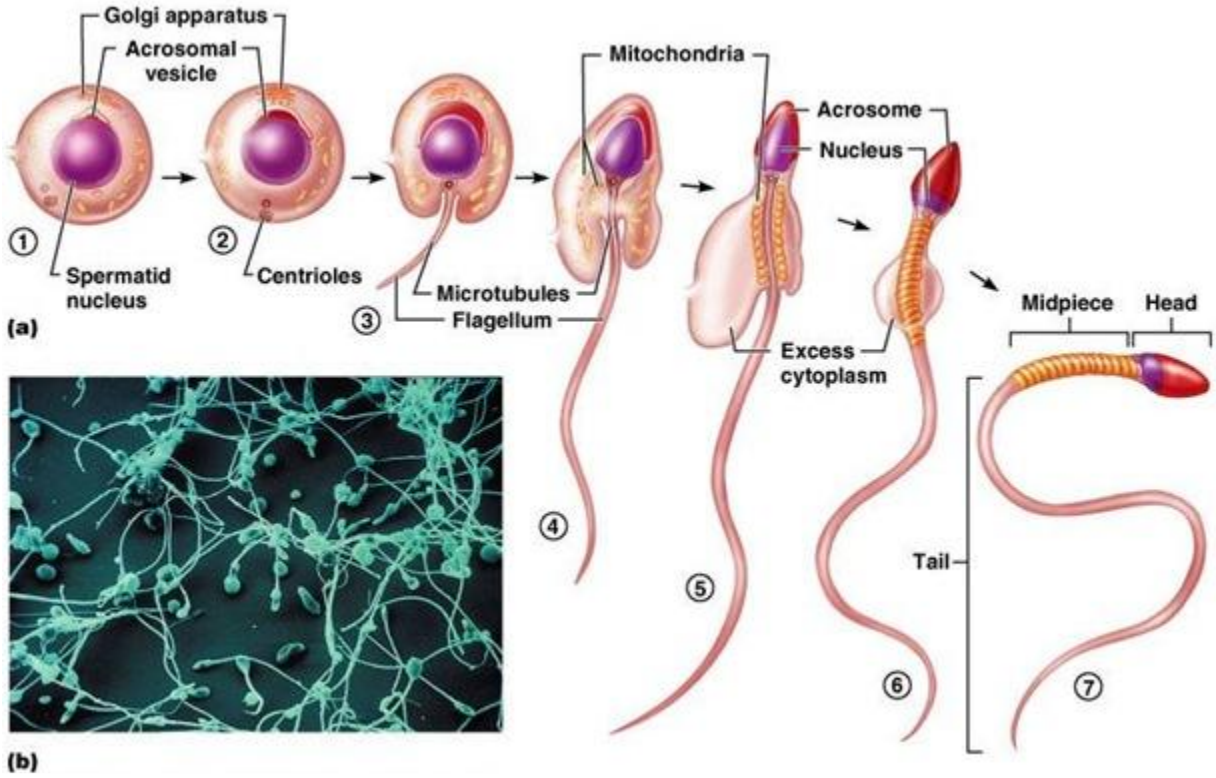


Figure 7: Development of human sperm

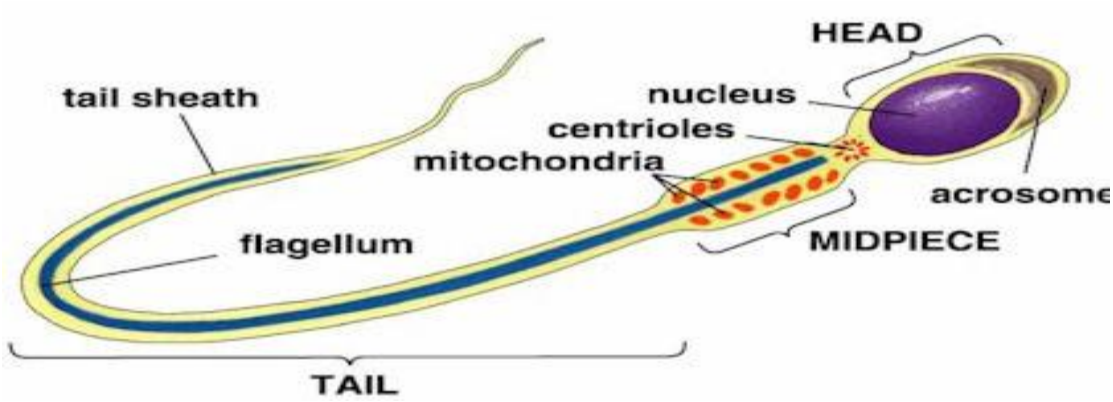


Figure 8 : structure of human sperm

Hormonal Factors That Stimulate Spermatogenesis

The role of hormones in reproduction is discussed later in detail; for now, note that several hormones play essential roles in spermatogenesis. Some of these roles are as follows:

1. Testosterone, secreted by the Leydig cells located in the interstitium of the testis, is essential for growth and division of the testicular germinal cells, which is the first stage in forming sperm.
2. Luteinizing hormone, secreted by the anterior pituitary gland, stimulates the Leydig cells to secrete testosterone.
3. Follicle-stimulating hormone, also secreted by the anterior pituitary gland, stimulates the Sertoli cells; without this stimulation, the conversion of the spermatids to sperm (the process of spermiogenesis)
will not occur.
4. Estrogens, formed from testosterone by the Sertoli cells when they are stimulated by follicle stimulating hormone, are probably also essential for spermiogenesis.
5. Growth hormone (as well as most of the other body hormones) is necessary for controlling background metabolic functions of the testes. Growth hormone specifically promotes early division of the spermatogonia
themselves; in its absence, as in pituitary dwarfs, spermatogenesis is severely deficient or absent, thus causing infertility.

Maturation of Sperm in the Epididymis

After formation in the seminiferous tubules, the sperm require several days to pass through the 6-meter-long tubule of the epididymis. Sperm removed from the seminiferous tubules and from the early portions of the epididymis
are nonmotile and cannot fertilize an ovum. However, after the sperm have been in the epididymis for 18 to 24 hours, they develop the capability of motility, even though several inhibitory proteins in the epididymal
fluid still prevent final motility until after ejaculation.

Storage of Sperm in the Testes

The two testes of the human adult form up to 120 million sperm each day. Most of these sperm are stored in the epididymis, although a small quantity is stored in the vas deferens. They can remain stored, while maintaining their fertility, for at least a month. During this time, they are kept in a deeply suppressed, inactive state by multiple inhibitory substances in the secretions of the ducts. Conversely, with a high level of sexual activity and ejaculations, they may be stored no longer than a few days.

After ejaculation, the sperm become motile and capable of fertilizing the ovum, a process called maturation. The Sertoli cells and the epithelium of the epididymis secrete a special nutrient fluid that is ejaculated along with the sperm. This fluid contains hormones (including both testosterone and estrogens), enzymes, and special nutrients that are essential for sperm maturation.

Physiology of the Mature Sperm.

The normal motile, fertile sperm are capable of flagellated movement through the fluid medium at velocities of 1 to 4 mm/min. The activity of sperm is greatly enhanced in a neutral and slightly alkaline medium, as exists in the ejaculated semen, but it is greatly depressed in a mildly acidic medium. A strong acidic medium can cause the rapid death of sperm.

The activity of sperm increases markedly with increasing temperature, but so does the rate of metabolism, causing the life of the sperm to be considerably shortened.

Although sperm can live for many weeks in the suppressed state in the genital ducts of the testes, the life expectancy of ejaculated sperm in the female genital tract is only 1 to 2 days.

FUNCTION OF THE SEMINAL VESICLES

Each seminal vesicle is a tortuous, loculated tube lined with a secretory epithelium that secretes a mucoid material containing an abundance of fructose, citric acid, and other nutrient substances, as well as large quantities of prostaglandins and fibrinogen. During the process of emission and ejaculation, each seminal vesicle empties its contents into the ejaculatory duct shortly after the vas deferens empties the sperm. This action adds greatly to the bulk of the ejaculated semen, and the fructose and other substances in the seminal fluid are of considerable nutrient value for the ejaculated sperm until one of the sperm fertilizes the ovum.

Prostaglandins are believed to aid fertilization in two ways: (1) by reacting with the female cervical mucus to make it more receptive to

sperm movement and (2) by possibly causing backward, reverse peristaltic contractions in the uterus and fallopian tubes to move the ejaculated sperm toward the ovaries (a few sperm reach the upper ends of the fallopian tubes within 5 minutes).

Role of Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the **ductus deferens** (also called the vas deferens). The ductus deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the **spermatic cord** because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of male birth control.

Sperm make up only 5 percent of the final volume of **semen**, the thick, milky fluid that the male ejaculates. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

FUNCTION OF THE PROSTATE GLAND

The prostate gland secretes a thin, milky fluid that contains calcium, citrate ion, phosphate ion, a clotting enzyme, and a profibrinolysin. During emission, the capsule of the prostate gland contracts simultaneously

with the contractions of the vas deferens so that the thin, milky fluid of the prostate gland adds further to the bulk of the semen. A slightly alkaline characteristic of the prostatic fluid may be quite important for successful fertilization of the ovum because the fluid of the vas deferens is relatively acidic owing to the presence of citric acid and metabolic end

products of the sperm and, consequently, helps inhibit sperm fertility. Also, the vaginal secretions of the female are acidic (with a pH of 3.5 to 4.0). Sperm do not become optimally motile until the pH of the surrounding fluids rises to about 6.0 to 6.5. Consequently, it is probable that the slightly alkaline prostatic fluid helps neutralize the acidity of the other seminal fluids during ejaculation and thus enhances the motility and fertility of the sperm.

Role of Bulbourethral Glands

The final addition to semen is made by two bulbourethral glands (or Cowper's glands) that release a *thick, salty fluid that lubricates the end of the urethra and the vagina*, and *helps to clean urine residues from the penile urethra*.

Role of the Penis

The penis is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.

SEMEN

Semen, which is ejaculated during the male sexual act, is composed of the fluid and sperm from the vas deferens (about 10 percent of the total), fluid from the seminal vesicles (almost 60 percent), fluid from the prostate gland (about 30 percent), and small amounts from the mucous glands, especially the bulbourethral glands. Thus, the bulk of the semen is seminal vesicle fluid, which is the last to be ejaculated and serves to wash the sperm through the ejaculatory duct and urethra.

The average pH of the combined semen is about 7.5, with the alkaline prostatic fluid having more than neutralized the mild acidity of the other portions of the semen.

The prostatic fluid gives the semen a milky appearance, and fluid from the seminal vesicles and mucous glands gives the semen a mucoid consistency. Also, a clotting enzyme from the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak fibrin coagulum that holds the semen in the deeper regions of the vagina where the uterine cervix lies. The coagulum then dissolves during the next 15 to 30 minutes because of lysis by fibrinolysin formed from the prostatic profibrinolysin.

In the early minutes after ejaculation, the sperm remain relatively immobile, possibly because of the viscosity of the coagulum. As the coagulum dissolves, the sperm simultaneously become highly motile.

Although sperm can live for many weeks in the male genital ducts, once they are ejaculated in the semen, their maximal life span is only 24 to 48 hours at body temperature. At lowered temperatures, however, semen can be stored for several weeks, and when frozen at temperatures below −100°C, sperm have been preserved for years.

“Capacitation” of Spermatozoa Is Required for Fertilization of the Ovum

Although spermatozoa are said to be “mature” when they leave the epididymis, their activity is held in check by multiple inhibitory factors secreted by the genital duct epithelia. Therefore, when they are first expelled in the semen, they are unable to fertilize the ovum. However, on coming in contact with the fluids of the female genital tract, multiple changes occur that activate the sperm for the final processes of fertilization. These collective changes are called capacitation of the

spermatozoa, which normally requires from 1 to 10 hours. The following changes are believed to occur:

1. The uterine and fallopian tube fluids wash away the various inhibitory factors that suppress sperm activity in the male genital ducts.
2. While the spermatozoa remain in the fluid of the male genital ducts, they are continually exposed to many floating vesicles from the seminiferous tubules containing large amounts of cholesterol. This cholesterol is continually added to the cellular membrane covering the sperm acrosome, toughening this membrane and preventing release of its enzymes. After ejaculation, the sperm deposited in the vagina swim away from the cholesterol vesicles upward into the uterine cavity, and they gradually lose much of their other excess cholesterol during the next few hours. In so doing, the membrane at the head of the sperm (the acrosome) becomes much weaker.
3. The membrane of the sperm also becomes much more permeable to calcium ions, so calcium now enters the sperm in abundance and changes the activity of the flagellum, giving it a powerful whiplash motion in contrast to its previously weak undulating motion. In addition, the calcium ions cause changes in the cellular membrane that cover the leading edge of the acrosome, making it possible for the acrosome to release its enzymes rapidly and easily as the sperm penetrates the granulosa cell mass surrounding the ovum, and even more so as it attempts to penetrate the zona pellucida of the ovum.

Thus, multiple changes occur during the process of capacitation. Without these changes, the sperm cannot make its way to the interior of the ovum to cause fertilization.

Acrosome Enzymes, the “Acrosome Reaction,” and Penetration of the Ovum

Stored in the acrosome of the sperm are large quantities of hyaluronidase and proteolytic enzymes. Hyaluronidase depolymerizes the hyaluronic acid polymers in the intercellular cement that holds the ovarian granulosa cells together. The proteolytic enzymes digest proteins in the structural elements of tissue cells that still adhere to the ovum.

When the ovum is expelled from the ovarian follicle into the fallopian tube, it still carries with it multiple layers of granulosa cells. Before a sperm can fertilize the ovum, it must dissolute these granulosa cell layers, and then it must penetrate through the thick covering of the ovum itself, the zona pellucida. To achieve this penetration, the stored enzymes in the acrosome begin to be released. It is believed that the hyaluronidase among these enzymes is especially important in opening pathways between the granulosa cells so that the sperm can reach the ovum.

When the sperm reaches the zona pellucida of the ovum, the anterior membrane of the sperm binds specifically with receptor proteins in the zona pellucida.

Next, the entire acrosome rapidly dissolves and all the acrosomal enzymes are released. Within minutes, these enzymes open a penetrating pathway for passage of the sperm head through the zona pellucida to the inside of the ovum. Within another 30 minutes, the cell membranes of the sperm head and of the oocyte fuse with each other to form a single cell. At the same time, the genetic material of the sperm and the oocyte combine to form a completely new cell genome, containing equal numbers of chromosomes and genes from mother and father. This is the process of fertilization; the embryo then begins to develop.

Why Does Only One Sperm Enter the Oocyte?

With nas many sperm as there are, why does only one enter the oocyte? The reason is not entirely known, but within a few minutes after the first sperm penetrates the zona pellucida of the ovum, calcium ions diffuse inward through the oocyte membrane and cause multiple cortical granules to be released by exocytosis from the oocyte into the perivitelline space. These granules contain substances that permeate all portions of the zona pellucida and prevent binding of additional sperm, and they even cause any sperm that have already begun to bind to fall off. Thus, almost never does more than one sperm enter the oocyte during fertilization.

Abnormal Spermatogenesis and Male Fertility

The seminiferous tubular epithelium can be destroyed by several diseases. For instance, bilateral orchitis (inflammation) of the testes resulting from mumps causes sterility in some affected males. Also, some male infants are born with degenerate tubular epithelia as a result of strictures in the genital ducts or other abnormalities. Finally, another cause of sterility, usually temporary, is excessive temperature of the testes.

Effect of Temperature on Spermatogenesis. Increasing the temperature of the testes can prevent spermatogenesis by causing degeneration of most cells of the seminiferous tubules besides the spermatogonia. It has often been stated that the reason the testes are located in the dangling scrotum is to maintain the temperature of these glands below the internal temperature of the body, although usually only about 2°C below the internal temperature. On cold days, scrotal reflexes cause the musculature of the scrotum to contract, pulling the testes close to the body to maintain this 2-degree differential. Thus, the scrotum acts as a

cooling mechanism for the testes (but a controlled cooling), without which spermatogenesis might be deficient during hot weather.

Cryptorchidism. Cryptorchidism means failure of a testis to descend from the abdomen into the scrotum at or near the time of birth of a fetus. During development of the male fetus, the testes are derived from the genital ridges in the abdomen. However, at about 3 weeks to 1 month before birth of the baby, the testes normally descend through the inguinal canals into the scrotum.

Occasionally this descent does not occur or occurs incompletely, and as a result one or both testes remain in the abdomen, in the inguinal canal, or elsewhere along the route of descent.

A testis that remains in the abdominal cavity throughout life is incapable of forming sperm. The tubular epithelium becomes degenerate, leaving only the interstitial structures of the testis. It has been claimed that even the few degrees' higher temperature in the abdomen than in the scrotum is sufficient to cause this degeneration of the tubular epithelium and, consequently, to cause sterility, although this effect is not certain. Nevertheless, for this reason, operations to relocate the cryptorchid testes from the abdominal cavity into the scrotum before the beginning of adult sexual life can be performed on boys who have undescended testes.

Testosterone secretion by the fetal testes is the normal stimulus that causes the testes to descend into the scrotum from the abdomen. Therefore, many, if not most, instances of cryptorchidism are caused by abnormally formed testes that are unable to secrete enough testosterone. The surgical operation for cryptorchidism in these patients is unlikely to be successful.

Effect of Sperm Count on Fertility. The usual quantity of semen ejaculated during each coitus averages about 3.5 milliliters, and each milliliter of semen contains an average of about 120 million sperm, although even in “normal” males this quantity can vary from 35 million to 200 million. This means an average total of 400 million sperm are usually present in the several milliliters of each ejaculate. When the number of sperm in each milliliter falls below about 20 million, the person is likely to be infertile. Thus, even though only a single sperm is necessary to fertilize the ovum, for reasons that are not understood, the ejaculate usually must contain a tremendous number of sperm for only one sperm to fertilize the ovum.

Effect of Sperm Morphology and Motility on Fertility.

Occasionally a man has a normal number of sperm but is still infertile. When this situation occurs, sometimes as many as one half of the sperm are found to be abnormal physically, having two heads, abnormally shaped heads, or abnormal tails. At other times, the sperm appear to be structurally normal, but for reasons not understood, they are either entirely nonmotile or relatively nonmotile. Whenever most of the sperm are morphologically abnormal or are nonmotile, the person is likely to be infertile, even though the remainder of the sperm appear to be normal.(Figure 9)

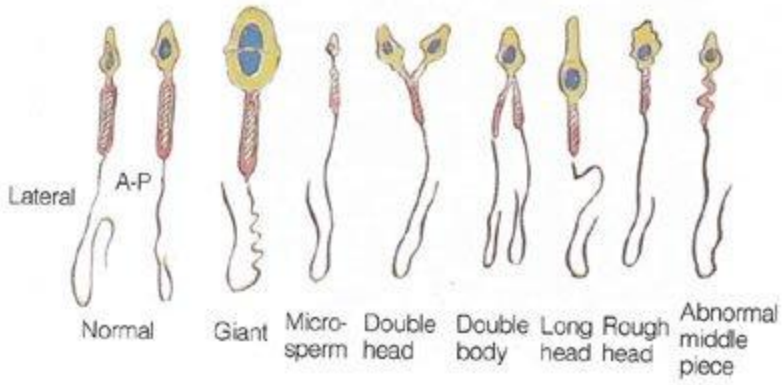


Figure 9: Normal and Abnormal infertile sperm

MALE SEXUAL ACT

NEURONAL STIMULUS FOR PERFORMANCE OF THE MALE SEXUAL ACT

The most important source of sensory nerve signals for initiating the male sexual act is the glans penis. The glans contains an especially sensitive sensory end-organ system that transmits into the central nervous system that special modality of sensation called sexual sensation. The slippery massaging action of intercourse on the glans stimulates the sensory end organs, and the sexual signals in turn pass through the pudendal nerve, then through the sacral plexus into the sacral portion of the spinal cord, and finally up the cord to undefined areas of the brain.

Impulses may also enter the spinal cord from areas adjacent to the penis to aid in stimulating the sexual act. For instance, stimulation of the anal epithelium, the scrotum, and perineal structures in general can send signals into the cord that add to the sexual sensation.

Sexual sensations can even originate in internal structures, such as in areas of the urethra, bladder, prostate, seminal vesicles, testes, and vas deferens. Indeed, one of the causes of “sexual drive” is filling of the sexual organs with secretions. Mild infection and inflammation of these sexual organs may sometimes stimulate sexual desire, and some “aphrodisiac” drugs, such as cantharidin, irritate the bladder and urethral mucosa, inducing inflammation and vascular congestion.

Psychic Element of Male Sexual Stimulation. Appropriate psychic stimuli can greatly enhance the ability of a person to perform the sexual act. Simply thinking sexual thoughts or even dreaming that the act of intercourse is being performed can initiate the male act, culminating in ejaculation. Indeed, nocturnal emissions during dreams,

often called “wet dreams,” occur in many males during some stages of sexual life, especially during the teens.

Integration of the Male Sexual Act in the Spinal Cord. Although psychic factors usually play an important part in the male sexual act and can initiate or inhibit it, brain function is probably not necessary for its performance because appropriate genital stimulation can cause ejaculation in some animals and occasionally in humans after their spinal cords have been cut above the lumbar region. The male sexual act results from inherent reflex mechanisms integrated in the sacral and lumbar spinal cord, and these mechanisms can be initiated by either psychic stimulation from the brain or actual sexual stimulation from the sex organs, but usually it is a combinationof both.

STAGES OF THE MALE SEXUAL ACT

Penile Erection—Role of the Parasympathetic Nerves.

Penile erection is the first effect of male sexual stimulation, and the degree of erection is proportional to the degree of stimulation, whether psychic or physical. Erection is caused by parasympathetic impulses that pass from the sacral portion of the spinal cord through the pelvic nerves to the penis. These parasympathetic nerve fibers, in contrast to most other parasympathetic fibers, are believed to release nitric oxide and/or vasoactive intestinal peptide in addition to acetylcholine. Nitric oxide activates the enzyme guanylyl cyclase, causing increased formation of cyclic guanosine monophosphate (GMP). The cyclic GMP especially relaxes the arteries of the penis and the trabecular meshwork of smooth muscle fibers in the erectile tissue of the corpora cavernosa and corpus spongiosum in the shaft of the penis. As the vascular smooth muscles relax, blood flow into the penis increases, causing release of nitric oxide from the vascular endothelial cells and further rvasodilation.

The erectile tissue of the penis consists of large cavernous sinusoids that are normally relatively empty of blood but become dilated tremendously when arterial blood flows rapidly into them under pressure while the venous outflow is partially occluded. Also, the erectile bodies, especially the two corpora cavernosa, are surrounded by strong fibrous coats; therefore, high pressure within the sinusoids causes ballooning of the erectile tissue to such an extent that the penis becomes hard and elongated, which is the phenomenon of erection.

Lubrication Is a Parasympathetic Function. During sexual stimulation, the parasympathetic impulses, in addition to promoting erection, cause the urethral glands and the bulbourethral glands to secrete mucus. This mucus flows through the urethra during intercourse to aid in the lubrication during coitus. However, most of the lubrication of coitus is provided by the female sexual organs rather than by the male organs. Without satisfactory lubrication, the male sexual act is seldom successful because unlubricated intercourse causes grating, painful sensations that inhibit rather than excite sexual sensations.

Emission and Ejaculation Are Functions of the Sympathetic Nerves. Emission and ejaculation are the culmination of the male sexual act. When the sexual stimulus becomes extremely intense, the reflex centers of the spinal cord begin to emit sympathetic impulses that leave the cord at T12 to L2 and pass to the genital organs through the hypogastric and pelvic sympathetic nerve plexuses to initiate emission, the forerunner of ejaculation.

Emission begins with contraction of the vas deferens and the ampulla to cause expulsion of sperm into the internal urethra. Then, contractions of the muscular coat of the prostate gland followed by contraction of the

seminal vesicles expel prostatic and seminal fluid also into the urethra, forcing the sperm forward. All these fluids mix in the internal urethra with mucus already secreted by the bulbourethral glands to form the semen. The process to this point is emission. The filling of the internal urethra with semen elicits sensory signals that are transmitted through the pudendal nerves to the sacral regions of the cord, giving the feeling of sudden fullness in the internal genital organs. Also, these sensory signals further excite rhythmical contraction of the internal genital organs and cause contraction of the ischio cavernosus and bulbo cavernosus muscles that compress the bases of the penile erectile tissue. These effects together cause rhythmical, wavelike increases in pressure in both the erectile tissue of the penis and the genital ducts and urethra, which "ejaculate" the semen from the urethra to the exterior. This final process is called ejaculation. At the same time, rhythmical contractions of the pelvic muscles and even of some of the muscles of the body trunk cause thrusting movements of the pelvis and penis, which also help propel the semen into the deepest recesses of the vagina and perhaps even slightly into the cervix of the uterus. This entire period of emission and ejaculation is called the male orgasm. At its termination, the male sexual excitement disappears almost entirely within 1 to 2 minutes and erection ceases, a process called resolution.

Testosterone

Testosterone, an androgen, is a steroid hormone produced by **Leydig cells**. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical

differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

Chemistry of the Androgens.

All androgens are steroid compounds; testosterone and dihydro testosterone. Both in the testes and in the adrenals, the androgens can be synthesized either from cholesterol or directly from acetyl coenzyme A.

Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

Effect of Testosterone on Development of Adult Primary and Secondary Sexual Characteristics

After puberty, increasing amounts of testosterone secretion cause the penis, scrotum, and testes to enlarge about eightfold before the age of 20 years. In addition, testosterone causes the secondary sexual

characteristics of the male to develop, beginning at puberty and ending at maturity. These secondary sexual characteristics, in addition to the sexual organs themselves, distinguish the male from the female as follows.

Effect on the Distribution of Body Hair. Testosterone causes growth of hair (1) over the pubis, (2) upward along the linea alba of the abdomen sometimes to the umbilicus and above, (3) on the face, (4) usually on the chest, and (5) less often on other regions of the body, such as the back. It also causes the hair on most other portions of the body to become more prolific.

Male Pattern Baldness. Testosterone decreases the growth of hair on the top of the head; a man who does not have functional testes does not become bald. However, many virile men never become bald because baldness is a result of two factors: first, a genetic background for the development of baldness and, second, superimposed on this genetic background, large quantities of androgenic hormones. When a long-sustained androgenic tumor develops in a woman who has the appropriate genetic background, she becomes bald in the same manner as does a man.

Effect on the Voice. Testosterone secreted by the testes or injected into the body causes hypertrophy of the laryngeal mucosa and enlargement of the larynx. The effects at first cause a relatively discordant, “cracking” voice that gradually changes into the typical adult masculine voice.

Testosterone Increases Thickness of the Skin and Can Contribute to the Development of Acne. Testosterone increases the thickness of the skin over the entire body and the ruggedness of the subcutaneous tissues. Testosterone also increases the rate of secretion by some or perhaps all of the body’s sebaceous glands. Especially important is excessive

secretion by the sebaceous glands of the face, which can result in acne. Therefore, acne is one of the most common features of male adolescence when the body is first becoming introduced to increased testosterone. After several years of testosterone secretion, the skin normally adapts to the testosterone in a way that allows it to overcome the acne.

Testosterone Increases Protein Formation and Muscle Development.

One of the most important male characteristics is development of increasing musculature after puberty, averaging about a 50 percent increase in muscle mass over that in the female. This increase in muscle mass is associated with increased protein in the nonmuscle parts of the body as well. Many of the changes in the skin are due to deposition of proteins in the skin, and the changes in the voice also result partly from this protein anabolic function of testosterone. Because of the great effect that testosterone and other androgens have on the body musculature, synthetic androgens are widely used by athletes to improve their muscular performance. This practice is to be severely deprecated because of prolonged harmful effects of excess androgens, in relation to sports physiology. Testosterone or synthetic androgens are also occasionally used in old age as a "youth hormone" to improve muscle strength and vigor, but with questionable results.

Testosterone Increases Bone Matrix and Causes Calcium Retention. After the great increase in circulating testosterone that occurs at puberty (or after prolonged injection of testosterone), the bones grow considerably thicker and deposit considerable additional calcium salts. Thus, testosterone increases the total quantity of bone matrix and causes calcium retention. The increase in bone matrix is believed to result from the general protein anabolic function of testosterone plus

deposition of calcium salts in response to the increased protein. Testosterone has a specific effect on the pelvis to (1) narrow the pelvic outlet, (2) lengthen it, (3) cause a funnel-like shape instead of the broad ovoid shape of the female pelvis, and (4) greatly increase the strength of the entire pelvis for load bearing. In the absence of testosterone, the male pelvis develops into a pelvis that is similar to that of the female. Because of the ability of testosterone to increase the size and strength of bones, it is sometimes used in older men to treat osteoporosis.

When great quantities of testosterone (or any other androgen) are secreted abnormally in the still-growing child, the rate of bone growth increases markedly, causing a spurt in total body height. However, the testosterone also causes the epiphyses of the long bones to unite with the shafts of the bones at an early age. Therefore, despite the rapidity of growth, this early uniting of the epiphyses prevents the person from growing as tall as he would have grown had testosterone not been secreted at all. Even in normal men, the final adult height is slightly less than that which occurs in males castrated before puberty.

Testosterone Increases the Basal Metabolic Rate. Injection of large quantities of testosterone can increase the basal metabolic rate by as much as 15 percent. Also, even the usual quantity of testosterone secreted by the testes during adolescence and early adult life increases the rate of metabolism some 5 to 10 percent above the value that it would be were the testes not active. This increased rate of metabolism is possibly an indirect result of the effect of testosterone on protein anabolism, with the increased quantity of proteins—the enzymes especially— increasing the activities of all cells.

Testosterone Increases Red Blood Cells. When normal quantities of testosterone are injected into a castrated adult, the number of red blood cells per cubic millimeter of blood increases 15 to 20 percent. Also, the average man has about 700,000 more red blood cells per cubic millimeter than the average woman. Despite the strong association of testosterone and increased hematocrit, testosterone does not appear to directly increase erythropoietin levels or have a direct effect on red blood cell production. The effect of testosterone to increase red blood cell production may be at least partly indirect because of the increased metabolic rate that occurs after testosterone administration.

Effect on Electrolyte and Water Balance. many steroid hormones can increase the reabsorption of sodium in the distal tubules of the kidneys. Testosterone also has such an effect, but only to a minor degree in comparison with the adrenal mineralocorticoids. Nevertheless, after puberty, the blood and extracellular fluid volumes of the male in relation to body weight increase as much as 5 to 10 percent.

Control of Testosterone

The regulation of testosterone concentrations throughout the body is critical for male reproductive function. The intricate interplay between the endocrine system and the reproductive system is shown in Figure 10

The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called **gonadotropin-releasing hormone (GnRH)** from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and folliclestimulating hormone (FSH). These two

hormones are critical for reproductive function in both men and women. In men, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. In men, LH binds to receptors on Leydig cells in the testes and up regulates the production of testosterone. A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulate the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

Role of Inhibin in Negative Feedback Control of Seminiferous Tubule Activity. When the seminiferous tubules fail to produce sperm, secretion of FSH by the anterior pituitary gland increases markedly. Conversely, when spermatogenesis proceeds too rapidly, pituitary secretion of FSH diminishes. The cause of this negative feedback effect on the anterior pituitary is believed to be secretion by the Sertoli cells of still another hormone called inhibin . This hormone has a strong direct effect on the anterior pituitary gland to inhibit the secretion of FSH.

Inhibin is a glycoprotein, like both LH and FSH, with a molecular weight between 10,000 and 30,000. It has been isolated from cultured Sertoli cells. Its potent inhibitory feedback effect on the anterior pituitary gland provides an important negative feedback mechanism for control of spermatogenesis, operating simultaneously with and in parallel to the negative feedback mechanism for control of testosterone secretion.

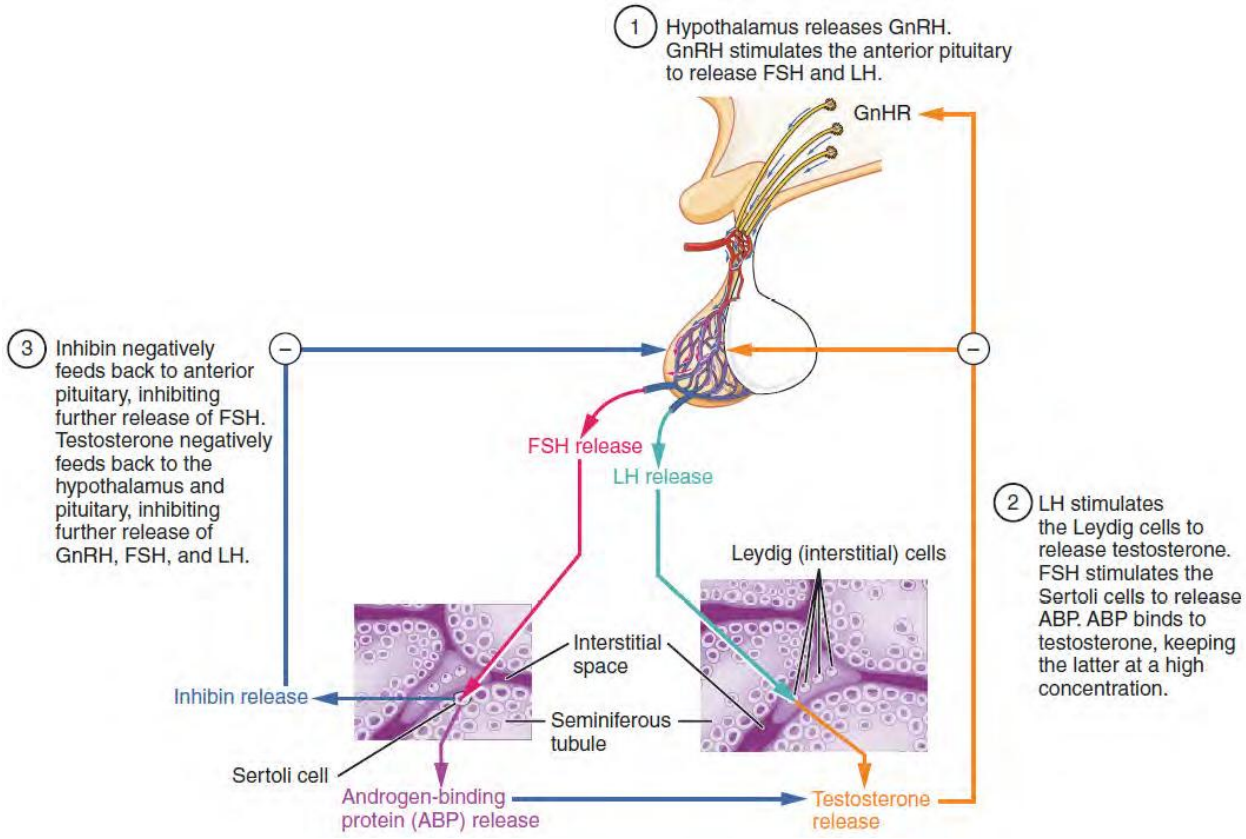


Figure 10 :Regulation of Testosterone Production The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of GnRH to inhibit their own production.

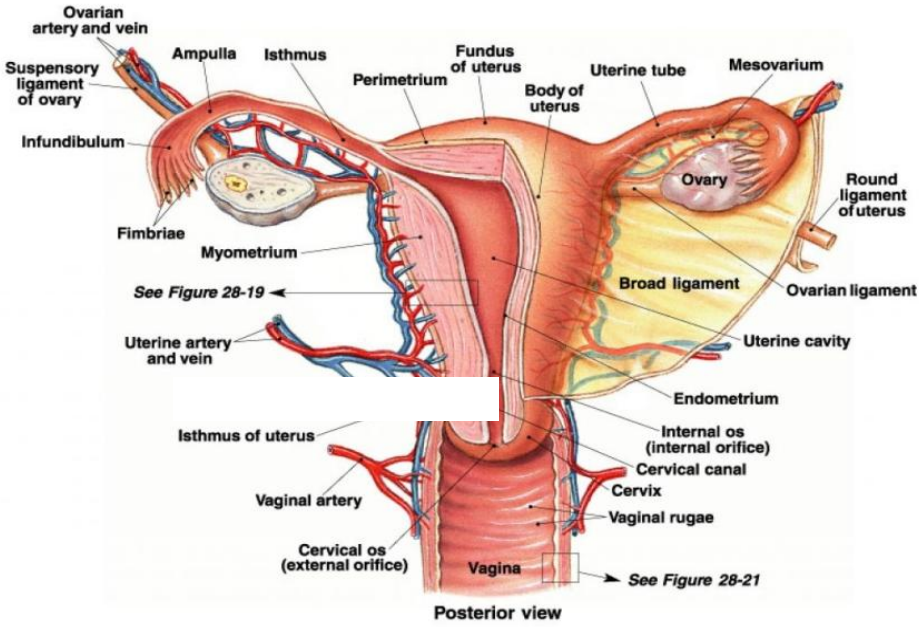
AGING AND MALE REPRODUCTIVE SYSTEM

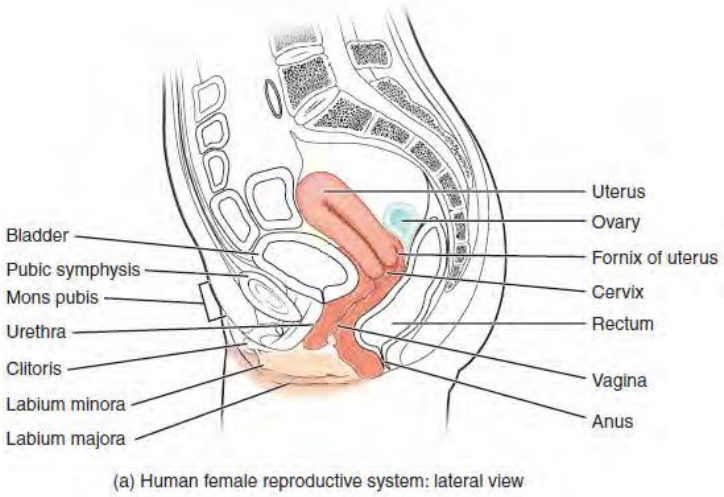
Declines in Leydig cell activity can occur in men beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids in men is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, men report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms. Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly men; however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

Chapter 3: Anatomy and Physiology of the Female Reproductive System

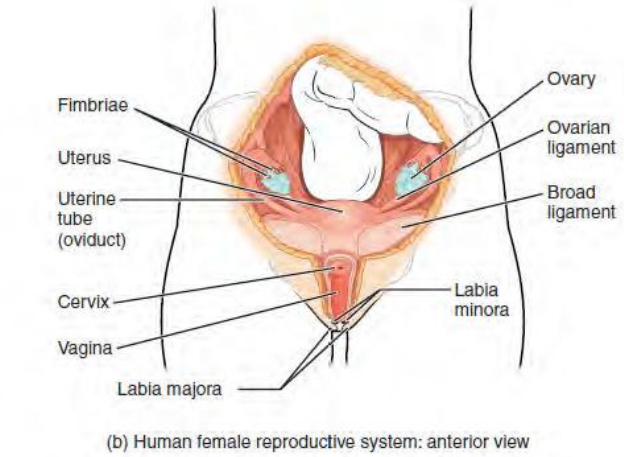
The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity (Figure 11). Recall that the ovaries are the female gonads. The gamete they produce is called an **oocyte**. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system.

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.





(a) Human female reproductive system: lateral view



(b) Human female reproductive system: anterior view

Figure 11 Female Reproductive System The major organs of the female reproductive system are located inside the pelvic cavity.

Ovaries

The **ovaries** are the female gonads (see **Figure 11, 12**). Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an extension of the peritoneum that connects the ovaries to the **broad ligament**. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary.

Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a **follicle**. The growth and development of ovarian follicles will be described shortly. Beneath the cortex lies the inner ovarian medulla, the site of blood vessels, lymph vessels, and the nerves of the ovary. You will learn more about the overall anatomy of the female reproductive system at the end of this section. The Uterine Tubes

The uterine tubes (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus (Figure 10). Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections.

The isthmus is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal infundibulum flares out with

slender, finger-like projections called fimbriae. The middle region of the tube, called the ampulla, is where fertilization often occurs. The uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.

Following ovulation, the secondary oocyte surrounded by a few granulosa cells is released into the peritoneal cavity.

The nearby uterine tube, either left or right, receives the oocyte. Unlike sperm, oocytes lack flagella, and therefore cannot move on their own. So how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the uterine tube. These contractions occur every 4 to 8 seconds, and the result is a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is generated by coordinated beating of the cilia that line the outside and lumen of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube. Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meet the egg while it is still moving through the ampulla.

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.

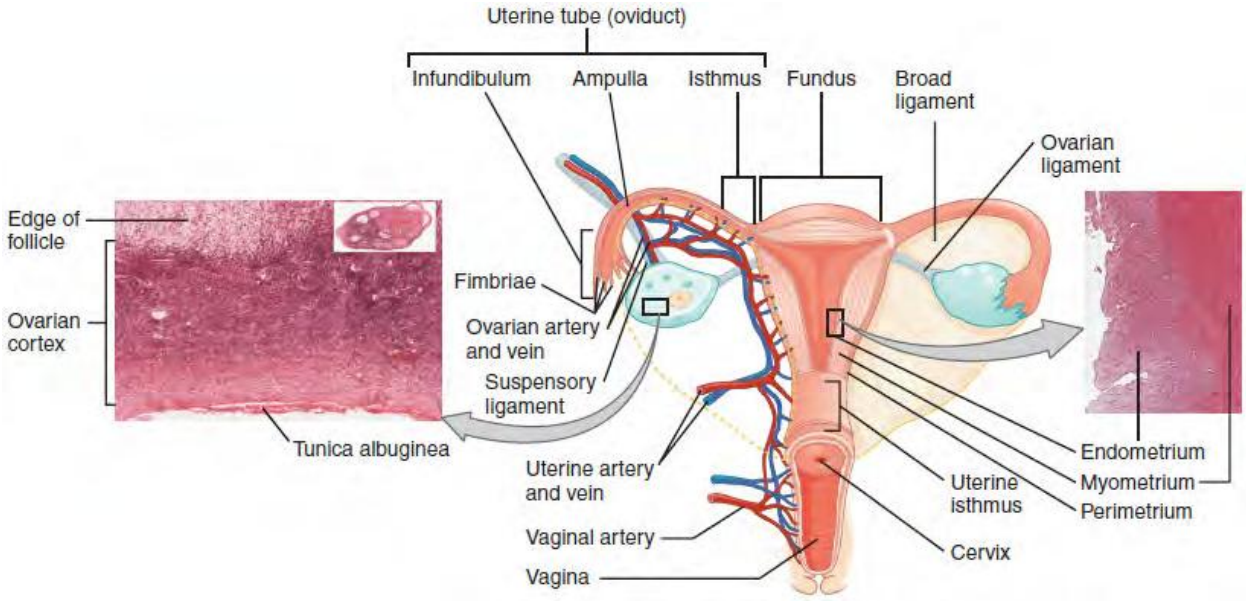


Figure 12 Ovaries, Uterine Tubes, and Uterus This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School c 2012)

The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a woman's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

The Uterus and Cervix

The **uterus** is the muscular organ that nourishes and supports the growing embryo (see **Figures 11, 12**). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections.

The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the **body of uterus** (or corpus). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

Several ligaments maintain the position of the uterus within the abdominopelvic cavity. The broad ligament is a fold of peritoneum that serves as a primary support for the uterus, extending laterally from both sides of the uterus and attaching it to the pelvic wall. The round ligament attaches to the uterus near the uterine tubes, and extends to the labia majora. Finally, the uterosacral ligament stabilizes the uterus posteriorly by its connection from the cervix to the pelvic wall.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or **perimetrium**, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or **myometrium**, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman’s period. Anteriorly directed myometrial contractions also occur

near the time of ovulation, and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

The innermost layer of the uterus is called the **endometrium**. The endometrium contains a connective tissue lining, the lamina propria, which is covered by epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers). The stratum basalis layer is part of the lamina propria and is adjacent to the myometrium; this layer does not shed during menses. In contrast, the thicker stratum functionalis layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. It is the stratum functionalis that grows and thickens in response to increased levels of estrogen and progesterone. In the luteal phase of the menstrual cycle, special branches off of the uterine artery called spiral arteries supply the thickened stratum functionalis. This inner functional layer provides the proper site of implantation for the fertilized egg, and—should fertilization not occur—it is only the stratum functionalis layer of the endometrium that sheds during menstruation. Recall that during the follicular phase of the ovarian cycle, the tertiary follicles are growing and secreting estrogen. At the same time, the stratum functionalis of the endometrium is thickening to prepare for a potential implantation. The postovulatory increase in progesterone, which characterizes the luteal phase, is key for maintaining a thick stratum functionalis.

As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium, and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus

luteum and it degrades, ceasing progesterone production and ending the luteal phase. Without progesterone, the endometrium thins and, under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation, or the **menses**. The first menses after puberty, called

menarche, can occur either before or after the first ovulation.

Vagina

The **vagina** is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract (Figures 11, 12). It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the fornix—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called **rugae**. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholins glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy woman, the most

predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ.

External Female Genitals

The external female reproductive structures are referred to collectively as the **vulva (figure11)** .The **mons pubis** is a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. The **labia majora** are folds of hair-covered skin . The thinner and more pigmented **labia minora** extend medial to the labia majora. Although they naturally vary in shape and size from woman to woman, the labia minora serve to protect the female urethra and the entrance to the female reproductive tract.

OOGENESIS AND FOLLICULAR DEVELOPMENT IN THE OVARIES

A developing egg (oocyte) differentiates into a mature egg (ovum) through a series of steps called oogenesis(Figure13) . During early embryonic development, primordial germ cells from the dorsal endoderm of the yolk sac migrate along the mesentery of the hindgut to the outer surface of the ovary, which is covered by a germinal epithelium, derived embryologically from the epithelium of the germinal ridges. During this migration, the germ cells divide repeatedly. Once these primordial germ cells reach the germinal epithelium, they migrate into the substance of the ovarian cortex and become oogonia or primordial ova.

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

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

The first meiotic division of the oocyte occurs after puberty. Each oocyte divides into two cells, a large ovum (secondary oocyte) and a small first polar body. Each of these cells contains 23 duplicated chromosomes. The first polar body may or may not undergo a second meiotic division and then disintegrates. The ovum undergoes a second meiotic division, and after the sister chromatids separate, there is a pause in meiosis. If the ovum is fertilized, the final step in meiosis occurs and the sister chromatids in the ovum go to separate cells. When the ovary releases the ovum (ovulation) and if the ovum is fertilized, the final meiosis occurs. Half of the sister chromatids remain in the fertilized ovum and the other half are released in a second polar body, which then disintegrates.

At puberty, only about 300,000 oocytes remain in the ovaries, and only a small percentage of these oocytes become mature. The many thousands of oocytes that do not mature degenerate. During all the reproductive years

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

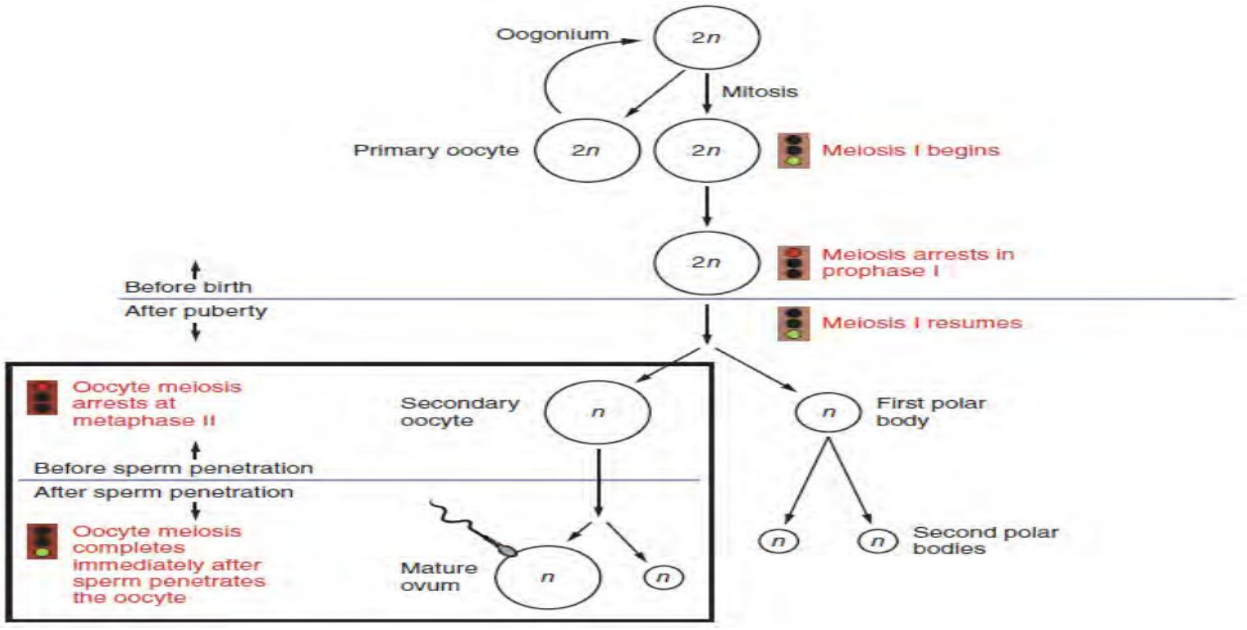


Figure 13 Oogenesis

FEMALE HORMONAL SYSTEM

The female hormonal system, like that of the male hormonal system, consists of three hierarchies of hormones(figure 14), as follows:

1. A hypothalamic releasing hormone, called gonadotropin-releasing hormone (GnRH)
2. The anterior pituitary sex hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH), both of which are secreted in response to therelease of GnRH from the hypothalamus
3. The ovarian hormones, estrogen and progesterone, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland These various hormones are

secreted at drastically differing rates during different parts of the female monthly sexual cycle.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.

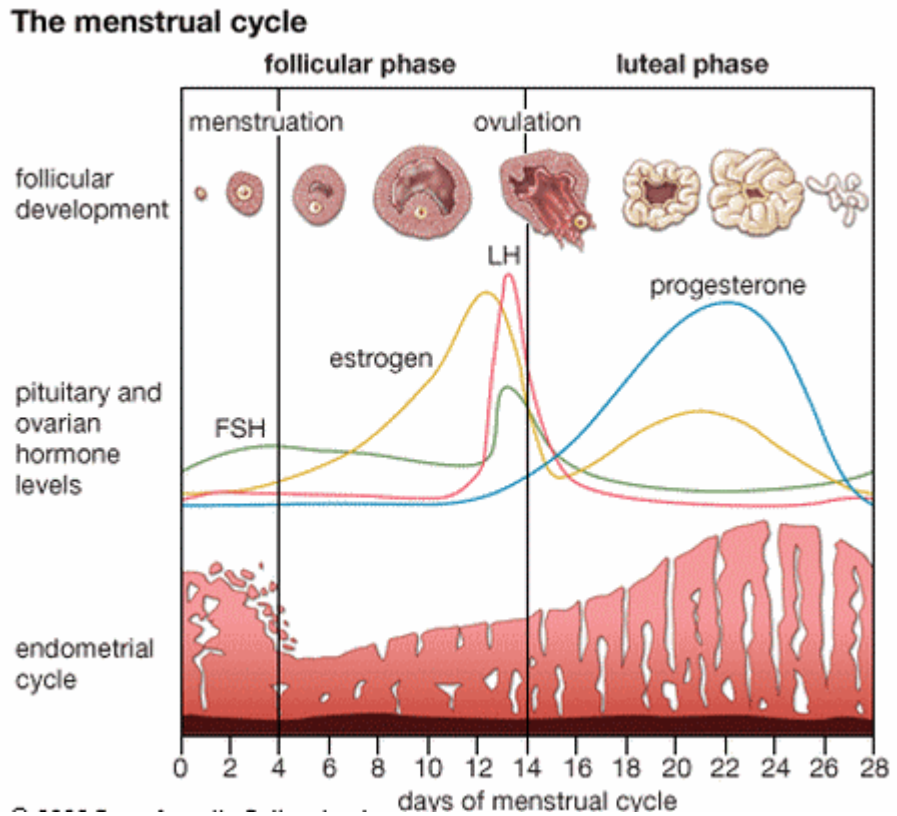


Figure 14 : gonadotropins and ovarian hormones during the normal female sexual cycle.

FSH, follicle-stimulating hormone; LH, luteinizing hormone

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

GONADOTROPIC HORMONES AND THEIR EFFECTS ON THE OVARIES

The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH, which are secreted by the anterior pituitary gland. Both FSH and LH are small glycoproteins that have molecular weights of about 30,000. In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood, when almost no pituitary gonadotropic hormones are secreted. At age 9 to 12 years, the pituitary begins to secrete progressively more FSH and LH, which leads to the onset of normal monthly sexual cycles beginning between the ages of 11 and 15 years. This period of change is called puberty, and the time of the first menstrual cycle is called menarche. During each month of the female sexual cycle, there is a cyclical increase and decrease of FSH and LH. 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 system in the cell cytoplasm, which causes the formation of protein kinase and multiple phosphorylations of key enzymes that stimulate sex hormone synthesis.

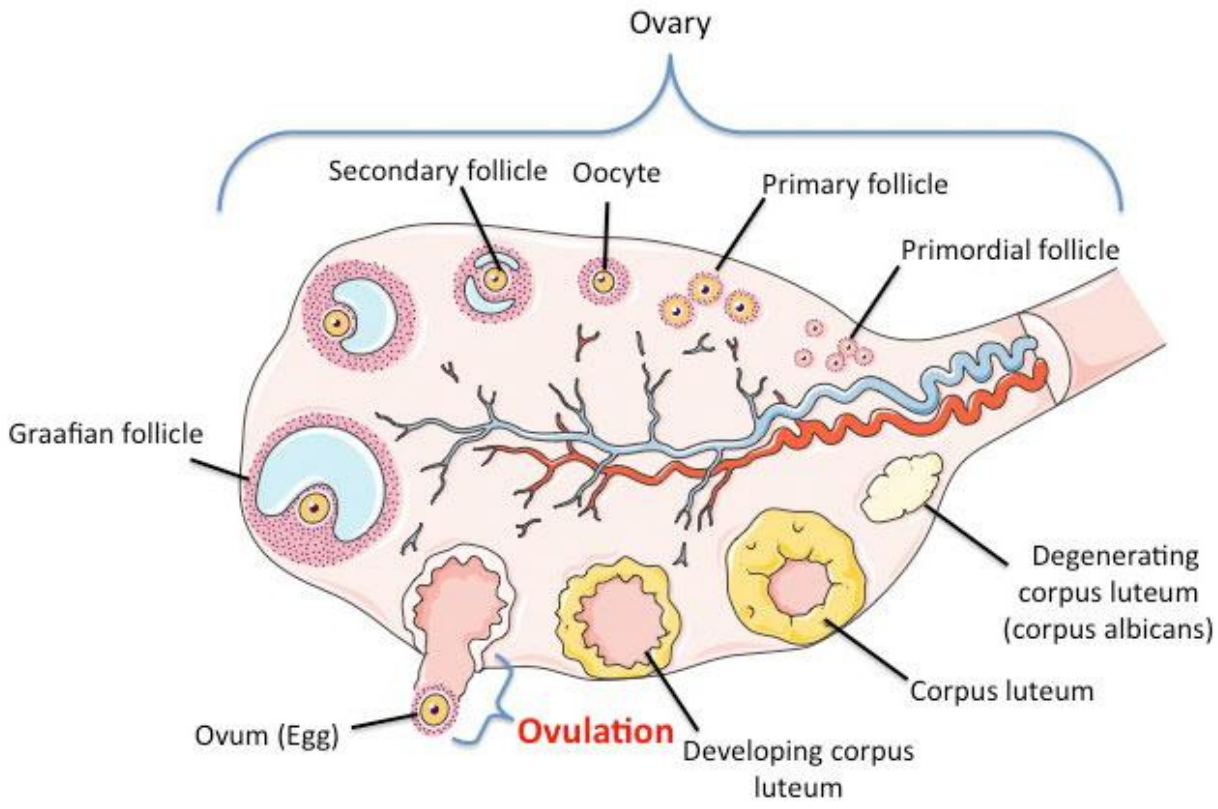


Figure 15 : Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

OVARIAN FOLLICLE GROWTH—THE FOLLICULAR PHASE OF THE OVARIAN CYCLE

Figure 15 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, which increases in diameter twofold to threefold. That stage is followed by growth of additional layers of granulosa cells in some of the follicles. These follicles are known as primary follicles.

Development of Antral and Vesicular Follicles. During the first few days of each monthly female sexual cycle, the concentrations of 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. The theca is divided into two layers. In the theca interna, the cells take on epithelioid characteristics similar to those of the granulosa cells and develop the ability to secrete additional steroid sex hormones (estrogen and progesterone). The outer layer, the theca externa, develops into a highly vascular connective tissue capsule that becomes the capsule of the developing follicle. After the early proliferative phase of growth, which lasts for a few days, the mass of granulosa cells secretes a follicular fluid that contains a high concentration of estrogen, one of the important female sex hormones . Accumulation of this fluid causes an antrum to appear within the mass of granulosa cells, as shown in Figure 15.

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

1. Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors, which causes a positive feedback effect because it makes the granulosa cells even more sensitive to FSH.
2. The pituitary FSH and the estrogens combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even more rapid increase in follicular secretion.
3. The increasing estrogens from the follicle plus the increasing LH from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion as well. Once the antral follicles begin to grow, their growth occurs almost explosively. The ovum 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, and the remaining 5 to 11 developing follicles involute (a process called atresia); these follicles are said to become atretic. The cause of the atresia is unclear, but it has been postulated to be the following: The large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well-developed follicles. Therefore, the largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute. This

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

Ovulation

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

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

About 2 days before ovulation , the rate of secretion of LH by the anterior pituitary gland increases markedly, rising 6- to 10-fold and peaking about 16 hours before ovulation. FSH also increases about 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.

This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are necessary for ovulation:

1. The theca externa (i.e., the capsule of the follicle) begins to release proteolytic enzymes from lysosomes, and these enzymes cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma.
2. Simultaneously there is rapid growth of new blood vessels into the follicle wall, 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—THE LUTEAL PHASE OF THE OVARIAN CYCLE

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca interna cells change rapidly into lutein cells. They enlarge in diameter two or more times and become filled with lipid inclusions that give them a yellowish appearance.

This process is called luteinization, and the total mass of cells together is called the corpus luteum, A well-developed vascular supply also grows into the corpus luteum. The granulosa cells in the corpus luteum develop

extensive intracellular smooth endoplasmic reticula that form large amounts of the female sex hormones progesterone and estrogen (with more progesterone than estrogen during the luteal phase). The theca cells form mainly the androgens androstenedione and testosterone rather than female sex hormones. However, most of these hormones are also converted by the enzyme aromatase in the granulosa cells into estrogens, the 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 the corpus luteum begins to involute and eventually loses its secretory function and its yellowish, lipid characteristic about 12 days after ovulation, becoming the corpus albicans; during the ensuing few weeks, the corpus albicans is replaced by connective tissue and over months is absorbed. Luteinizing Function of Luteinizing Hormone. The change of granulosa and theca interna cells into luteincells 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 Luteinizing Hormone. 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 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 FSH secretion by the anterior pituitary gland. 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

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.

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.

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. At least part of this effect is due to stimulation of osteoprotegerin, which is also called osteoclastogenesis inhibitory factor, a cytokine that inhibits bone resorption.

At puberty, when the female enters her reproductive years, her growth in height becomes rapid for several years. However, estrogens 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. Because osteoporosis can greatly weaken the bones and lead to bone fracture, especially fracture of the vertebrae, many

postmenopausal women are treated prophylactically with estrogen replacement to prevent the osteoporotic effects.

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

FUNCTIONS OF PROGESTERONE

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

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

Progesterone Promotes Development of the Breasts.

Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory. However, progesterone does not cause the alveoli to secrete milk; 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

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

Secretory Phase (Progestational Phase) of the Endometrial Cycle, 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, and an excess of secretory substances accumulates in the glandular epithelial cells. In addition, the cytoplasm of the stromal cells increases, lipid and glycogen deposits

increase greatly in the stromal cells, and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters.

The 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 involutes and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion . Menstruation follows. Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle. The first effect is decreased stimulation of the endometrial cells by these two hormones, followed rapidly by involution of the endometrium to about 65 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 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 disease.

Within 4 to 7 days after menstruation starts, the loss of blood ceases because, by this time, the endometrium has become re-epithelialized. Leukorrhea During Menstruation. During menstruation, large numbers of leukocytes are released along with the necrotic material and blood. A substance liberated by the endometrial necrosis likely causes this outflow of leukocytes. As a result of these leukocytes and possibly other factors, the uterus is highly resistant to infection during menstruation, even though the endometrial surfaces are denuded. This resistance to infection is of extreme protective value.

tion —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of maternal origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your mother, her mother, and so on back through your female ancestors.

Hormonal Control of the Ovarian Cycle

The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

As in men, the hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH(Figure16). These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH stimulates the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone estradiol, a type of estrogen. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase.

The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase. Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia).

Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte. Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle.

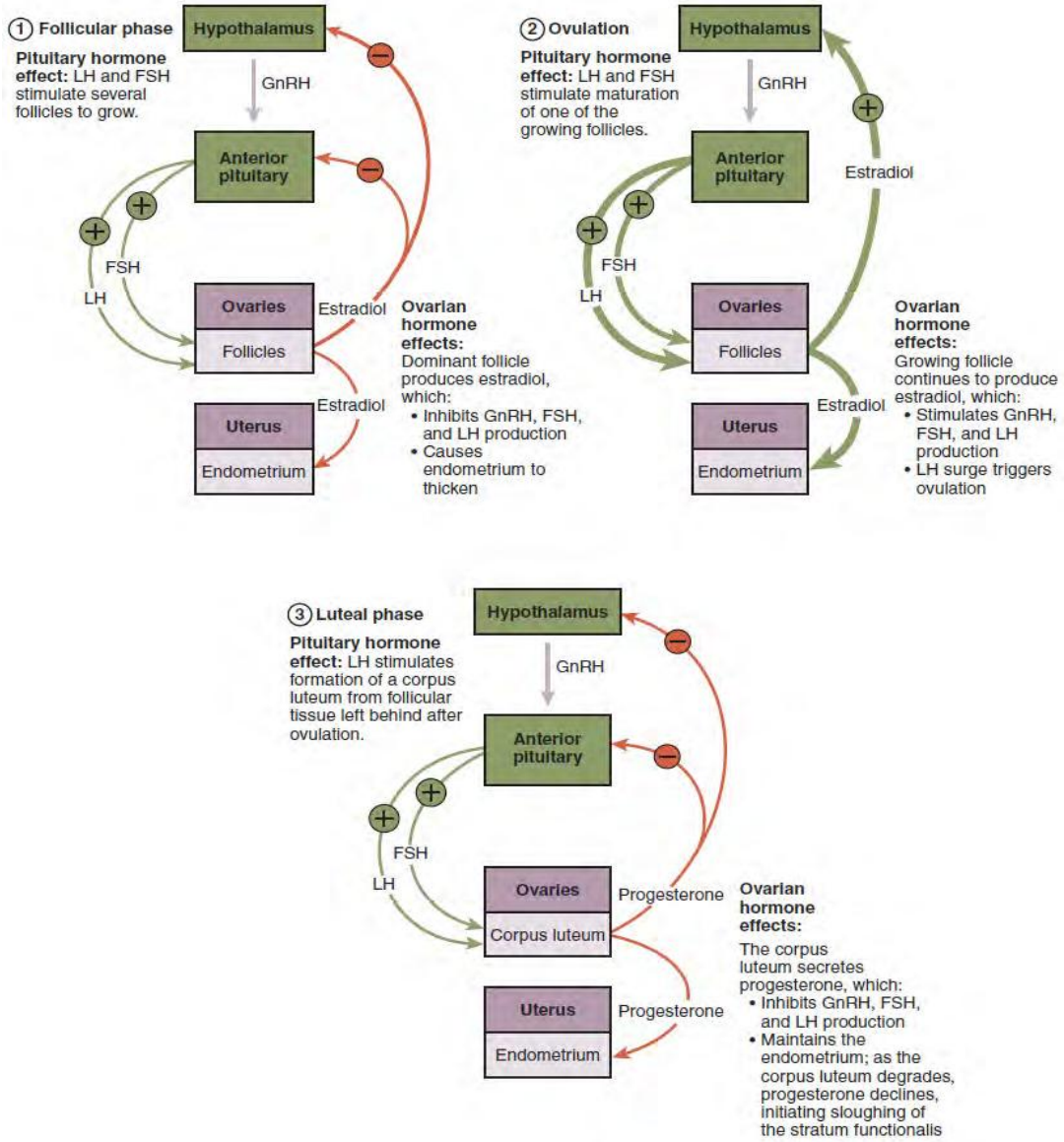


Figure 16 Hormonal Regulation of Ovulation The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries.

When only the one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback doesn't occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream (see **Figure 16**). The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation.

In the next section, you will follow the ovulated oocyte as it travels toward the uterus, but there is one more important event that occurs in the ovarian cycle. The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after the oocyte has been ovulated. This change is called luteinization (recall that the full name of LH is luteinizing hormone), and it transforms the collapsed follicle into a new endocrine structure called the **corpus luteum**, a term meaning "yellowish body" (see **Figure 16**). Instead of estrogen, the

luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone progesterone, a hormone that is critical for the establishment and maintenance of pregnancy. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time.

The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. If pregnancy does not occur within 10 to 12 days, the corpus luteum `will` stop secreting progesterone and degrade into the **corpus albicans**, a nonfunctional “whitish body” that will disintegrate in the ovary over a period of several months. During this time of reduced progesterone secretion, FSH and LH are once again stimulated, and the follicular phase begins again with a new cohort of early tertiary follicles beginning to grow and secrete estrogen.(Figure17)

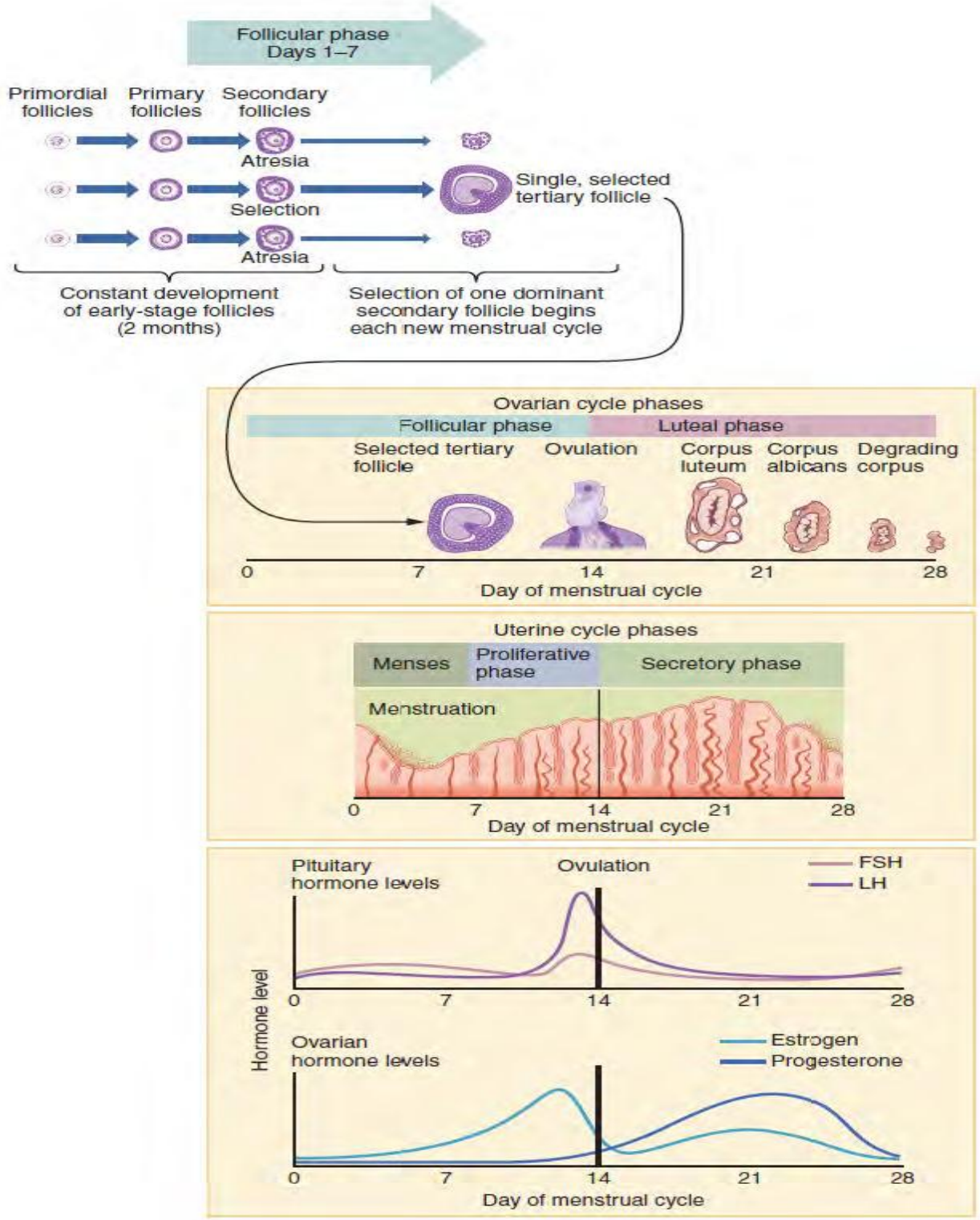


Figure 17 Hormone Levels in Ovarian and Menstrual Cycles The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by theLH surge.

MAPPING HUMAN HISTORY WITH MITOCHONDRIAL DNA

When we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from our father, and half from our mother.

However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. She received her mtDNA from her mother, who got it from her mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one woman who lived in Africa about 200,000 years ago. Scientists have given this woman the biblical name Eve, although she is not, of course, the first *Homo sapiens* female. More precisely, she is our most recent common ancestor through matrilineal descent.

This doesn't mean that everyone's mtDNA today looks exactly like that of our ancestral Eve. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different " branches" off of the "main trunk" of our mtDNA family tree. Your mtDNA might have a pattern of mutations that aligns more closely with one branch, and your neighbor's may align with another branch. Still, all branches eventually lead back to Eve.

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 the cycle’s rhythm.

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

PUBERTY AND MENARCHE

Puberty means the onset of adult sexual life, and menarche means the beginning of the cycle of menstruation. The period of puberty is caused by a gradual increase in gonadotropic hormone secretion by the pituitary, beginning in about the eighth year of life, 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 they are appropriately stimulated. However, as is also true in the male, and for reasons that are not understood, the hypothalamus does not secrete significant quantities of GnRH during childhood. Experiments have shown that the hypothalamus is capable of secreting this hormone, but the appropriate signal from some other area of the brain to cause 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.

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, 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, 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, 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. 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. Daily administration of estrogen in small quantities usually reverses the symptoms, and by gradually decreasing the dose, postmenopausal women can likely avoid severe symptoms.

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

Female Fertility

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

Rhythm Method of Contraception. One commonly practiced method of contraception is to avoid intercourse near the time of ovulation. The difficulty with this method of contraception is predicting the exact time of ovulation. Yet, the interval from ovulation until the next succeeding

onset of menstruation is almost always between 13 and 15 days. Therefore, if the menstrual cycle is regular, with an exact periodicity of 28 days, ovulation usually occurs within 1 day of the 14th day of the cycle. If, in contrast, the periodicity of the cycle is 40 days, ovulation usually occurs within 1 day of the 26th day of the cycle. Finally, if the periodicity of the cycle is 21 days, ovulation usually occurs within 1 day of the seventh day of the cycle. Therefore, it is usually stated that avoidance of intercourse for 4 days before the calculated day of ovulation and 3 days afterward prevents conception. However, such a method of contraception can be used only when the periodicity of the menstrual cycle is regular. The failure rate of this method of contraception, resulting in an unintentional pregnancy, may be as high as 20 to 25 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.

It is not fully understood why administration of estrogen or progesterone prevents the preovulatory surge of LH secretion. However, experimental work has suggested that immediately before the surge occurs, a sudden depression of estrogen secretion by the ovarian follicles probably occurs, which might be the necessary signal that causes the subsequent feedback effect on the anterior pituitary that leads to the LH surge. The administration of sex hormones (estrogens or progesterone) could

prevent the initial ovarian hormonal depression that might be the initiating signal for ovulation.

The challenge in devising methods for the hormonal suppression of ovulation has been in developing appropriate combinations of estrogens and progestins that suppress ovulation but do not cause other, unwanted effects. For 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.

AGING AND FEMALE REPRODUCTIVE SYSTEM:

Female fertility (the ability to conceive) peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman's forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause. As a woman reaches the age of menopause, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is

primarily the lack of estrogens that leads to the symptoms of menopause. The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a women's cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe. After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in women as in men, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many women find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures. Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women's Health

Initiative began a study to observe women for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when women first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that women on HT have regular pelvic and breast exams.

The Breasts:

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented **areola** (Figure 18), whose coloration may deepen during pregnancy. The areola is typically circular

and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the **mammary glands**, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 **lactiferous ducts** that open on the surface of the nipple. These lactiferous ducts each extend to a **lactiferous sinus** that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli** (see Figure 18). The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called **suspensory ligaments** that connect the breast tissue to the dermis of the overlying skin.

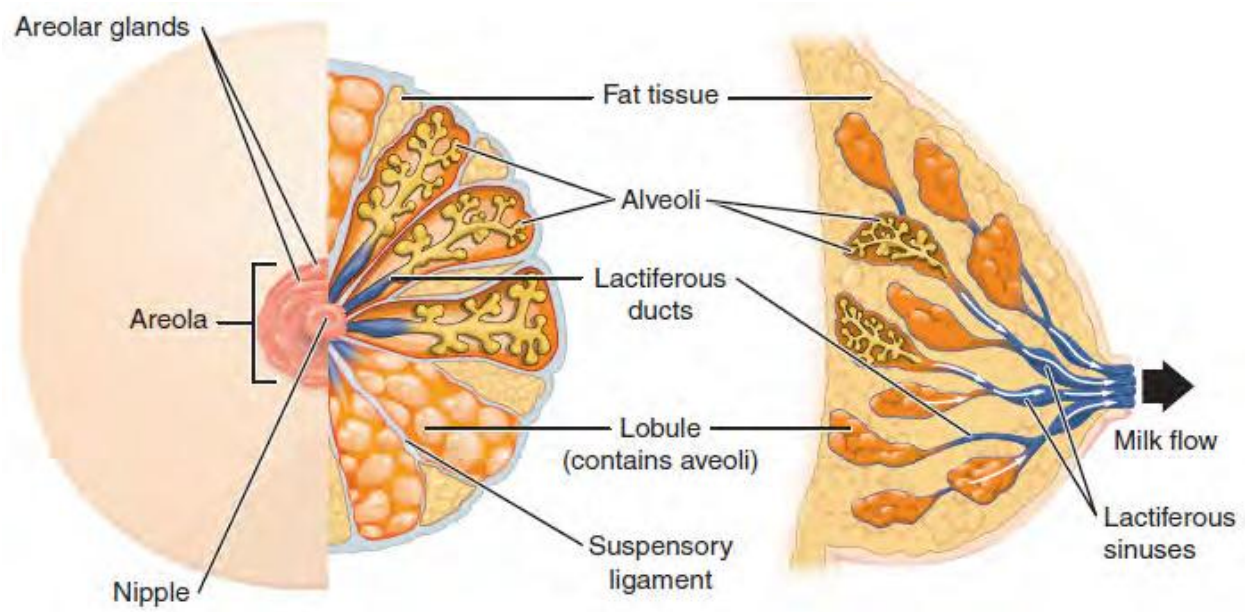


Figure 18 Anatomy of the Breast During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple.

During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones leads to further development of the mammary tissue and enlargement of the breasts.

CHAPTER 4: DISORDERS OF MALE REPRODUCTIVE SYSTEM

Benign prostatic hyperplasia (BPH)

The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of men have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Another common disorder involving the prostate is prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the *second most common cancer in men*. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the *lungs and brain*. There is no link between BPH and prostate cancer, but the symptoms are similar.

Hypogonadism in the Male

When the testes of a male fetus are nonfunctional during fetal life, none of the male sexual characteristics develop in the fetus. Instead, female organs are formed. The reason for this is that the basic genetic characteristic of the fetus, whether male or female, is to form female sexual organs if there are no sex hormones. However, in the presence of testosterone, formation of female sexual organs is suppressed and male organs are induced instead. When a boy loses his testes before puberty, a state of eunuchism ensues in which he continues to have infantile sex organs and other infantile sexual characteristics throughout life. The height of an adult eunuch is slightly greater than that of a normal man because the bone epiphyses are slow to unite, although the bones are quite thin and the muscles are considerably weaker than those of a normal man. The voice is childlike, there is no loss of hair on the head, and the normal adult masculine hair distribution on the face and elsewhere does not occur.

When a man is castrated after puberty, some of his male secondary sexual characteristics revert to those of a child and others remain of adult masculine character. The sexual organs regress slightly in size but not to a childlike state, and the voice regresses from the bass quality only slightly.

However, there is loss of masculine hair production, loss of the thick masculine bones, and loss of the musculature of the virile male.

Also in a castrated adult male, sexual desires are decreased but not lost, provided sexual activities have been practiced previously. Erection can still occur as before, although with less ease, but it is rare that ejaculation can take place, primarily because the semen-forming organs

degenerate and there has been a loss of the testosterone driven psychic desire.

Some instances of hypogonadism are caused by a genetic inability of the hypothalamus to secrete normal amounts of GnRH. This condition is often associated with a simultaneous abnormality of the feeding center of the hypothalamus, causing the person to greatly overeat. Consequently, obesity occurs along with eunuchism. The condition is called adiposogenital syndrome, Fröhlich's syndrome, or hypothalamic eunuchism.

Testicular Tumors and Hypergonadism in the Male

Interstitial Leydig cell tumors develop in rare instances in the testes. These tumors sometimes produce as much as 100 times the normal quantities of testosterone. When such tumors develop in young children, they cause rapid growth of the musculature and bones but also early uniting of the epiphyses, so that the eventual adult height is actually considerably less than that which would have been achieved otherwise. Such interstitial cell tumors also cause excessive development of the male sexual organs, all skeletal muscles, and other male sexual characteristics. In the adult male, small interstitial cell tumors are difficult to diagnose because masculine features are already present. Much more common than interstitial Leydig cell tumors are tumors of the germinal epithelium. Because germinal cells are capable of differentiating into almost any type of cell, many of these tumors contain multiple tissues, such as placental tissue, hair, teeth, bone, skin, and so forth,all found together in the same tumorous mass called a teratoma. These tumors often secrete few hormones, but if a significant quantity of placental tissue develops in the tumor, it may secrete large quantities of hCG with functions similar to those of LH. Also, estrogenic hormones are

sometimes secreted by these tumors and cause the condition called gynecomastia (overgrowth of the breasts).

Erectile Dysfunction in the Male

Erectile dysfunction, also called “impotence,” is characterizedby an inability of the man to develop or maintain an erection of sufficient rigidity for satisfactory sexual intercourse.

Neurological problems, such as trauma to the parasympathetic nerves from prostate surgery, deficient levels of testosterone, and some drugs (e.g., nicotine, alcohol, and antidepressants) can also contribute to erectile dysfunction.

In men older than 40 years, erectile dysfunction is most often caused by underlying vascular disease. As discussed previously, adequate blood flow and nitric oxide formation are essential for penile erection. Vascular disease, which can occur as a result of uncontrolled hypertension, diabetes, and atherosclerosis, reduces the ability of the body’s blood vessels, including those in the penis, to dilate. Part of this impaired vasodilation is due to decreased release of nitric oxide.

Erectile dysfunction caused by vascular disease can often be successfully treated with phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil (Viagra), vardenafil(Levitra), or tadalafil (Cialis). These drugs increase cyclic GMP levels in the erectile tissue by inhibiting the enzyme phosphodiesterase-5, which rapidly degrades cyclic GMP.

Thus, by inhibiting the degradation of cyclic GMP, the PDE-5 inhibitors enhance and prolong the effect of cyclic GMP to cause erection.

CHAPTER 5 : DISORDERS OF FEMALE REPRODUCTIVE SYSTEM

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 failure can result from hyposecretion of gonadotropic hormones, in which case the intensity of the hormonal stimuli is simply insufficient to cause ovulation, or it can result from abnormal ovaries that do not allow ovulation. For 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 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 that is extracted from the human placenta. This hormone, although secreted by the placenta, has almost the same effects as LH and is therefore a powerful stimulator of ovulation. However, excess use of this hormone can cause ovulation from many follicles simultaneously, which results in multiple births, an effect that has caused as many as eight babies (stillborn in many cases) to be born to mothers treated for infertility with this hormone.

One of the most common causes of female sterility is endometriosis, a common condition in which endometrial tissue almost identical to that of the normal uterine endometrium grows and even menstruates in the pelvic cavity surrounding the uterus, fallopian tubes, and ovaries. Endometriosis causes fibrosis throughout the pelvis, and this fibrosis sometimes so enshrouds the ovaries that anovum cannot be released into the abdominal cavity. Often, endometriosis occludes the fallopian tubes, either at the fimbriated ends or elsewhere along their extent. Another common cause of female infertility is salpingitis, that is, inflammation of the fallopian tubes; this inflammation causes fibrosis in the tubes, thereby occluding them. In the past, such inflammation occurred mainly as a result of gonococcal infection. However, with modern therapy, salpingitis is becoming a less prevalent cause of female infertility.

Still another cause of infertility is secretion of abnormal mucus by the uterine cervix. Ordinarily, at the time of ovulation, the hormonal environment of estrogen causes 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, such as low-grade infection or inflammation, or abnormal hormonal stimulation of the cervix, can lead to a viscous mucous plug that prevents fertilization.

Cervical cancer:

Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with human papillomavirus (HPV). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell’s metabolic machinery and produce more virus particles. HPV infections are common in both men and women. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These women ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among women aged 20 to 24 years, the age group with the highest infection rate.

HPV strains are classified as high or low risk according to their potential to cause cancer. Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the male or female human host to develop genital warts. Often, the body is able to clear an HPV infection by normal immune responses within 2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the cervix (Figure 19). Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked

to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes. Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

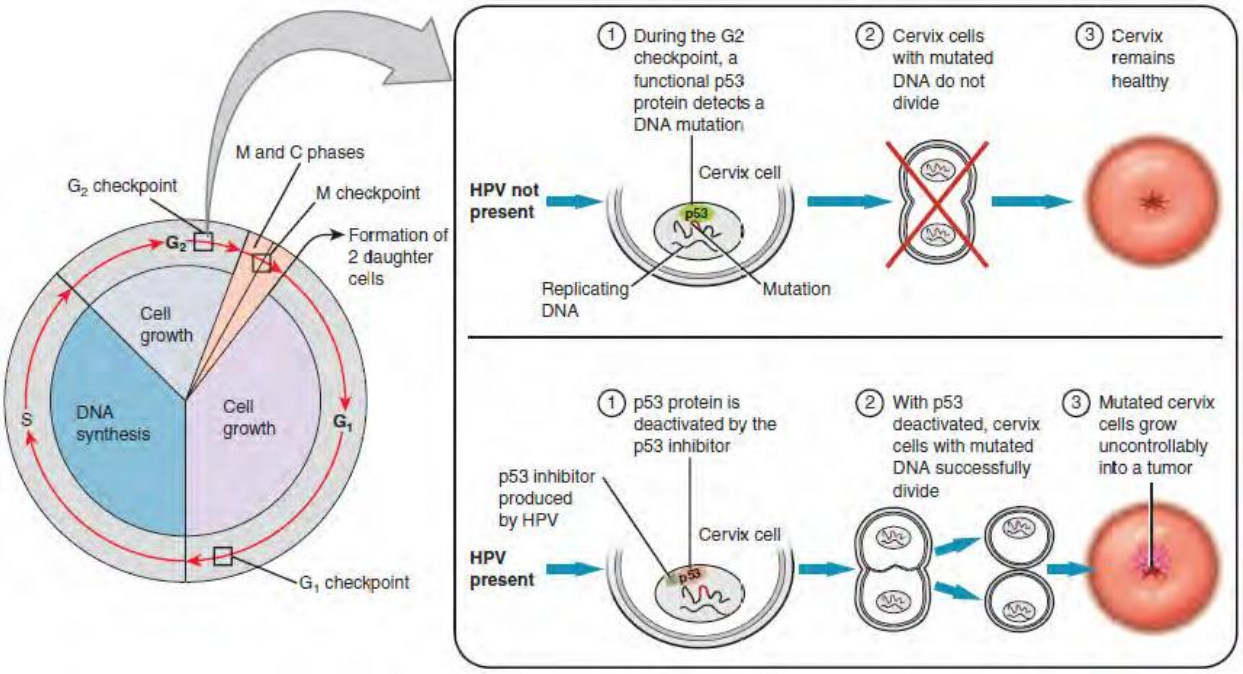


Figure 19 Development of Cervical Cancer In most cases, cells infected with the HPV virus heal on their
own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates apoptosis. Both of these processes prevent the accumulation of

mutations in a cell's genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, women in developing countries often do not have access to regular pap smears. As a result, these women account for as many as 80 percent of the cases of cervical cancer worldwide.

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: GardasilR and CervarixR. Whereas these vaccines were initially only targeted for women, because HPV is sexually transmitted, both men and women require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many women worldwide

Menstrual Disorders

Types of Menstrual Disorders

These include:

- **Abnormal uterine bleeding (AUB),** which may include heavy menstrual bleeding, no menstrual bleeding (amenorrhea) or bleeding between periods (irregular menstrual bleeding)
- **Dysmenorrhea** (painful menstrual periods)
- **Premenstrual syndrome (PMS)**
- **Premenstrual dysphonic disorder (PMDD)**

A brief discussion of menstrual disorders follows below.

Heavy menstrual bleeding:

One in five women bleeds so heavily during their periods that they have to put their normal lives on hold just to deal with the heavy blood flow.

Bleeding is considered heavy if it interferes with normal activities. Blood loss during a normal menstrual period is about 5 tablespoons, heavy menstrual bleeding, bleed as much as 10 to 25 times that amount each month. By changing a tampon or pad every hour, for example, instead of three or four times a day.

Heavy menstrual bleeding can be common at various stages of your life —during teen years when female first begin to menstruate and in your late 40s or early 50s, as she get closer to menopause.

Any vaginal bleeding after menopause isn't normal and should be evaluated immediately by a health care professional.

Heavy menstrual bleeding can be caused by: Hormonal imbalances ,Structural abnormalities in the uterus, such as polyps or fibroids

,Medical conditions For example, many women with heavy menstrual bleeding don't ovulate regularly. Ovulation, when one of the ovaries releases an egg, occurs around day 14 in a normal menstrual cycle. Changes in hormone levels help trigger ovulation.

Certain medical conditions can cause heavy menstrual bleeding. These include:

- thyroid problems
- blood clotting disorders such as Von Willebrand's disease, a mild-to-moderate bleeding disorder
- idiopathic thrombocytopenic purpura (ITP), a bleeding disorder characterized by too few platelets in the blood
- liver or kidney disease
- leukemia
- medications, such as anticoagulant drugs such as Plavix (clopidogrel) or heparin and some synthetic hormones.

Other gynecologic conditions that may be responsible for heavy bleeding include:

- complications from an IUD
- fibroids
- miscarriage
- ectopic pregnancy, which occurs when a fertilized egg begins to grow outside your uterus, typically in your fallopian tubes
- infections
- precancerous conditions of the uterine lining cells

Amenorrhea

Females may also have experienced the opposite problem of heavy menstrual bleeding—no menstrual periods at all. This condition, called amenorrhea, or the absence of menstruation, is normal before puberty, after menopause and during pregnancy.

There are two kinds of amenorrhea: primary and secondary.

- **Primary amenorrhea** is diagnosed if female turns 16 and haven't menstruated. It's usually caused by some problem in her endocrine system, which regulates hormones. Sometimes this results from low body weight associated with eating disorders, excessive exercise or medications. This medical condition can be caused by a number of other things, such as a problem with ovaries or the hypothalamus or genetic abnormalities. Delayed maturing of your pituitary gland is the most common reason
- **Secondary amenorrhea** is diagnosed in regular periods, but they suddenly stop for three months or longer. It can be caused by problems that affect estrogen levels, including stress, weight loss, exercise or illness.

Additionally, problems affecting the pituitary gland (such as elevated levels of the hormone prolactin) or thyroid (including hyperthyroidism or hypothyroidism) may cause secondary amenorrhea. This condition can also occur if you've had an ovarian cyst or had your ovaries surgically removed.

Severe menstrual cramps (dysmenorrhea):

Most women have experienced menstrual cramps before or during their period at some point in their lives. For some, it's part of the regular monthly routine. But if cramps are especially painful and persistent, this is called dysmenorrhea.

Pain from menstrual cramps is caused by uterine contractions, triggered by prostaglandins, hormone-like substances that are produced by the uterine lining cells and circulate in bloodstream. severe menstrual pain, also associated with some diarrhea or an occasional feeling of faintness where you suddenly become pale and sweaty. That's because prostaglandins speed up contractions in your intestines, resulting in diarrhea, and lower your blood pressure by relaxing blood vessels, leading to lightheadedness.

Premenstrual syndrome (PMS)

PMS is a term commonly used to describe a wide variety of physical and psychological symptoms associated with the menstrual cycle. About 30 to 40 percent of women experience symptoms severe enough to disrupt their lifestyles. PMS symptoms are more severe and disruptive than the typical mild premenstrual symptoms that as many as 75 percent of all women experience.

There are more than 150 documented symptoms of PMS, the most common of which is depression. Symptoms typically develop about five to seven days before menstruation and disappear once your period begins or soon after.

Physical symptoms associated with PMS include:

- bloating
- swollen, painful breasts
- fatigue
- constipation
- headaches
- clumsiness

Emotional symptoms associated with PMS include:

- anger
- anxiety or confusion
- mood swings and tension
- crying and depression
- inability to concentrate

PMS appears to be caused by rising and falling levels of the hormones estrogen and progesterone, which may influence brain chemicals, including serotonin, a substance that has a strong effect on mood. It's not clear why some women develop PMS or PMDD and others do not, but researchers suspect that some women are more sensitive than others to changes in hormone levels.

PMS differs from other menstrual cycle symptoms because symptoms:

- tend to increase in severity as the cycle progresses
- are relieved when menstrual flow begins or shortly after
- are present for at least three consecutive menstrual cycles

Symptoms of PMS may increase in severity following each pregnancy and may worsen with age until they stop at menopause. Women with this condition often have a sister or mother who also suffers from PMS, suggesting a genetic component exists for the disorder.

Premenstrual Dysphoric Disorder (PMDD)

Premenstrual dysphoric disorder is far more severe than the typical PMS. Women who experience PMDD (about 3 to 8 percent of all women) say it significantly interferes with their lives. Experts equate the difference between PMS and PMDD to the difference between a mild tension headache and a migraine.

The most common symptoms of PMDD are heightened irritability, anxiety and mood swings. Women who have a history of major depression, postpartum depression or mood disorders are at higher risk for PMDD than other women. Although some symptoms of PMDD and major depression overlap, they are different:

- PMDD-related symptoms (both emotional and physical) are cyclical. When a woman starts her period, the symptoms subside within a few days.

- Depression-related symptoms, however, are not associated with the menstrual cycle. Without treatment, depressive mood disorders can persist for weeks, months or years.

Diagnosis

To help diagnose menstrual disorders, female prepare keep a record of the frequency and duration of her menstruation. Also jot down any additional symptoms, such as cramping, and be prepared to discuss health history. Here is how your health care professional will help specifically diagnose abnormal uterine bleeding, dysmenorrhea, PMS and PMDD.

Heavy menstrual bleeding

To diagnose heavy menstrual bleeding—also called menorrhagia—The examination involves a series of tests. These may include:

- **Ultrasound**. High-frequency sound waves are reflected off pelvic structures to provide an image.
- **Endometrial biopsy**. A scraping method is used to remove some tissue from the lining of uterus. The tissue is analyzed under a microscope to identify any possible problem, including cancer.
- **Hysteroscopy**. In this diagnostic procedure, health care professional looks into uterine cavity through a miniature telescope-like instrument called a hysteroscope. Local, or sometimes general, anesthesia is used, and the procedure can be performed in the hospital or in a d2octor's office.
- **Dilation and curettage (D&C)**. During a D&C, your cervix is dilated and instruments are used to scrape away uterine lining. A D&C may also be used as a treatment for excessive bleeding and for bleeding that doesn't respond to other treatments. It is performed on an outpatient basis under local anesthesia.

Polycystic ovaries syndrome

It is a problem in which a woman's hormones are out of balance. It can cause problems with your periods and make it difficult to get pregnant. PCOS also may cause unwanted changes in the way you look. If it isn't treated, over time it can lead to serious health problems, such as diabetes and heart disease.

Most women with PCOS grow many small cysts on their ovaries. That is why it is called polycystic ovary syndrome. The cysts are not harmful but lead to hormone imbalances.

Early diagnosis and treatment can help control the symptoms and prevent long-term problems.

The cause of polycystic ovary syndrome (PCOS) is not fully understood, but genetics may be a factor.

WHAT IS POLYCYSTIC OVARIAN SYNDROME?

Polycystic ovarian syndrome (PCOS) is a condition in which a woman’s levels of the sex hormones estrogen and progesterone are out of balance. This leads to the growth of ovarian cysts (benign masses on the ovaries). PCOS can affect a woman’s menstrual cycle, fertility, cardiac function, and appearance.

According to the U.S. Department of Health and Human Services, between 1 in 10 and 1 in 20 women of childbearing age has PCOS. The condition currently affects up to 5 million women in the United States.

WHAT CAUSES PCOS?

While the exact cause of PCOS is unknown, doctors believe that hormonal imbalances and genetics play a role. Women are more likely to develop PCOS if their mother or sister also has the condition.

Overproduction of the hormone androgen may be another contributing factor. Androgen is a male sex hormone that women's bodies also produce. Women with PCOS often produce higher-than-normal levels of androgen. This can affect the development and release of eggs during ovulation. Excess insulin(a hormone that helps convert sugars and starches into energy) may cause high androgen levels.

SYMPTOMS OF PCOS

Symptoms of PCOS typically start soon after a woman begins to menstruate for the first time. The type and severity of symptoms varies from person to person. The most common characteristic of PCOS is irregular menstrual periods. Difficulty getting pregnant may be another reason that leads to diagnosis.

Because PCOS is marked by a decrease in female sex hormones, this condition may cause women to develop certain masculine characteristics, such as:

- excess hair on the face, chest, stomach, thumbs, or toes
- decrease in breast size
- deeper voice
- hair loss

Other symptoms may include:

acne / weight gain / pelvic pain / depression / infertility

While not symptoms of the disease, many women with PCOS have other concurrent health problems, such as diabetes, hypertension, and high cholesterol. These are linked to the weight gain typical in women with PCOS.

HOW IS PCOS DIAGNOSED?

There is no definitive test for PCOS. To make a diagnosis, your doctor will review your medical history and symptoms and perform tests to rule out other possible conditions. Doctor will perform a physical and pelvic examination to look for signs of PCOS, such as swollen ovaries or a swollen clitoris.

Blood tests to measure sex hormone levels are typically ordered, as well as:

- thyroid function tests to determine how much of the thyroid hormone your body produces
- fasting glucose tests to measure your blood sugar levels
- lipid level tests to assess the amount of cholesterol in your blood

A vaginal ultrasound allows your gynecologist to create real-time images of your reproductive organs. A pelvic laparoscopy is a surgical procedure in which a doctor makes a small incision in your abdomen and inserts a tiny camera to check for growths on your ovaries. If growths are present, your doctor may take a small tissue sample (biopsy) for further examination.

HOW IS PCOS TREATED?

PCOS can be treated, but there's no cure. Treatment focuses on controlling symptoms and managing the condition to prevent complications. The treatment will vary from woman to woman, depending on specific symptoms. Tips for controlling symptoms may include:

- **Eat a healthy diet.** A healthy diet and regular exercise are recommended for all women with PCOS, particularly those who are overweight. This can help to regulate your menstrual cycle and lower your blood glucose levels.
- **Take birth control pills when not planning to become pregnant.** Women who don't want to become pregnant may be prescribed birth control pills. These can help treat acne, regulate the menstrual cycle, and lower levels of male hormones, such as testosterone, in the body. If a woman with PCOS is infertile, fertility drugs may be prescribed to aid in ovulation.
- **Other medications that may help .** Anti-androgens are drugs that reduce male hormone levels. These can help stop excess hair growth and reduce acne. Diabetes medications may also be prescribed to lower blood glucose and testosterone levels

Sexually Transmitted Diseases

a. ETIOLOGY

i. Transmission of 20-24 organisms is possible through sexual contact between humans including:

b. • • Vaginal intercourse • • Oral-genital intercourse

c. • • Anal intercourse • • Oral-anal intercourse

i. Common sites of infection include:

d. • • Genitals

e. • • Urinary tract

f. • • Pharynx

g. • • Rectum

h. • • Perineum

i. • • Eyes (children and adults)

j. • • Systemic

i. Risk Factors

k. • • Sexually active < 25 years

l. • • Multiple sexual partners within the previous 6 months

m. • • Previous history of STD

n. • • Prostitutes, homosexuals, and drug abusers

o. • • Persons having sexual contact with prostitutes, homosexuals, and drug abusers

p. • • Inmates of detention centers

i. Higher Risk

q. • • Young: two-thirds of all STD's occur in people in their teens and twenties

r. • • Single > separated > divorced > married

s. ・・ Male vs Female: rates are now thought to be similar due to higher number of asymptomatic

t. infections in females

u. ・・ Number of sexual partners (more is not always better)

i. Appropriate Care

v. ・・ History

w. ・・ Behavioral risk assessment

x. ・・ Physical exam

y. ・・ Laboratory exam

z. ・・ Diagnosis

aa. ・・ Curative or palliative therapy

bb. ・・ Counseling and education

cc. Present episode of STD

dd. Prevention of future episodes

ee. ・・ Reporting of case when required

ff. ・・ Sexual partner identification, notification, evaluation

DISEASE BY PATHOGEN and disease Associated Pathogen

Bacterial

Gonorrhea: *Neisseria gonorrhoeae* Syphilis: Treponema pallidum

Chancroid: Hemophilus ducreyi Enteric disease: Gardnerella vaginalis Bacterial vaginosis : Mycoplasma hominis

Chlamydial

Nongonococcal urethritis: Chlamydia trachomatis

Lymphogranuloma venereum: *Chlamydia trachomatis*, type L

Viral

Herpes genitalis: Herpes simplex virus, types I and II

Hepatitis B: Hepatitis B virus Condylomata acuminate: Human papillomavirus

Protozoal

Trichomoniasis: Trichomonas vaginalis Amebiasis Entamoeba histolytica: Giardiasis: Giardia lamblia

Fungal

Vaginal candidiasis *Candida albicans*

Parasitic

Scabies: Sarcoptes scabiei Pediculosis pubis: Phthirus pubis

GONORRHEA

Caused by Neisseria gonorrhoeae, an intracellular gram-negative diplococcus that attaches to non-ciliated columnar epithelial cells, penetrates, and multiplies on the basement membrane. Adherence is facilitated through pili and opa proteins. Gonococcal lipopolysaccharide stimulates the production of tumor necrosis factor, which causes cell damage.

Incidence:

New cases have continued to decline over the last two decades, from 1 million in 1977 to 650,000 in 1996. However, rates remain disproportionately high among teens and ethnic minorities.

Transmission:

• Non-sexual transmission is possible but very rare

• Male risk of acquiring urethral infection

i. 20% after single exposure (vaginal intercourse)

ii. Moves to 80% after 4 exposures

• Female risk of acquiring cervical infection

i. 60-80% after single exposure

• Asymptomatic infection in males and females is an important reservoir of spread within the community

Presentation:

Gonorrhea in women can involve any portion of the genital tract, the oropharynx or become disseminated. Infection in women is often asymptomatic compared to men who are asymptomatic only 10% of the time.

• Most common site of mucosal infection is the cervix.

• Approximately 50% of infected women with cervical infection are asymptomatic

• Symptomatic infection typically manifests as vaginal pruritis and/or a mucopurulent discharge

• Gonococcal infections in men can involve any part of the genital tract, either alone or in combination with other sites. Genital infections are generally symptomatic

• Urethritis is the most common symptom in men, including copious, spontaneous, mucopurulent penile discharge and/or dysuria.

• Epididymitis (unilateral testicular pain and swelling), proctitis, and pharyngitis occur less frequently

Diagnosis:

Gram stain due to its high specificity and sensitivity is the most practical although culture for N. gonorrhoeae on Thayer-Martin agar remains the "gold standard"

Treatment:

• Adults – uncomplicated urethral, endocervical, or rectal infections
o Ceftriaxone 125mg IM once
o Cefixime 400mg PO once
o ALL must be followed by doxycycline 100mg PO twice daily for 7 days OR azithromycin 1000mg PO once
o Fluoroquinolones no longer recommended due to resistance
• Disseminated infection
o Ceftriaxone 1g IM or IV every 24 hours
o Cefotaxime 1 g IV every 8 hours
o Ciprofloxacin 500mg IV every 12 hours
o Regimen should be continued until 24-48 hours after symptoms resolve
o Then follow with cefixime 400mg PO twice daily or ciprofloxacin 500mg PO twice
daily for the remainder of 1 week.
• Meningitis and endocarditis
o Ceftriaxone 1-2 g IV every 12 hours for 10-14 days

SYPHILIS

Caused by Treponema pallidum, an anaerobic bacteria 3–8 μm in length, with acute, regular, or irregular spirals and no obvious protoplasmic structure. It is solely a human pathogen and does not naturally occur in other species. Transmission occurs by penetration of the spirochetes through mucosal membranes and abrasions on epithelial surfaces. Incubation time from exposure to development of primary lesions averages 3 weeks but can range from 10-90 days. Lesions develop at the primary site of inoculation.

A. Incidence

• Rates of syphilis in the US are at the lowest levels in 20 years with only 70,000 cases annually (50% are male homosexual). Infection levels are so low that the CDC has concluded it is possible to eliminate syphilis in the United States.

Can spread transplacentally and infect unborn child 50% of sexual contacts will be infected

B. Presentation:

The presentation of patients with syphilis is variable (the great imitator)

• Primary lesions (chancre) are painless

o 5-10% are painful

o Penetrates the intact mucosa and reaches bloodstream via lymphatics

o Usually heals in 3-6 week

o Lymphadenopathy (unilateral or bilateral) may persist for months

• Secondary syphilis presents 6-8 weeks after chancre with a skin rash. The rash may be macular, papular, pustular, or mixed.

• Late syphilis

o Seen in 1-10 years in 15% of patients

o Cardiovascular involvement occurs in 10% in 10 years

o CNS involvement occurs in 8% in 5-35 years

C. Diagnosis

• Presence of T. pallidum on dark-field microscopic exam of material from lesions

• Direct fluorescent-antibody test (DFA-TP) has greater sensitivity and specificity than darkfield

• Serologic tests are common but can be unreactive early in the disease

• Laboratory testing

o Treponemal tests: once tests are positive they remain so for life and do not correlate with activity

o Nontreponemal antibody titers (RPR) do correlate with disease activity

D. Treatment

• Primary and Secondary Syphilis

o Benzathine penicillin G 2.4 million units IM in 1 dose for adults

o Benzathine penicillin G 50,000 units/kg IM up to the adult dose in children

o Penicillin allergic

1. Doxycycline 100mg PO twice daily for 2 weeks

2. Tetracycline 500mg PO 4 times daily for 2 weeks

• Early Latent Syphilis

o Benzathine penicillin G 2.4 million units IM in 1 dose for adults

o Benzathine penicillin G 50,000 units/kg IM up to the adult dose in children

• Latent Syphilis

o Benzathine penicillin G 7.2 million units total (3 doses of 2.4 million units IM one week apart for 3 weeks)
o Benzathine penicillin G 150,000 units/kg total (3 doses of 50,000 units/kg IM one week apart for 3 weeks)
o Penicillin allergic
1. Doxycycline 100mg PO twice daily for 2 weeks
2. Tetracycline 500mg PO 4 times daily for 2 weeks
• Congenital syphilis
o 100,000 – 150,000 units/kg of aqueous penicillin G daily (50,000 units IV Q12 hours
during the first 7 days of life, then Q8 hours thereafter) for 10 days
o 50,000 units /kg procaine penicillin G in a single dose daily IM for 10 days

BACTERIAL VAGINOSIS

Caused by overgrowth of anaerobic organisms most commonly Gardnerella vaginalis and Mycoplasma hominis.

A. Incidence: The rate of occurrence depends upon the population studied: 17 to 19 percent in familyplanning or student health clinics; 24 to 37 percent in STD clinics; and 10 to 35 percent among pregnant women in the U.S. Unlike most STDs, there is a high prevalence of infection among women who have sex with women (WSW)
B. May be associated with important complications of pregnancy and with pelvic inflammatory disease.
C. Presentation: Most women are asymptomatic.

• Those with symptoms present with an unpleasant, "fishy smelling" discharge that is more noticeable after unprotected intercourse

• The discharge is off-white, thin, and homogeneous

• Dysuria and dyspareunia are rare

• Pruritus and inflammation are absent

D. Treatment:

• Recommended

o Metronidazole 500mg PO twice daily for 7 days

o Metronidazole gel 0.75% daily for 5 days

o Clindamycin cream 2% qhs for 7 days

• Alternatives

o Metronidazole 2g PO once (not as effective)

o Clindamycin 300mg PO twice daily for 7 days

o Clindamycin ovules 100mg intravaginally qhs for 3 days

• Pregnancy

o Treat symptomatic women due to association with adverse pregnancy outcomes

o Metronidazole 250mg every 8 hours for 7 days

o Clindamycin 300mg every 12 hours for 7 days

CHLAMYDIA

Caused by Chlamydia trachomatis, a small, gram-negative, obligate, intracellular bacterium not detectable by usual light microscopy. Distinct life-cycle:

• The small elementary bodies attach and penetrate into cells, changing into the metabolically active form (reticulate body) within six to eight hours post-exposure.

• The reticulate bodies then reorganize into small elementary bodies, and within two to three days the cell ruptures, releasing newly formed elementary bodies.

A. Incidence: The number of reported chlamydia cases has risen in recent years but this is mainly due to screening rather than infections. Overall the number of new cases in the US has fallen from 4 million to about 3 million a year.

B. More common than gonorrhea and a major cause of involuntary infertility

C. Risk of transmission not established but probably less than gonorrhea

D. Non-sexual transmission is possible but not established (25-30% of non-sexually active children have antibodies

E. Presentation: overlaps with gonorrhea and coexisting infection very common

• In women, cervical infection is the most common syndrome. However, more than 50% of women are asymptomatic. When symptoms occur, vaginal discharge, poorly differentiated abdominal pain, or lower abdominal pain are the most frequent.

• Women with urethral infection present with symptoms of a urinary tract infection (UTI) such as frequency and dysuria, and occasionally of lower abdominal pain.

• Approximately 30% of women with chlamydia infection will develop pelvic inflammatory disease (PID) if left untreated. While PID caused by N. gonorrhoeae infection may be more acutely symptomatic, PID due to C. trachomatis tends to be associated with higher rates of subsequent infertility.

• In men, chlamydia presents as non-gonococcal urethritis (NGU), epididymitis and proctocolitis (homosexual men). The symptoms are considered milder than the gonococcal equivelant.

F. Diagnosis: Noninvasive screening options, such as urine testing or self-collected vaginal swabs are more acceptable to patients than traditional speculum examination.

• Tissue culture is expensive (only used in cases of forensic investigation eg, rape, child abuse)

• Rapid diagnosis by monoclonal antibody techniques or nucleic acid amplification (NAAT)

• Clinical practice guidelines strongly recommend routine chlamydia screening for sexuallyactive women below the age of 25

G. Treatment:

• Azithromycin 1000mg PO once

• Doxycycline 100mg PO twice daily for 7 days

• Pregnant woman

o Erythromycin base 500mg PO four times daily for 7 days

o Erythromycin ethylsuccinate 800mg PO four times daily for 7 days

o Amoxicillin 500mg PO every 8 hours for 7 days

GENITAL HERPES

Caused by herpes simplex virus (HSV), a ubiquitous double-stranded DNA virus characterized by the following unique biological properties: neurovirulence (the capacity to invade and replicate in the nervous system), latency (the establishment and maintenance of latent infection in nerve cell ganglia), and reactivation of latent HSV induced by a variety of stimuli (eg, fever, trauma, emotional stress, sunlight, menstruation)

A. Incidence:

• HSV-2 in 70-90% of cases

• 3% (nuns) to 70% (prostitutes)

• Usually found in 20-30% of adults

B. Types I and II can cause genital ulcers

C. Presentation: The initial presentation can be severe with painful genital ulcers, dysuria, fever, tender local inguinal lymphadenopathy, and headache. In other patients, however, the infection is mild, subclinical, or entirely asymptomatic.

• Primary episodes are associated with systemic symptoms such as headache, photophobia, and malaise

• Lesions

o Typically cause pain (5-10% are painless)

o Occur 2-7 days after contact with infected secretions

o Males – seen on glans or penile shaft

o Females – seen on the vulva, perineum, buttocks, cervix and vaginal wall

o Homosexuals – perianal and anus

• Infected persons without lesions can still transmit disease

• Increased abortion in pregnancy associated with active disease and babies should be delivered via Cesarean

• Diagnosis is made on clinical presentation or chemical immunological detection with a
specific antibody or by cell culture

D. Treatment:

• First clinical episode of genital herpes:

o Acyclovir 400mg PO 3 times daily for 7-10 days or until clinical resolution

o Acyclovir 200mg PO 5 times daily for 7-10 days or until clinical resolution

o Valacyclovir 1000mg PO twice daily for 7-10 days or until clinical resolution

o Famciclovir 250mg PO 3 times daily for 7-10 days or until clinical resolution

• First clinical episode of herpes proctitis:

o Acyclovir 400mg PO 5 times daily for 10 days or until cinical resolution

o Little evidence exists that a higher dose of antivirals are needed to treat herpes
proctitis

• Recurrent episodes:

o Acyclovir 400mg PO 3 times daily for 5 days, or

o Acyclovir 200mg PO 5 times daily for 5 days, or

o Acyclovir 800mg PO twice daily for 5 days

o Famciclovir 1000mg PO twice daily for 1 day

o Valacyclovir 500mg PO twice daily for 5 days

• Daily suppressive therapy (patients with > 6 episodes per year)

o Acyclovir 400-800mg PO twice daily

o Famciclovir 500mg PO twice daily

o Valacyclovir 250mg PO twice daily, 500mg once daily or 1000mg once daily

• Severe disease:

o Acyclovir 5-10 mg/kg IV every 8 hours for 5-7 days or until clinical resolution

GENITAL WARTS

Caused by Condylomata acuminate, a human papillomavirus (HPV). HPV infects epithelial tissues of skin and mucous membranes.

A. Incidence: 5.5 million cases occur each year resulting in nearly 20 million people in the U.S. infected

B. Presentation: Clinical manifestations of infection occur as cutaneous disease or anogenital disease, and can be clinically obvious or subclinical.

C. Association with cervical dysplasia and carcinoma of the cervix

- Genotype 16 and 18 are the “high-risk” HPVs that cause most (70 percent) cervical cancers
- Genotype 6 and 11 cause most (90 percent) genital warts
- Gardasil® protects against these four genotypes

E. Treatment:

- Podofilox 0.5% solution applied twice daily for 3 days followed by 4 days no therapy. This cycle is repeated for a total of 4 cycles

• Imiquimod 5% cream applied 3 times weekly for up to 16 weeks
• Cryotherapy with liquid nitrogen (don't try this at home)

TRICHOMONIASIS

Caused by the flagellated protozoan Trichomonas vaginalis, which may be found in the vagina, urethra,

and paraurethral glands of infected women. The flagellated parasite is approximately the size of a white blood cell, although size may vary based on physical conditions. The protozoal pathogen causes direct damage to the epithelium, leading to microulcerations.

A. Incidence

a. Most common curable STD among young, sexually active woman with an estimated 5 million new cases every year in the US and 180 million cases worldwide.

b. The organism also is detected in 30-40% of men who are exposed but are usually asymptomatic

B. Patients with trichomoniasis are twice as likely to have gonorrhea as well.

C. Presentation:

a. Causes an intense inflammatory response

b. Purulent or homogenous vaginal discharge and vulvar or vaginal erythema are common

c. Colpitis macularis (strawberry cervix)

D. Treatment:

• Metronidazole 2g single dose, or

• Metronidazole 500mg PO twice daily for 7 days

a. Management of sex partners

o Sex partners should be treated

o Avoid intercourse until therapy is completed / patients are asymptomatic

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عمل فى التعليم الجامعى فى الجماهيريه الليبيه كاستاذ - ورئيس قسم علوم الحياه /كلية العلوم/جامعة الجبل الغربي / يفرن .

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وقد قام بالاشراف على عده رسائل

نبذة عن المؤلف

Professor

Dr. Ali Shalash Sultan

- حاصل على شهادة الماجستير والدكتوراه من جامعة بغداد
- عمل في التعليم الجامعي بكافة مراحله
- له العديد من البحوث المنشورة
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الطبعة الاولى

بغداد –شارع المتنبي - مطبعة العكيلي

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