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Human Reproductive Physiology

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مرحلة الدكتوراه/ علم الحيوان

الفصل الدراسي الثاني

استاذة المادة

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Reproductive Physiology **Dr. Suha Al-Jowari**

Lec. 1: General Concepts and Terminology

- The primary reproductive organs are known as the **gonads**: the **testes** in the male and the **ovaries** in the female.
- In both sexes, the gonads serve dual functions:

(1) **Gametogenesis** is the production of the reproductive cells, or **gametes**; these are **spermatozoa**, usually shortened to **sperm**) by males and **ova** by females.

(2) The gonads secrete particular steroid hormones, termed **sex hormones**; the primary sex hormones are **testosterone** in the male and **estradiol** and **progesterone** in the female.

- Testosterone belongs to a group of steroid hormones that have similar masculinizing actions and are collectively called **androgens.**
- In the male, only the testes secrete significant amounts of testosterone.
- Other circulating androgens are produced by the adrenal cortex, but they are much less potent than testosterone and are unable to maintain male reproductive function if testosterone secretion is inadequate.

- One of the adrenal androgens—**dihydroepiandrosterone, DHEA**, which is presently being sold as a dietary supplement and is touted as a miracle drug—can stop or reverse the aging process and the diseases associated with it, cure depression, strengthen the immune system, and improve athletic performance.
- DHEA is itself a weak androgen but can be converted in the body to testosterone in both men and women. Its secretion is high just before birth and again during puberty, and then falls off markedly with aging.)

- Estradiol—secreted in large amounts only by the ovaries—is one of several steroid hormones that have similar actions on the female reproductive tract and are collectively termed "**estrogens**"
- Estrogens are not unique to females, neither are androgens to males. Plasma estrogen arises in males from secretion of small amounts by the testes and from conversion of androgens to estrogen in many nongonadal tissues (adipose tissue).
- Conversely, in females androgens are secreted, in small amounts, by the ovaries and, in larger amounts, by the adrenal cortex. (Some of these androgens are then converted to estrogen in nongonadal tissues, and contribute to the plasma estrogen.)

Mechanism of steroid action

- All steroid hormones act in the same general way. They bind to intracellular receptors, and the hormone-receptor complex then binds to DNA in the nucleus, functioning as a transcription factor to alter the rate of formation of particular mRNAs.
- The result is a change in the rates of synthesis of the proteins coded for by the genes being transcribed. The resulting increase or decrease in the concentrations of these proteins in the target cells or their rates of secretion by the cells then account for the cells' responses to the hormone.

- Reproductive function is largely controlled by a chain of hormones. The first hormone in the chain is **gonadotropin releasing hormone (GnRH).**
- GnRH is a hormone secreted by neuroendocrine cells in the hypothalamus, and it reaches the anterior pituitary via the hypothalamo pituitary portal blood vessels. Accordingly, the brain is the primary regulator of the reproductive process.
- Secretion of GnRH is triggered by action potentials in GnRH-producing hypothalamic neuroendocrine cells. These action potentials occur periodically in brief bursts, with virtually no secretion in between. This pattern of GnRH secretion is important because the cells of the anterior pituitary that secrete the gonadotropins will not respond to GnRH if the plasma concentration of this hormone remains elevated over time.

- In the anterior pituitary, GnRH stimulates the release of the pituitary **gonadotropins—follicle stimulating hormone (FSH)** and **luteinizing hormone (LH).** These two protein hormones, which are produced by a single pituitary cell type, were named for their effects in the female, but their molecular structures are the same in both sexes.
- The two hormones act upon the gonads, the result being the development of sperm or ova and sex hormone secretion.
- In addition, the steroidal sex hormones exert feedback effects on the secretion of GnRH, FSH, and LH. A gonadal protein hormone, **inhibin**, also exerts feedback effects on the anterior pituitary.

Gametogenesis

- The developing gametes are termed **germ cells.** These cells undergo either mitosis or meiosis.
- The first stage in gametogenesis is proliferation of the primordial germ cells by mitosis. DNA of each nucleated human cell is contained in 23 pairs of chromosomes, giving a total of 46. The two corresponding chromosomes in each pair are homologous to each other, with one coming from each of the person's parents.
- In mitosis, all the dividing cell's 46 chromosomes are replicated, and each of the two daughter cells resulting from the division receives a full set of 46 chromosomes identical to those of the original cell.
- Thus each daughter cell receives identical genetic information.

- The timing of mitotic activity in germ cells differs greatly in females and males.
- In the female, mitosis of germ cells occurs exclusively during the embryonic development.
- In the male, some mitosis occurs in the embryo to generate the population of germ cells present at birth, but mitosis really begins at puberty and usually continues throughout life.
- The second stage of gametogenesis is **meiosis**, in which each resulting gamete receives only 23 chromosomes from a 46-chromosome germ cell, 1 chromosome from each homologous pair

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

Male Reproductive System

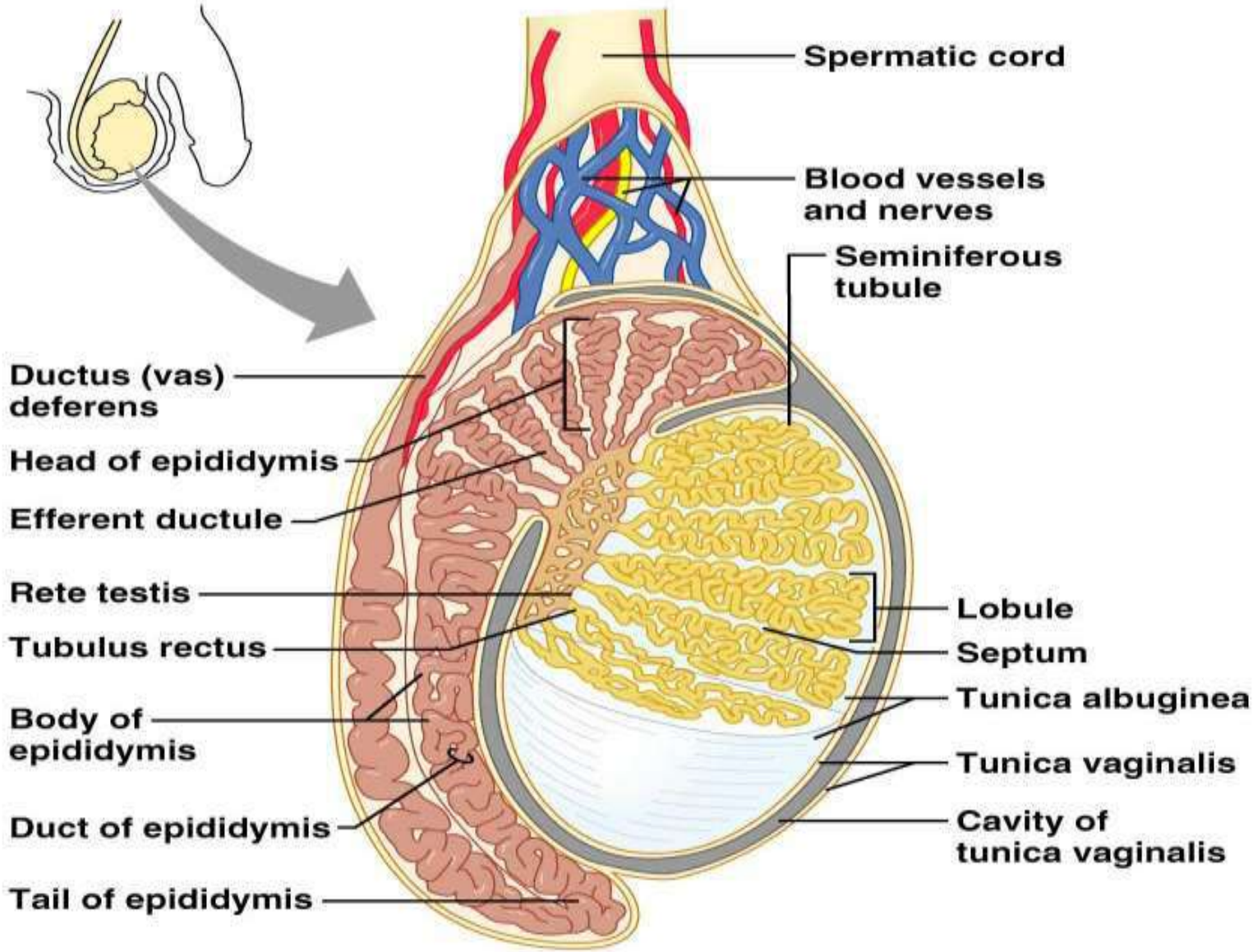
Testis : Sex organ that produces sperm in a process called **spermatogenesis** , and male sex hormones (**testosterone**).

- Developed in a male fetus near the kidneys , but during the seventh month of intrauterine development, they descend into the scrotum. which is an outpouching of the abdominal wall and is divided internally into two sacs, one for each testis.
- This descent is essential for normal sperm production during adulthood, since sperm formation requires a temperature several degrees lower than normal internal body temperature.
- Each testis contains about 250 functional units called lobules ; each lobule contains about 4 **seminiferous tubules** where spermatogenesis occurs .
- Each seminiferous tubule is bounded by a basement membrane. In the center of each tubule, is a fluid-filled lumen containing spermatozoa. The tubular wall is composed of developing germ cells and another cell type, called Sertoli cells.
- The **Leydig cells,** or interstitial cells, which lie in small connective tissue spaces *between* the tubules, are the cells that secrete testosterone.
- .

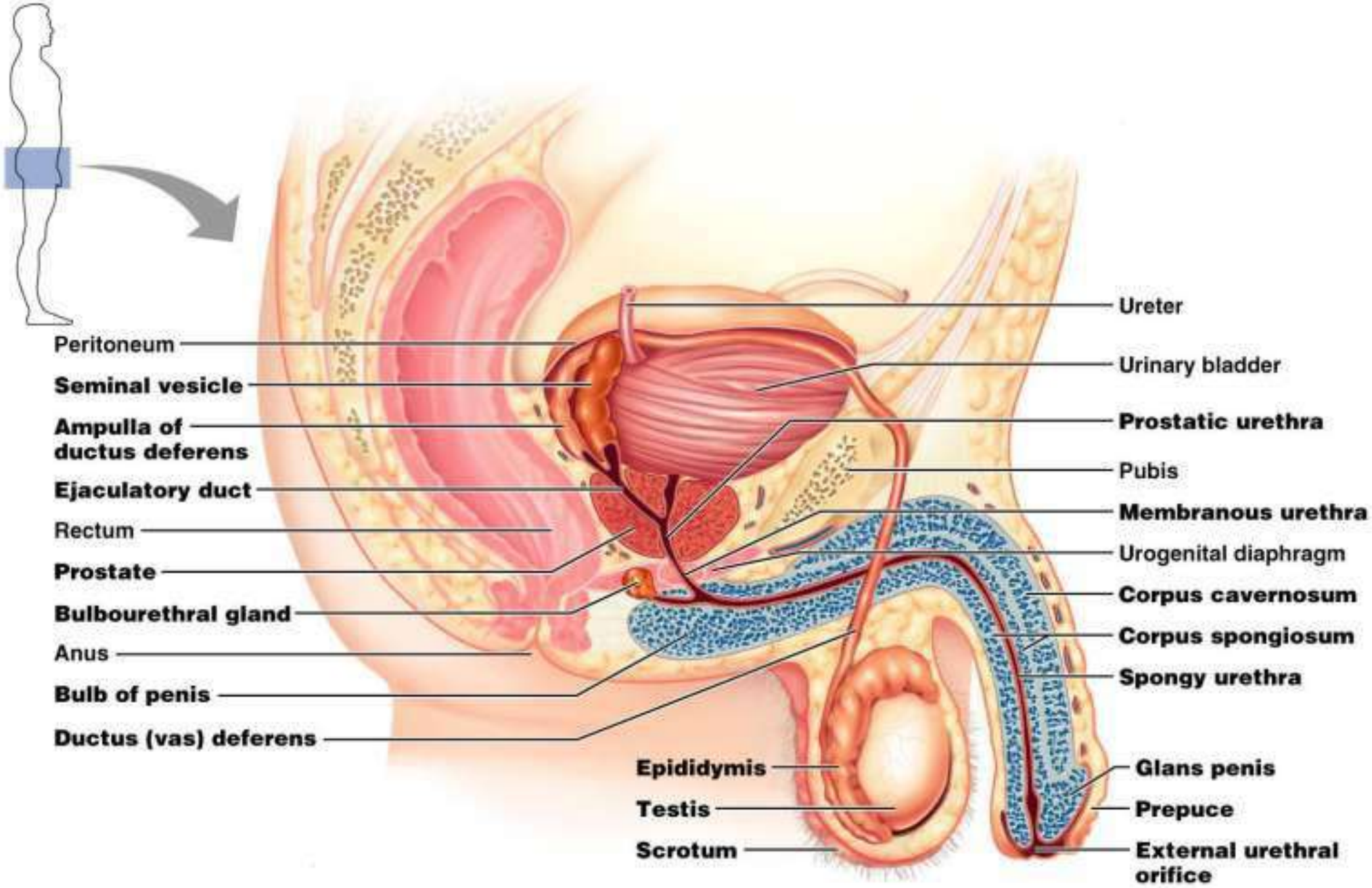
- All seminiferous tubules in a testis converge and form a channel called **rate testis.**
- Small ducts termed efferent ductules leave the rete testis, and empty into a single duct within a structure called the **epididymis.**
- The epididymis is loosely attached to the outside of the testis. The duct of the epididymis is so convoluted that, when straightened out at dissection, it measures 6 m.
- In turn, the epididymis draining each testis leads to a **vas** (or ductus) **deferens,** a large thick-walled tube lined with smooth muscle.

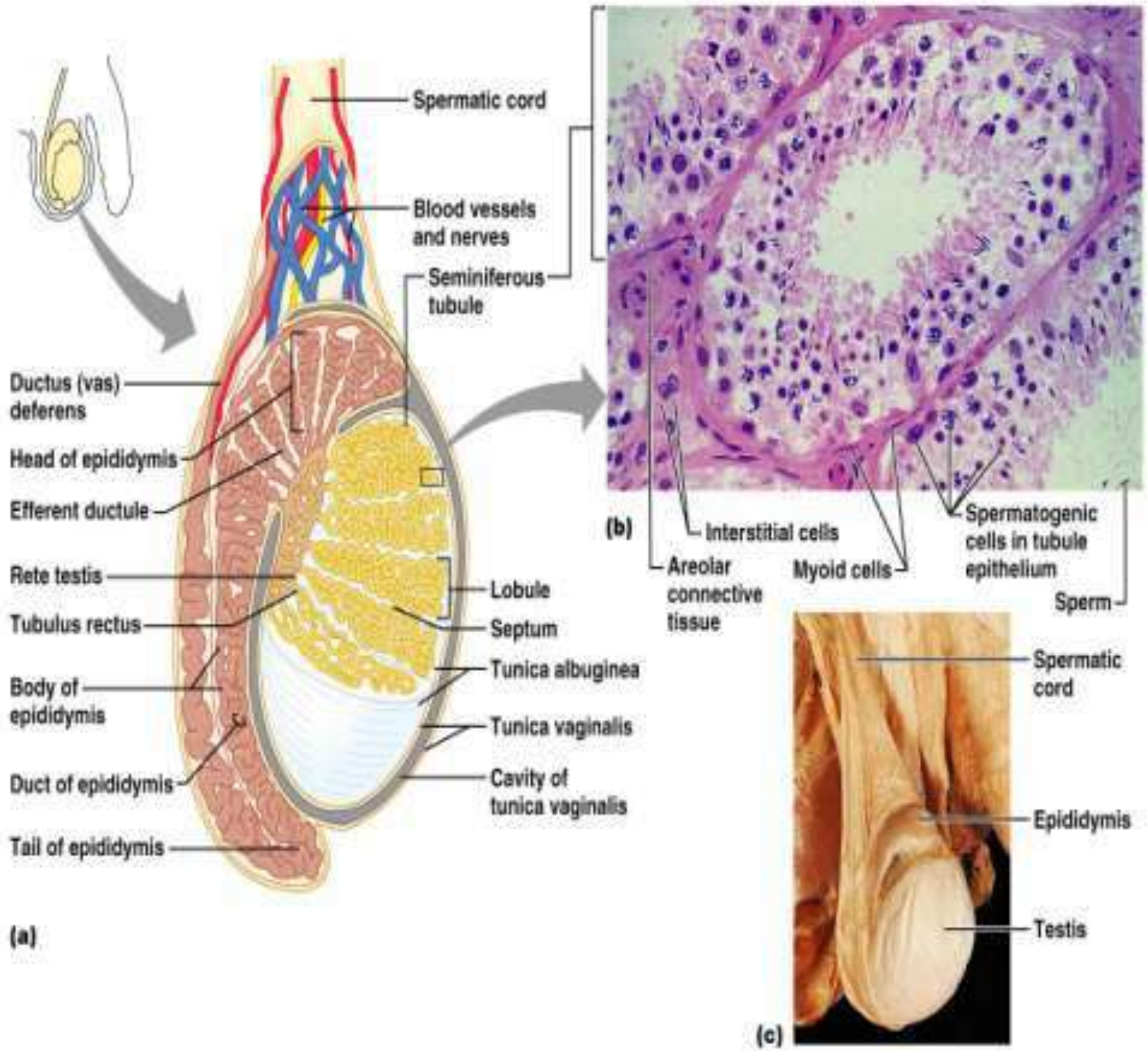
- After entering the abdomen, the two vas deferens course to the back of the urinary bladder base. The ducts from two large glands, the **seminal vesicles,** which lie behind the bladder, join the two vas deferens to form the two **ejaculatory ducts.** The ejaculatory ducts then enter the substance of the **prostate gland** and join the urethra, coming from the bladder.
- The prostate gland is a single donut-shaped gland below the bladder and surrounding the upper part of the urethra, into which it secretes fluid through hundreds of tiny openings in the side of the urethra. The urethra leaves the prostate gland to enter the penis.
- The paired **bulbourethral glands,** lying below the prostate, drain into the urethra after it leaves the prostate.

- The prostate gland and seminal vesicles secrete the bulk of the fluid in which ejaculated sperm are suspended. This fluid, plus the sperm cells, constitute **semen,** the sperm contributing only a few percent of the total volume.
- The glandular secretions contain a large number of different chemical substances, including nutrients, buffers for protecting the sperm against the acidic vaginal secretions, chemicals (particularly from the seminal vesicles) that increase sperm motility, and prostaglandins.
- The bulbourethral glands contribute a small volume of lubricating mucoid secretions



(a)



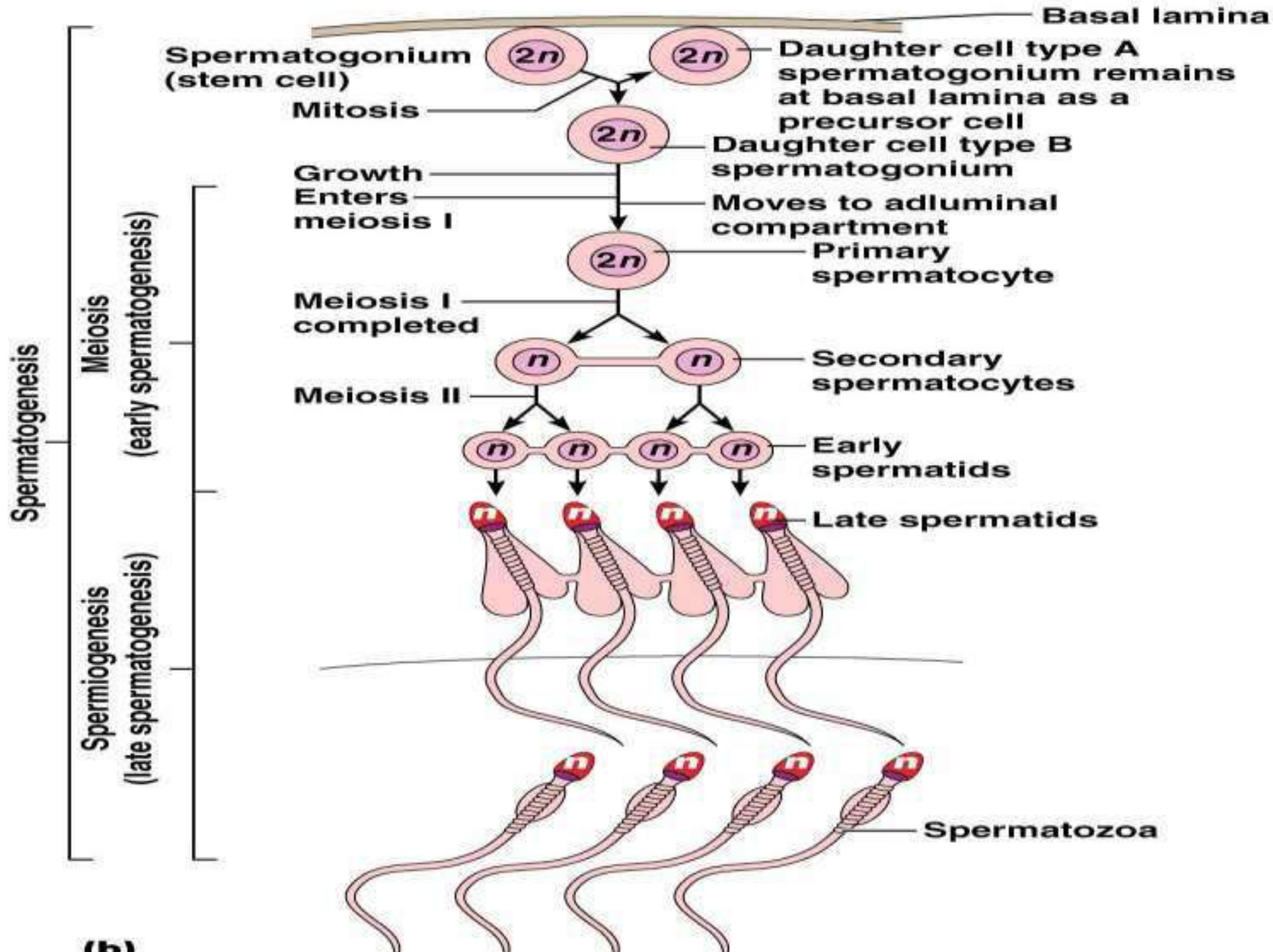

Spermatic cord
Blood vessels and nerves
Seminiferous tubule
Ductus (vas) deferens
Head of epididymis
Efferent ductule
Rete testis
Tubulus rectus
Body of epididymis
Duct of epididymis
Tail of epididymis
Lobule
Septum
Tunica albuginea
Tunica vaginalis
Cavity of tunica vaginalis
(a)
(b)
Interstitial cells
Areolar connective tissue
Myoid cells
Spermatogenic cells in tubule epithelium
Sperm
Spermatic cord
Epididymis
Testis
(c)

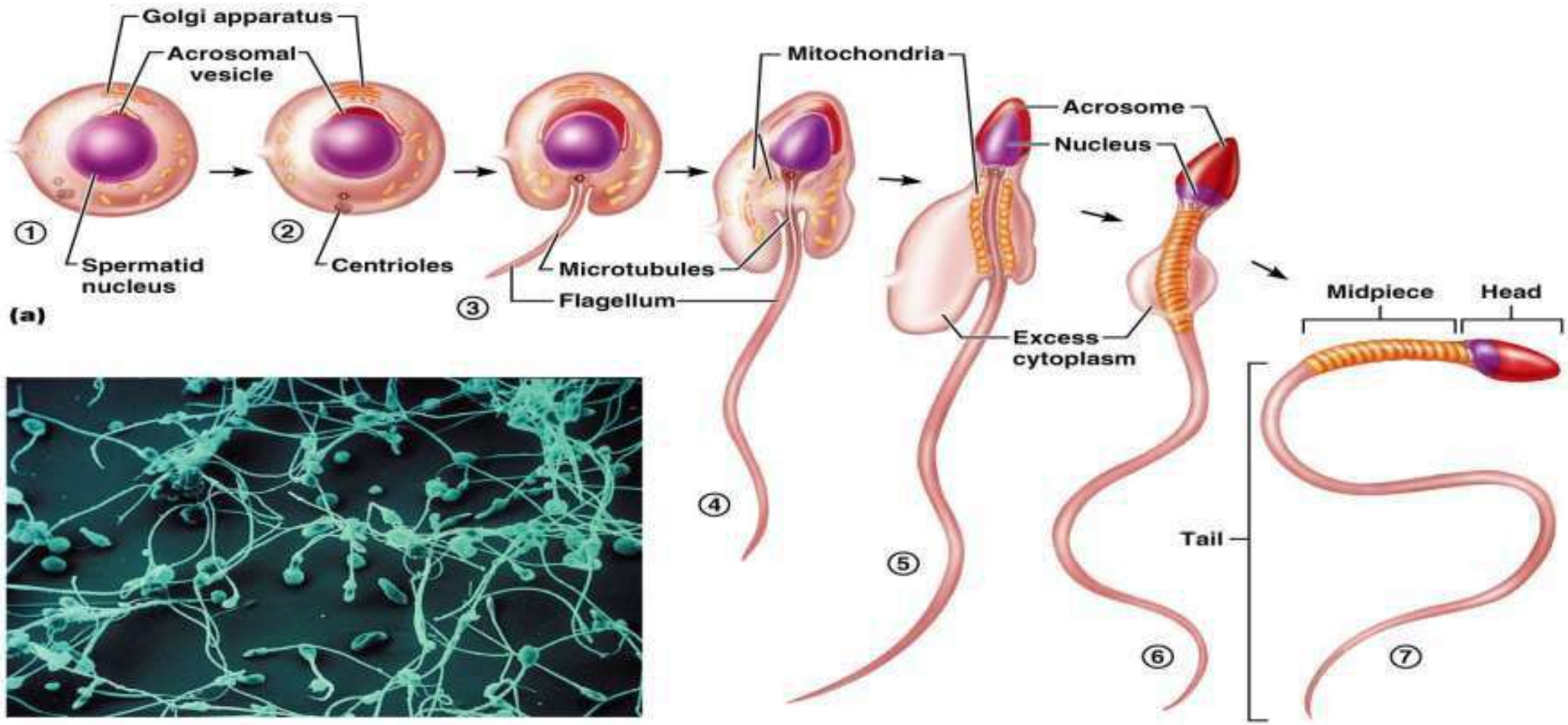
Spermatogenesis

- The undifferentiated germ cells, which are termed **spermatogonia** begin to divide mitotically at puberty. The daughter cells of this first division then divide, so that a clone of spermatogonia is produced from each original spermatogonium.
- Some differentiation occurs in addition to cell division. The cells that result from the final mitotic division and differentiation in the series are called **primary spermatocytes,** and these are the cells that will undergo the first meiotic division of spermatogenesis.

- Each primary spermatocyte increases markedly in size and undergoes the first meiotic division to form two **secondary spermatocytes,** each of which contains 23 two-chromatid chromosomes.
- Each secondary spermatocyte, in turn undergoes the second meiotic division into **spermatids.** Thus, each primary spermatocyte, containing 46 two-chromatid chromosomes, gives rise to four spermatids, each containing 23 one-chromatid chromosomes.

- The final phase of spermatogenesis is the differentiation of the **spermatids** into **spermatozoa** (sperm).
- This process involves extensive cell remodeling, including elongation, but no further cell divisions. The head of a sperm consists almost entirely of the nucleus, which contains the DNA bearing the sperm's genetic information. The tip of the nucleus is covered by the **acrosome,** a protein-filled vesicle containing several enzymes that play an important role in the sperm's penetration of the egg. Most of the tail is a flagellum that produce whiplike movements. The sperm's mitochondria form the midpiece of the sperm and provide the energy for the sperm's movement.
- The entire process of spermatogenesis, from primary spermatocyte to sperm, takes approximately 64 days. The normal human male manufactures approximately 30 million sperm per day.


Basal lamina
Spermatogonium (stem cell)
2n
2n
Daughter cell type A spermatogonium remains at basal lamina as a precursor cell
Mitosis
2n
Daughter cell type B spermatogonium
Growth
Enters meiosis I
Moves to adluminal compartment
2n
Primary spermatocyte
Meiosis I completed
n
n
Secondary spermatocytes
Meiosis II
n
n
n
n
Early spermatids
Late spermatids
Spermatozoa
Spermatogenesis
Meiosis (early spermatogenesis)
Spermiogenesis (late spermatogenesis)

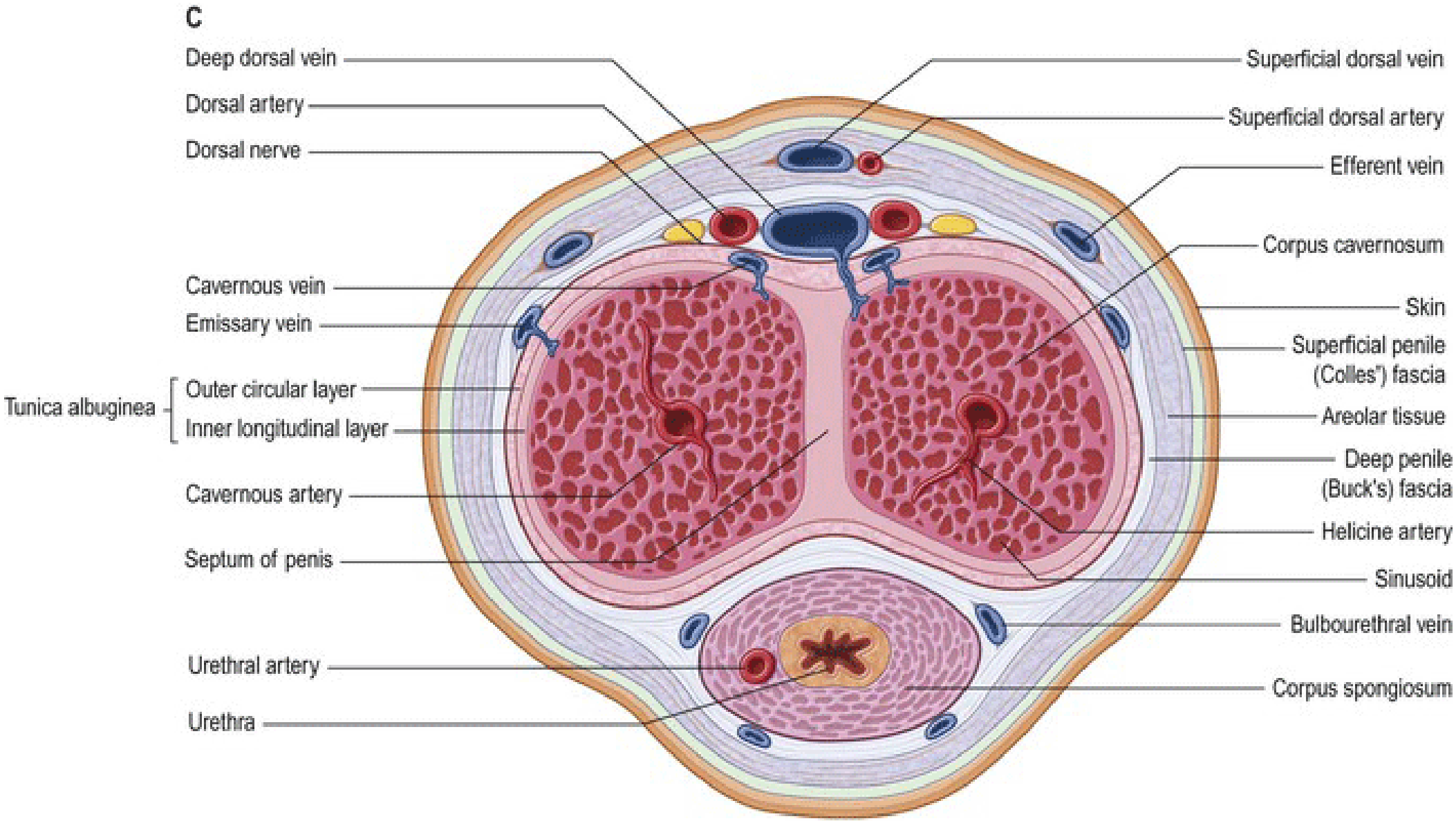


Transport of sperm

- From the **seminiferous tubules**, the sperm pass through the **rete testis** and **efferent ductules** into the **epididymis** and thence into the **vas deferens**.
- The vas deferens and the portion of the epididymis closest to it serve as a storage reservoir for sperm, holding them until sexual arousal leads to ejaculation.
- Also, in the epididymis the sperm undergo a further testosterone-dependent maturation process.
- During passage through the epididymis, there occurs a hundredfold concentration of the sperm by fluid absorption from the lumen of the epididymis. Therefore, as the sperm pass from the end of the epididymis into the vas deferens, they transport no a result of fluid movement but is due to peristaltic contractions of the smooth muscle in the epididymis and vas deferens.
- The next step in sperm transport is ejaculation, usually preceded by erection, which permits entry of the penis into the vagina.

Erection

- It is a vascular phenomenon.
- The penis consists almost entirely of three cylindrical vascular compartments running its entire length. Normally the small arteries supplying the vascular compartments are constricted so that the compartments contain little blood and the penis is flaccid.
- During sexual excitation, the small arteries dilate, the three vascular compartments become engorged with blood at high pressure, and the penis becomes rigid.
- The vascular dilation is initiated by neural input to the small arteries of the penis. Moreover, as the vascular compartments expand, the veins emptying them are passively compressed, thus contributing to the engorgement.
- This entire process occurs rapidly, complete erection sometimes taking only 5 to 10 s.


C
Deep dorsal vein
Dorsal artery
Dorsal nerve
Cavernous vein
Emissary vein
Tunica albuginea
Outer circular layer
Inner longitudinal layer
Cavernous artery
Septum of penis
Urethral artery
Urethra
Superficial dorsal vein
Superficial dorsal artery
Efferent vein
Corpus cavernosum
Skin
Superficial penile (Colles") fascia
Areolar tissue
Deep penile (Buck's) fascia
Helicine artery
Sinusoid
Bulbourethral vein
Corpus spongiosum

What are the neural inputs to the small arteries of the penis?

- At rest, the dominant input is via sympathetic neurons; they release norepinephrine, which causes the arterial smooth muscle to contract.
- During erection this sympathetic input is inhibited, but much more important is the activation of nonadrenergic, noncholinergic autonomic neurons to the arteries.
- These neurons release **nitric oxide,** which relaxes the arterial smooth muscle

Which receptors and afferent pathway initiate these reflexes?

- The primary stimulus comes from mechanoreceptors in the genital region, particularly in the head of the penis.
- The afferent fibers carrying the impulses synapse in the lower spinal cord on interneurons that control the efferent outflow.
- It must be stressed, however, that higher brain centers, via descending pathways, may also exert profound stimulatory or inhibitory effects upon the autonomic neurons to the small arteries of the penis. Thus, mechanical stimuli from areas other than the penis, as well as thoughts, emotions, sight, and odors, can induce erection in the complete absence of penile stimulation (or prevent erection though stimulation is present).

Erectile dysfunction

- Also termed impotence, the consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse.
- It is a common disorder and very much age-dependent, increasing from an incidence of 39 percent at age 40 to 67 percent at age 70.
- The organic causes are multiple and include damage to or malfunction of the efferent nerves or descending pathways, endocrine disorders, various therapeutic and “recreational” drugs (alcohol, for example), and certain diseases, particularly diabetes. Erectile dysfunction can also be due to psychological factors, which are mediated by the brain and the descending pathways.
- Recently, a drug known as ***Viagra;*** has been introduced that greatly improves the ability of a majority of men with erectile dysfunction to achieve and maintain an erection comparable to other men in their age group.

Ejaculation

- Ejaculation is the discharge of semen from the penis.
- It is also basically a spinal reflex. The afferent pathways from penile mechanoreceptors being identical to those described for erection.
- When the level of stimulation is high enough, there is a sequence of discharge of the efferent neurons.
- This sequence can be divided into two phases:

(1) The smooth muscles of the epididymis, vas deferens, ejaculatory ducts, prostate, and seminal vesicles contract as a result of sympathetic stimulation, emptying the sperm and glandular secretions into the urethra **(emission).**

(2) the semen (average volume 3 ml, containing 300 million sperm) is then expelled from the urethra by a series of rapid contractions of the urethral smooth muscle as well as the skeletal muscle at the base of the penis.

- During ejaculation, the sphincter at the base of the urinary bladder is closed so that sperm cannot enter the bladder nor can urine be expelled from it.
- Note: **erection** involves *inhibition* of sympathetic nerves (to the small arteries of the penis), **ejaculation** involves *stimulation* of sympathetic nerves (to the smooth muscles of the duct system).

Hormonal Control of Male Reproductive Functions

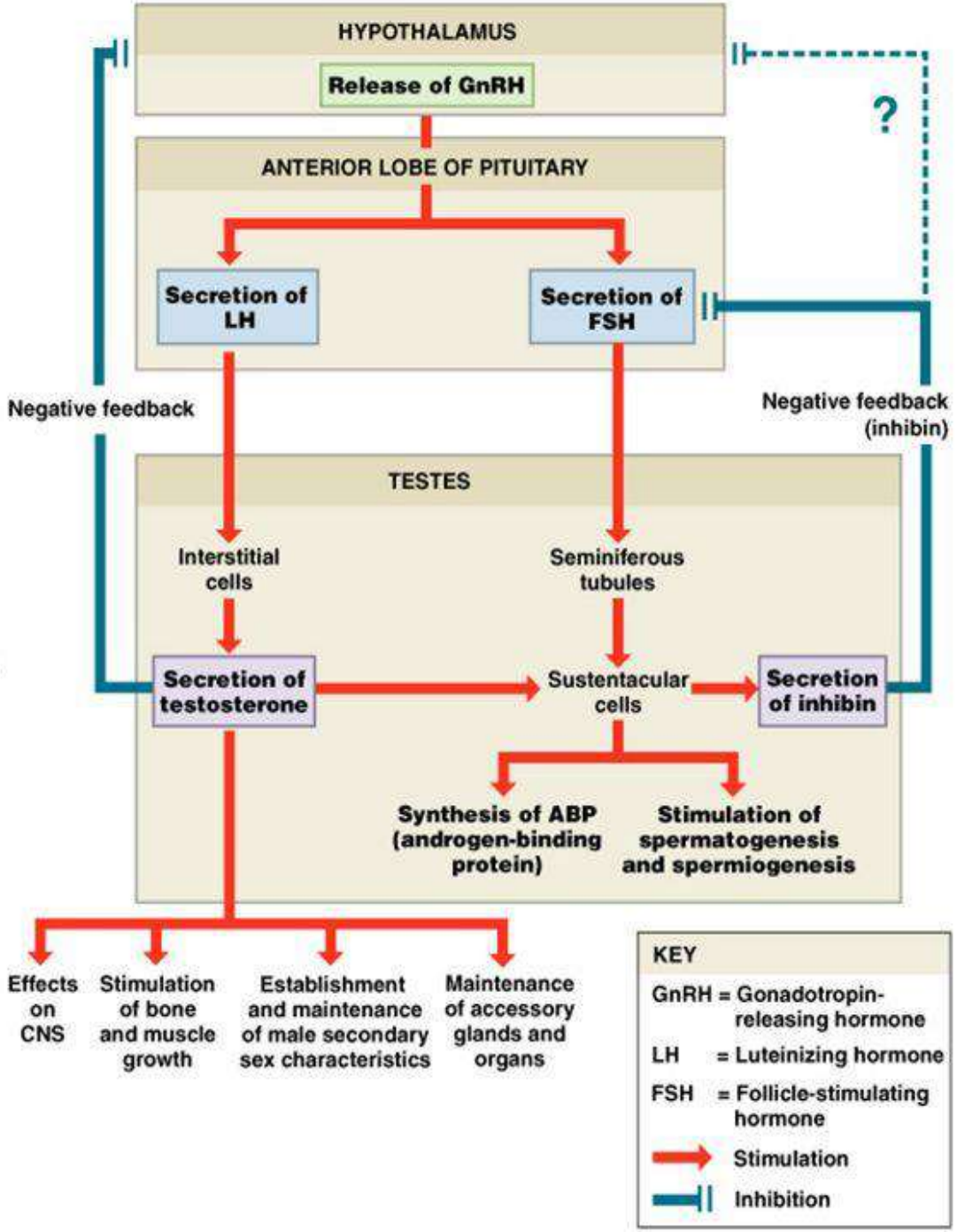
- In a normal adult man, the GnRH-secreting neuroendocrine cells fire a brief burst of action potentials approximately every 2 h, secreting GnRH at these times.
- The GnRH reaching the anterior pituitary via the hypothalamo-pituitary portal vessels during each periodic pulse triggers the release from the anterior pituitary of both LH and FSH from the same cell type, although not necessarily in equal amounts.
- There is a clear separation of the actions of FSH and LH within the testes. FSH acts on Sertoli cells to stimulate the secretion of paracrine agents that are essential for spermatogenesis; in contrast, LH acts on the Leydig cells to stimulate testosterone secretion

Hormonal Regulation of Male Reproductive Function

GnRH (pulses) →LH, FSH

LH → interstial cells → T

FSH → sustentaculars → inhibin, ABP, spermatogenesis (with T)



- In addition to its many important systemic effects as a hormone, the testosterone secreted by these cells also acts locally, as a paracrine agent, on spermatogenesis by moving from the interstitial spaces into the seminiferous tubules. There, testosterone enters Sertoli cells, and it is via these cells that it facilitates spermatogenesis.
- Thus, despite the absence of any *direct* effect of LH on cells in the seminiferous tubules, this hormone exerts an essential *indirect* effect because the testosterone secretion stimulated by LH is required for spermatogenesis.

Negative-feedback

- Testosterone inhibits mainly LH secretion. It does so in two ways:

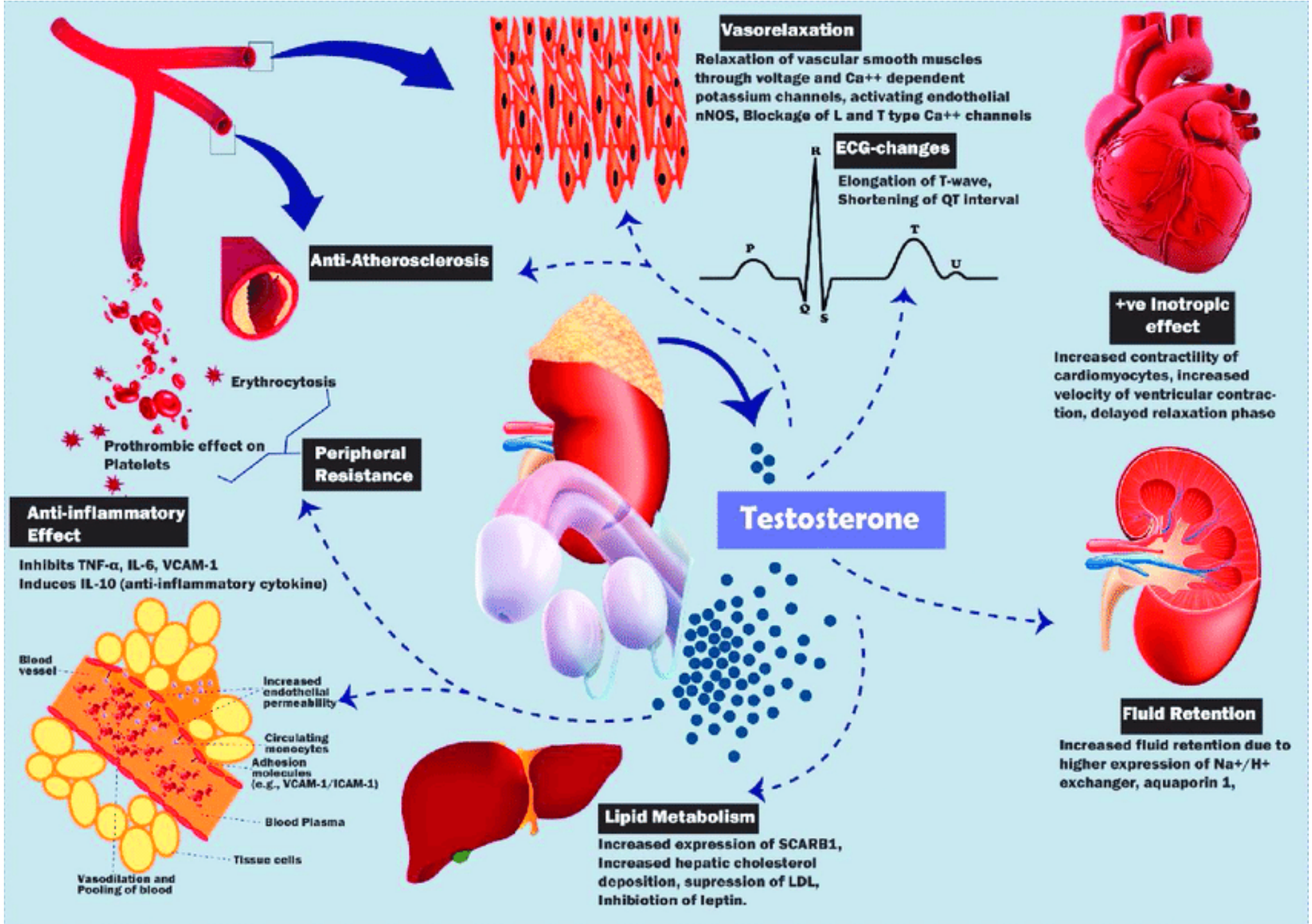
(1) It acts on the hypothalamus to decrease the frequency of GnRH bursts, and the decreased amount of GnRH reaching the pituitary results in less secretion of the gonadotropins; and (2) it acts directly on the anterior pituitary to cause mainly less LH secretion in response to any given level of GnRH.

- Concerning FSH hormone, the major inhibitory signal, exerted directly on the anterior pituitary, is the protein hormone **inhibin** secreted by the Sertoli cells. That the Sertoli cells, via inhibin, are the major source of feedback inhibition of FSH secretion.

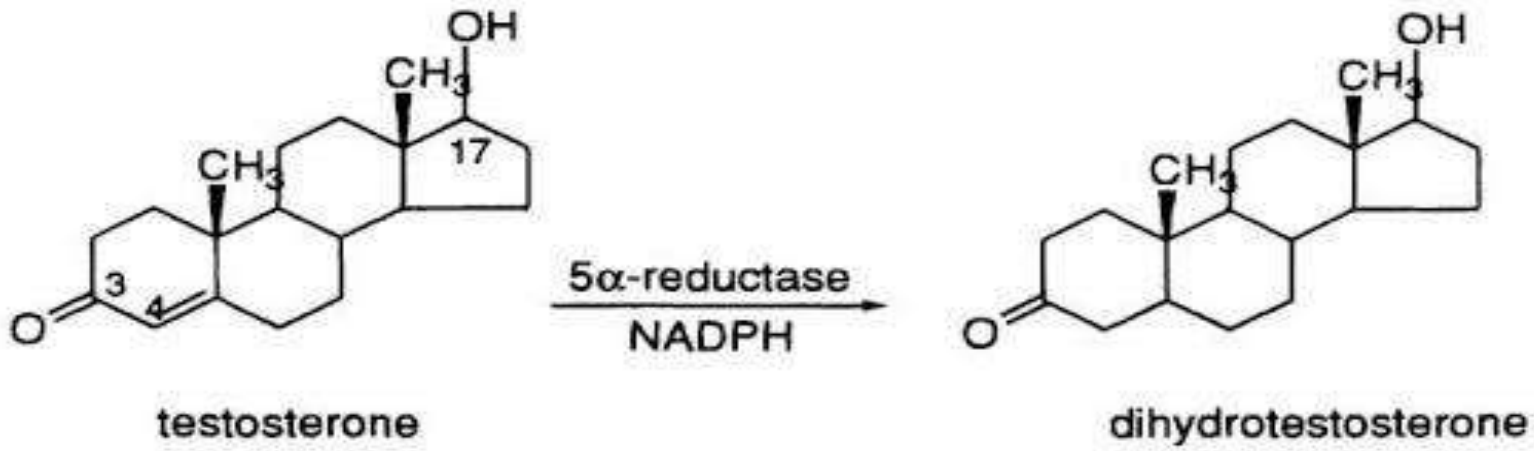
Testosterone

Effects of Testosterone in the Male

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


Vasorelaxation
Relaxation of vascular smooth muscles through voltage and Ca++ dependent potassium channels, activating endothelial nNOS, Blockage of L and T type Ca++ channels
ECG-changes
Elongation of T-wave, Shortening of QT interval
R
P
T
U
Q
S
+ve Inotropic effect
Increased contractility of cardiomyocytes, increased velocity of ventricular contraction, delayed relaxation phase
Anti-Atherosclerosis
Erythrocytosis
Prothrombic effect on Platelets
Peripheral Resistance
Anti-inflammatory Effect
Inhibits TNF-α, IL-6, VCAM-1
Induces IL-10 (anti-inflammatory cytokine)
Testosterone
Blood vessel
Increased endothelial permeability
Circulating monocytes
Adhesion molecules (e.g., VCAM-1/ICAM-1)
Blood Plasma
Tissue cells
Vasodilation and Pooling of blood
Lipid Metabolism
Increased expression of SCARB1, Increased hepatic cholesterol deposition, supression of LDL, Inhibiotion of leptin.
Fluid Retention
Increased fluid retention due to higher expression of Na+/H+ exchanger, aquaporin 1,

- Hormones sometimes must undergo transformation in their target cells in order to be effective. This is true of testosterone in many (but not all) of its target cells.
- In some cells of the adult prostate, after its entry into the cytoplasm, testosterone undergoes an enzyme mediated conversion to another steroid, **dihydrotestosterone**, and it is mainly this molecule that then binds to androgen receptors and elicits effects.



testosterone dihydrotestosterone

- This fact has important pathophysiological implications since some men lack the enzymes required to perform one or the other of the transformations of testosterone. Therefore, they will exhibit certain signs of testosterone deficiency but not others. For example, a man with absence of the enzyme for forming dihydrotestosterone will have normal differentiation of his reproductive duct structures (an effect of testosterone) but lack of development of his external genitalia (an effect requiring dihydrotestosterone).
- Therapy of ***prostate cancer*** also makes use of these facts: Prostate cancer cells are stimulated by dihydrotestosterone, and so the cancer can be treated with drugs that block the enzyme catalyzing the transformation of testosterone to dihydrotestosterone.

Accessory Reproductive Organs

- The fetal differentiation, and later growth and function of the entire male duct system, glands, and penis all depend upon testosterone. Following ***castration*** (removal of the gonads) in the adult male, all the accessory reproductive organs decrease in size, the glands markedly reduce their secretion rates, and the smooth-muscle activity of the ducts is diminished. Erection and ejaculation may be deficient. These defects disappear upon the administration of testosterone.

Secondary Sex Characteristics and Growth

- Secondary sex characteristics are dependent on testosterone. For example, a male castrated before puberty does not develop a beard or either underarm or pubic hair. Other testosterone dependent secondary sexual characteristics are deepening of the voice resulting from the growth of the larynx, thick secretion of the skin oil glands (this predisposes to acne), and the masculine pattern of fat distribution.
- testosterone also stimulates bone growth, largely indirectly through its stimulation of growth hormone secretion, but ultimately shuts off bone growth by causing closure of the bones' epiphyseal plates.
- testosterone is an "anabolic steroid"; it exerts a direct stimulatory effect on protein synthesis in muscle. Testosterone is necessary for expression of the genetic determinant of the common type of baldness ("male pattern") in men.
- Finally, testosterone stimulates the secretion of the hormone erythropoietin by the kidneys, and this is a major reason that men have a higher hematocrit than women.

Behavior

- Testosterone is essential in males for development of sex drive at puberty. It also plays an important role in maintaining sex drive in the adult male, although men often remain sexually active.

- **Lec. 3: Female Reproductive Physiology Dr. Suha Al-Jowari**

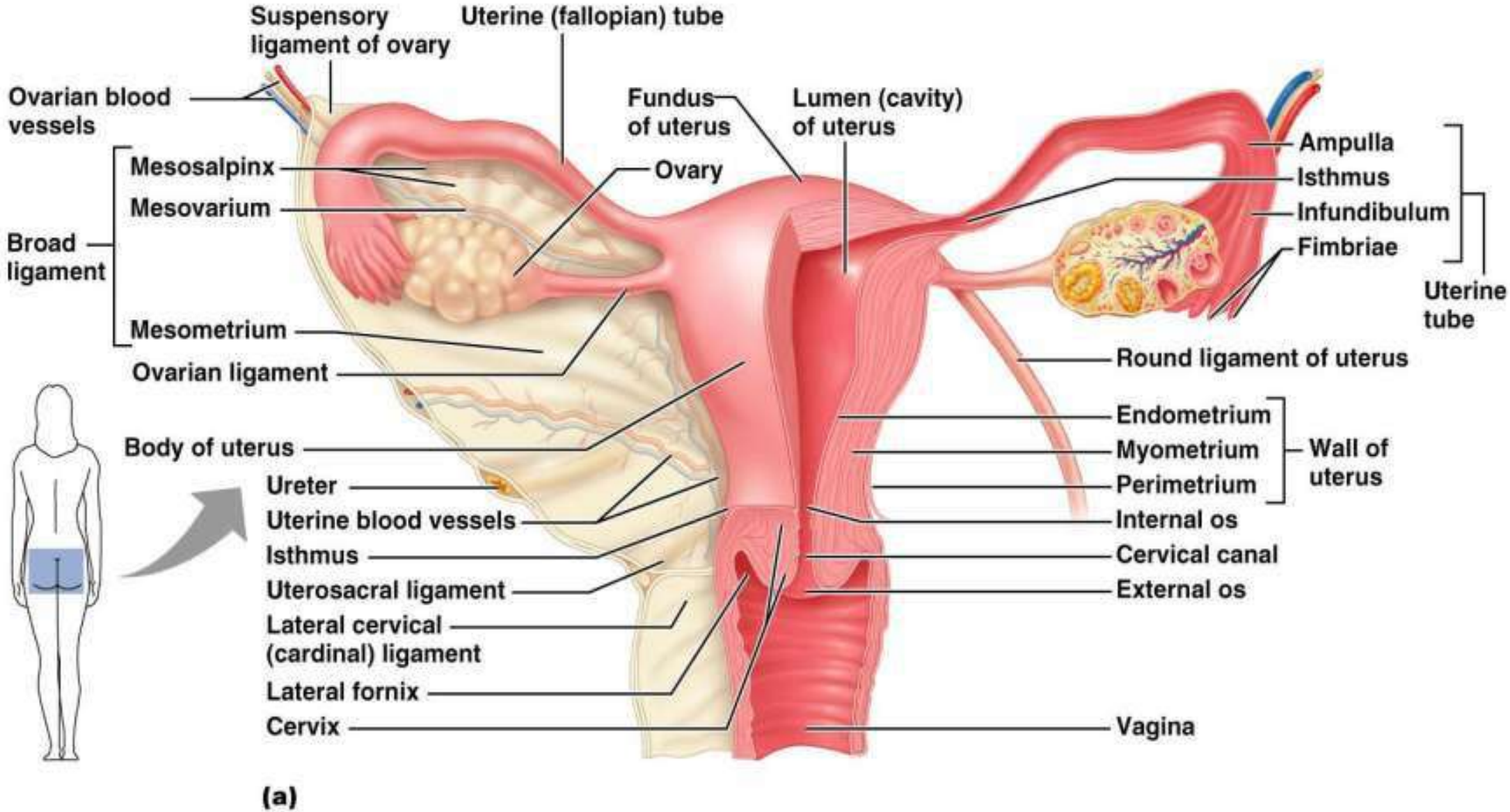
- Unlike the continuous sperm production of the male, the production of the female gamete, the egg, followed by its release from the ovary—**ovulation**—is cyclical.
- This cyclical pattern is also true for the function and structure of virtually the entire female reproductive system. In human, these cycles are called **menstrual cycles.**
- The length of a menstrual cycle varies considerably from woman to woman and in any particular woman, but averages about 28 days. The first day of menstrual bleeding **(menstruation)** is termed day 1.

- The events of the menstrual cycle are complex, the most obvious event of a menstrual cycle in which pregnancy does not occur is, menstruation, which is the result of events occurring in the uterus—the source of menstrual bleeding.
- However, the uterine events of the menstrual cycle are due entirely to cyclical changes in hormone secretion by the ovaries. Moreover, the ovaries, are the sites for production of gametes, one of which normally matures fully per menstrual cycle.

Anatomy

- The female reproductive system includes the two ovaries and the female reproductive tract—two uterine tubes, a uterus, and a vagina. These structures are also termed the **female internal genitalia**.
- In the female, unlike in the male, the urinary and reproductive duct systems are entirely separate from each other

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



(a)

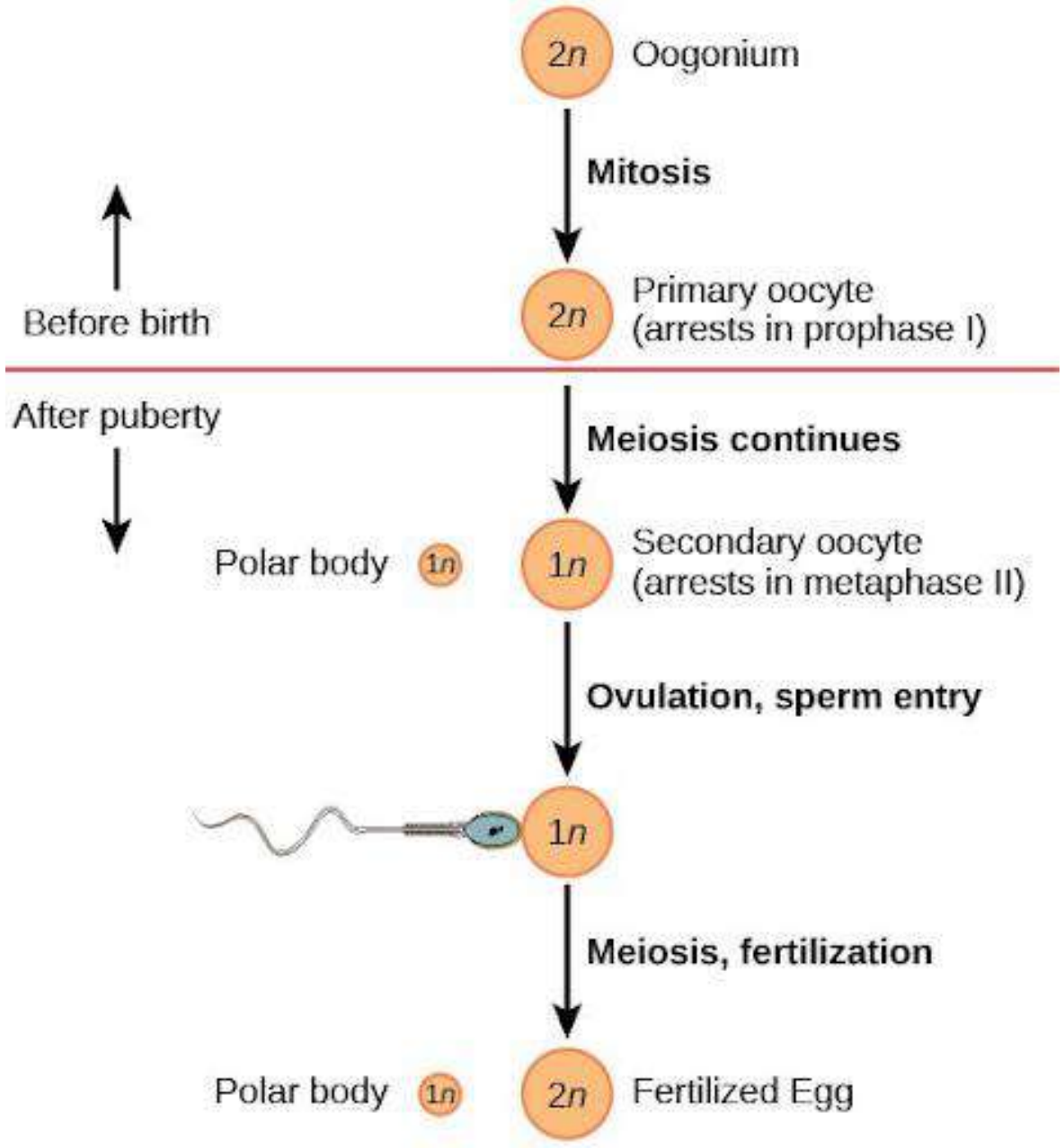
Ovarian Function

- The ovary, like the testis, serves a dual purpose: (1) **oogenesis,** the production of gametes—the ova; and (2) secretion of the female steroidal sex hormones, estrogen and progesterone, as well as the peptide hormone inhibin. (The ovaries secrete two other hormones—relaxin and activin—but the functions of these hormones in humans are not clear.)
- Before ovulation, the gametogenic and endocrine functions of the ovaries take place in a single structure, the follicle; after ovulation, the follicle, now without an egg, differentiates into a corpus luteum, which has only an endocrine function.

Oogenesis

- During early in utero development, the primitive germ cells, or **oogonia**, undergo numerous mitotic divisions. Around the third month after conception, the oogonia cease dividing, and from this point, no new germ cells are generated.
- Still in the fetus, all the oogonia develop into **primary oocytes,** which then begin a first meiotic division by replicating their DNA. They do not, complete the division in the fetus.
- All the eggs present at birth are primary oocytes containing 46 chromosomes, each with two sister chromatids. The cells are said to be in a state of **meiotic arrest.**
- This state continues until puberty and the onset of renewed activity in the ovaries. Indeed, only those primary oocytes destined for ovulation will ever complete the first meiotic division, for it occurs just before the egg is ovulated. and each daughter cell receives 23 chromosomes, each with two chromatids.
- In this division, however, one of the two daughter cells, the **secondary oocyte,** retains virtually all the cytoplasm. The other, termed the first polar body, is very small and nonfunctional.

- The second meiotic division occurs in a uterine tube *after ovulation,* but only if the secondary oocyte is fertilized (penetrated by a sperm). As a result of this second meiotic division, the daughter cells each receive 23 chromosomes, each with a single chromatid.
- One daughter cell, termed an ovum, retains nearly all the cytoplasm, whereas the other, termed the second polar body, is very small and nonfunctional.
- The net result of oogenesis is that each primary oocyte can produce only one ovum.
- Since the final stage of gametogenesis—formation of the ovum—occurs only after fertilization and since fertilization occurs *outside* the ovary "in a uterine tube", technically the *ovaries* do not themselves produce the fully mature gametes—the ova— but only secondary oocytes.


2n
Oogonium
Mitosis
Before birth
2n
Primary oocyte
(arrests in prophase I)
After puberty
Meiosis continues
Polar body
1n
1n
Secondary oocyte
(arrests in metaphase II)
Ovulation, sperm entry
1n
Meiosis, fertilization
Polar body
1n
2n
Fertilized Egg

Follicle Growth

- Throughout their life in the ovaries, the eggs exist in structures known as **follicles.**
- Follicles begin as **primordial follicles,** which consist of one primary oocyte surrounded by a single layer of cells called **granulosa cells.**
- Further development from the primordial follicle stage is characterized by an increase in the size of the oocyte, a proliferation of the granulosa cells into multiple layers, and the separation of the oocyte from the inner granulosa cells by a thick layer of material, the **zona pellucida.**
- The granulosa cells secrete estrogen, small amounts of progesterone before ovulation, and the peptide hormone inhibin.
- Despite the presence of a zona pellucida, the inner layer of granulosa cells remains intimately associated with the oocyte by means of cytoplasmic processes that traverse the zona pellucida and form gap junctions with the oocyte. Through these gap junctions, nutrients and chemical messengers are passed to the oocyte.

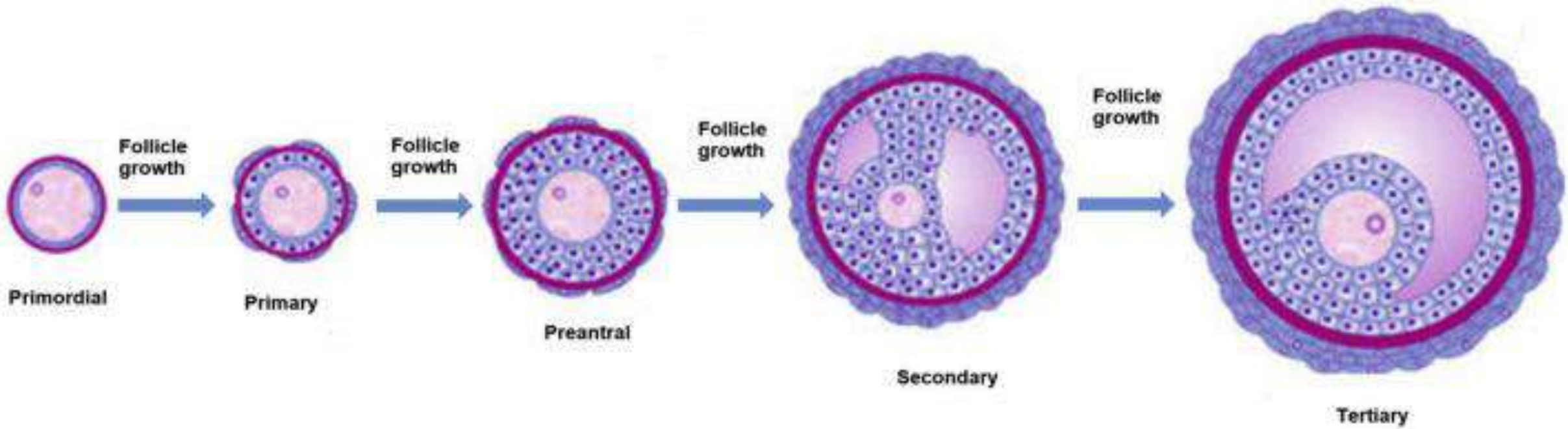
- For example, the granulosa cells produce one or more factors that act on the primary oocytes to maintain them in meiotic arrest.
- As the follicle grows by mitosis of granulosa cells, connective-tissue cells surrounding the granulosa cells differentiate and form layers known as the **theca,** which play an important role in estrogen secretion by the granulosa cells, as we shall see. Shortly after this, the primary oocyte reaches full size (115 m in diameter), and a fluid-filled space, the **antrum,** begins to form in the midst of the granulosa cells as a result of fluid they secrete.

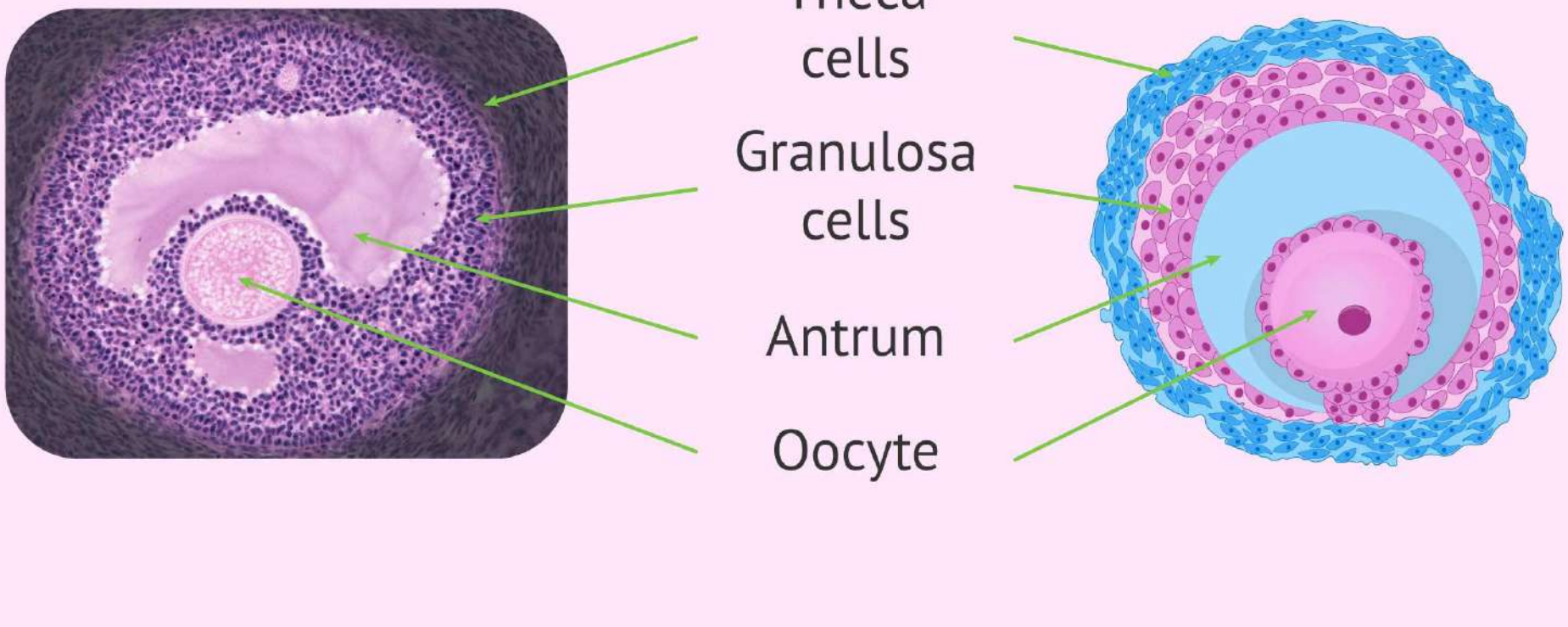
- The progression of some primordial follicles to the preantral and early antral stages occurs throughout infancy and childhood, and then during the entire menstrual cycle.
- At the beginning of each menstrual cycle, 10 to 25 of these preantral and early antral follicles begin to develop into larger antral follicles.
- About 1 week into the cycle, a further selection process occurs: Only one of the larger antral follicles, the **dominant follicle,** continues to develop, and the other follicles (in both ovaries) that had begun to enlarge undergo a degenerative process called **atresia** (an example of programmed cell death, or apoptosis).

- The eggs in the degenerating follicles also die.
- Atresia is not limited to just antral follicles, however, for follicles can undergo atresia at all stages of development.
- Atresia then continues all through prepubertal life so that only 200,000 to 400,000 follicles remain when active reproductive life begins.
- 99.99 percent of the ovarian follicles present at birth will undergo atresia.

- As the dominant follicle enlarges, mainly as a result of its expanding antrum, the granulosa cell layers surrounding the egg form a mound that projects into the antrum and is termed the cumulus oophorous.
- As the time of ovulation approaches, the egg (a primary oocyte) emerges from meiotic arrest and completes its first meiotic division to become a secondary oocyte.
- The cumulus separates from the follicle wall so that it and the oocyte float free in the antral fluid. The mature follicle (also termed a graafian follicle) becomes so large (diameter about 1.5 cm) that it balloons out on the surface of the ovary.

- Ovulation occurs when the thin walls of the follicle and ovary at the site where they are joined rupture because of enzymatic digestion.
- The secondary oocyte, surrounded by its tightly adhering zona pellucida and granulosa cells, as well as the cumulus, is carried out of the ovary and onto the ovarian surface by the antral fluid. All this happens on approximately day 14 of the menstrual cycle.
- On occasion (1 to 2 percent of all cycles), two or more follicles reach maturity, and more than one egg may be ovulated. This is the most common cause of multiple births.


Follicle growth
Follicle growth
Follicle growth
Follicle growth
Primordial
Primary
Preantral
Secondary
Tertiary


Theca cells
Granulosa cells
Antrum
Oocyte

Formation of the Corpus Luteum

- After the mature follicle discharges its antral fluid and egg, its remnant in the ovary collapses around the antrum and undergoes a rapid transformation.
- The granulosa cells enlarge greatly, and the entire gland like structure is known as **corpus luteum,** which secretes estrogen, progesterone, and inhibin.
- If the discharged egg, now in a uterine tube, is not fertilized, the corpus luteum reaches its maximum development within approximately 10 days and then rapidly degenerates by apoptosis. The loss of corpus luteum function leads to menstruation and the beginning of a new menstrual cycle.
- In terms of ovarian function, the menstrual cycle may be divided into two phases approximately equal in length and separated by ovulation: (1) the **follicular phase,** during which a single mature follicle and secondary oocyte develop; and (2) the **luteal phase,** beginning after ovulation and lasting until the demise of the corpus luteum.

Sites of Secretion of Ovarian Hormones

- Estrogen is secreted during the follicular phase mainly by the granulosa cells; following ovulation, it is secreted by the corpus luteum.
- Progesterone, the other major ovarian steroid hormone, is secreted in very small amounts by the granulosa and theca cells just before ovulation, but its major source is the corpus luteum.
- Inhibin, a peptide hormone, is secreted by both the granulosa cells and corpus luteum.

Control of Ovarian Function

- The basic factors controlling ovarian function are analogous to the controls described for testicular function in that they constitute a hormonal series made up of GnRH, the anterior pituitary gonadotropins FSH and LH, and gonadal sex hormones—estrogen and progesterone.
- We say “basic” factors because these hormones are not the exclusive regulators of ovarian function.
- Several other hormones (insulin, for example) and many paracrine growth factors (for example, the insulin like growth factors) play important but still poorly understood roles.

- As in the male, the entire sequence of basic controls depends upon the secretion of GnRH from hypothalamic neuroendocrine cells in episodic pulses.
- In the female, however, the frequency of these pulses and hence the total amount of GnRH secreted during a 24-h period change in a patterned manner over the course of the menstrual cycle. So does the responsiveness both of the anterior pituitary to GnRH and of the ovaries to FSH and LH.

- FSH is slightly elevated in the early part of the follicular phase and then steadily decreases throughout the remainder of the cycle except for a small midcycle peak.
- LH is constant during most of the follicular phase but then shows a very large midcycle rise—the **LH surge**—peaking approximately 18 h *before* ovulation, followed by a rapid return toward presurge values and then a further slow decline during the luteal phase.
- After remaining fairly low and stable for the first week, estrogen rises rapidly during the second week as the dominant ovarian follicle grows and secretes it.

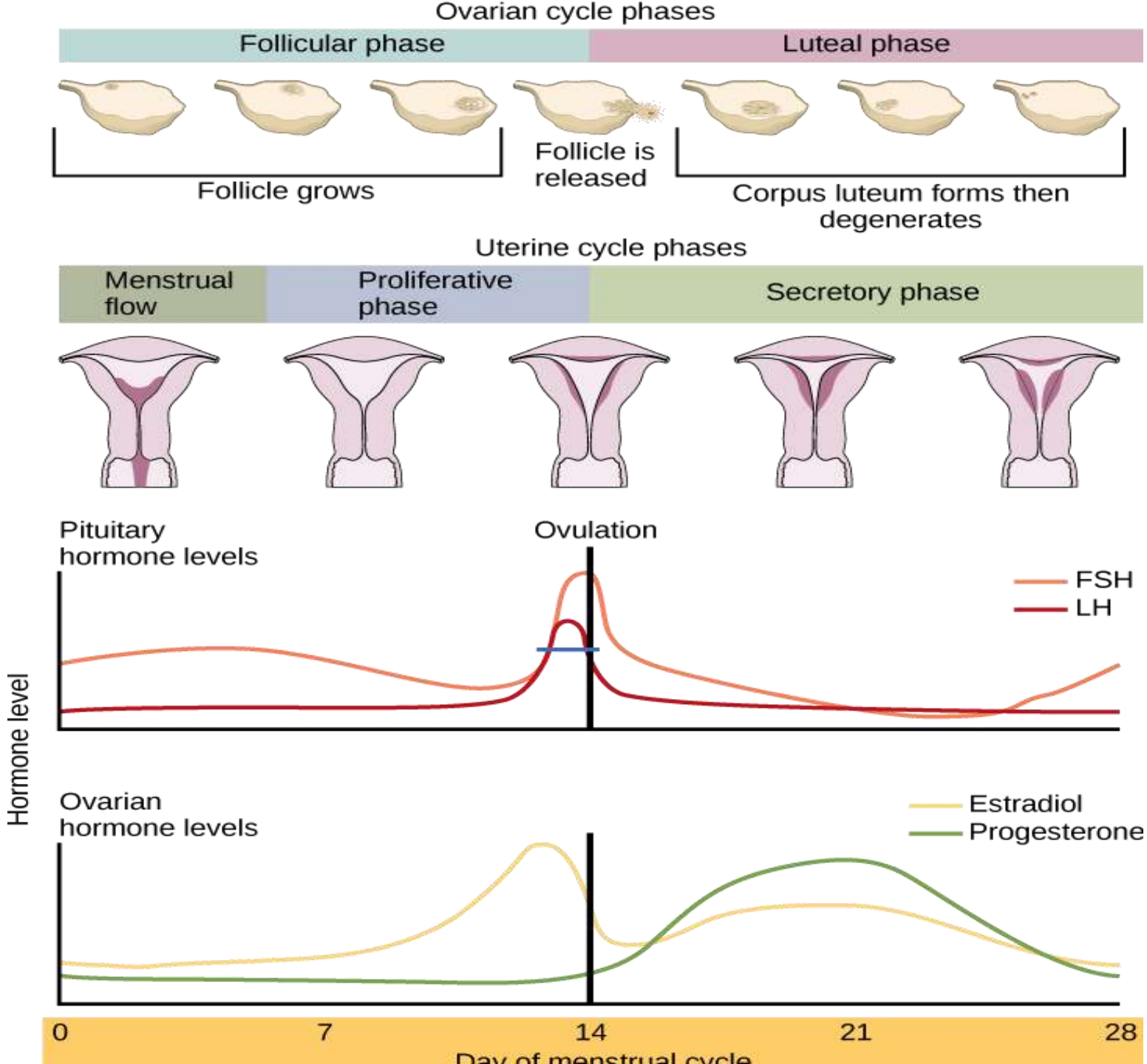
- Estrogen then starts falling shortly after LH has peaked. This is followed by a second rise, due to secretion by the corpus luteum, and finally, a rapid decline during the last days of the cycle.
- The progesterone pattern is simplest of all: Very small amounts of progesterone are secreted by the ovaries during the follicular phase before ovulation, but very soon after ovulation, the developing corpus luteum begins to secrete large amounts of progesterone, and from this point the progesterone pattern is similar to that for estrogen.
- Inhibin pattern is similar to that of estrogen: It increases during the late follicular phase, remains high during the luteal phase, and then decreases as the corpus luteum degenerates.

Follicle Development and Estrogen Secretion during the Early and Middle Follicular Phases

- As mentioned, there are always a number of preantral and early antral follicles in the adult ovary.
- Further development of the follicle beyond these stages requires stimulation by FSH. Prior to puberty, the plasma concentration of this gonadotropin is too low to induce such development. This all changes once sexual maturity has been reached and menstrual cycles commence: The increase in FSH secretion that occurs as one cycle ends and the next begins provides this stimulation, and a group of preantral and early antral follicles begins to enlarge.

- During the next week, there is a division of labor between the actions of FSH and LH on the follicles:

FSH acts on the granulosa cells, and LH acts on the theca cells. The reason is that at this point in the cycle, granulosa cells have FSH receptors but no LH receptors, the situation for the theca cells being just the reverse. FSH stimulates the granulosa cells to multiply and produce estrogen, and it also stimulates enlargement of the antrum. Some of the estrogen produced diffuses into the blood and maintains a relatively stable plasma concentration, and some estrogen functions as a paracrine/autocrine agent in the follicle, where, along with FSH, it stimulates the proliferation of granulosa cells, which causes a further increase in estrogen production.


Ovarian cycle phases
Follicular phase
Luteal phase
Follicle grows
Follicle is released
Corpus luteum forms then degenerates
Uterine cycle phases
Menstrual flow
Proliferative phase
Secretory phase
Pituitary hormone levels
Ovulation
FSH
LH
Hormone level
Ovarian hormone levels
Estradiol
Progesterone
0
7
14
21
28
Day of menstrual cycle

- The granulosa cells, however, require help to produce estrogen because they are deficient in the enzymes required to produce the androgens that are the precursors of estrogen. They are aided by the theca cells.
- LH acts upon the theca cells, stimulating them not only to proliferate but to synthesize androgens which converted into estrogen.
- Thus, the secretion of estrogen by the granulosa cells requires the interplay of both types of follicle cells and both pituitary gonadotropins.
- The granulosa cell is similar to the Sertoli cell in that it controls the microenvironment in which the germ cell develops and matures, and it is stimulated by both FSH and the major gonadal sex hormone. The thecal cell is similar to the Leydig cell in that it produces mainly androgens and is stimulated to do so by LH.

- By the beginning of the second week, one follicle has become dominant, and the other developing follicles undergo atresia by apoptosis. The reason for this apoptosis is that the plasma concentration of FSH, a crucial “survival factor” for the follicle cells, begins to decrease, and there is no longer enough FSH to prevent such apoptosis.
- The reasons beyond the dominant follicle not undergo atresia are two: First, its granular cells have achieved a greater sensitivity to FSH because of increased numbers of FSH receptors so that less FSH is needed to stimulate them; and second, its granulosa cells now begin to be stimulated not only by FSH but by LH as well.
- During the first week of the follicular phase, LH acts only on the thecal cells; as the dominant follicle matures, however, this situation changes, and LH receptors, induced by FSH, also begin to appear in large numbers on the granulosa cells.

- The dominant follicle now starts to secrete enough estrogen that the plasma concentration of this steroid begins to rise.
- Plasma FSH starts going down at this time. The reason is that estrogen, at these still relatively low concentrations, is exerting a *negative-feedback* inhibition over the secretion of gonadotropins.
- One site of estrogen's action is the anterior pituitary, where it reduces the amount of FSH and LH secreted in response to any given amount of GnRH. Estrogen probably also acts on the hypothalamus to decrease the amplitude of GnRH pulses and, hence, the total amount of GnRH secreted over any time period.

- Therefore, as expected from this negative feedback, the plasma concentration of FSH (and LH, to a lesser extent) begins to fall as a result of the rising level of estrogen as the follicular phase continues. One reason that FSH falls more than LH is that the granulosa cells also secrete inhibin, which, as in the male, inhibits mainly secretion of FSH.

Lec.4 Uterine Changes in the Menstrual Cycle

- The phases of the menstrual cycle in terms of ovarian events—follicular and luteal phases, separated by ovulation.
- However, the phases of the menstrual cycle can also be named in terms of uterine events. Day 1 is, the first day of menstrual bleeding, and the entire period of menstruation is known as the menstrual phase, which is generally about 3 to 5 days in a typical 28 day cycle.
- During this period, the epithelial lining of the uterus—the endometrium—degenerates, resulting in the menstrual flow. The menstrual flow then ceases, and the endometrium begins to thicken as it regenerates.
- This period of growth, the proliferative phase, lasts for the 10 days or so between cessation of menstruation and the occurrence of ovulation.

- Soon after ovulation, the endometrium begins to secrete various substances, and so the part of the menstrual cycle between ovulation and the onset of the next menstruation is called the secretory phase.
- The ovarian follicular phase includes the uterine menstrual and proliferative phases, whereas the ovarian luteal phase is the same as the uterine secretory phase.
- The uterine changes during a menstrual cycle are caused by changes in the plasma concentrations of estrogen and progesterone.

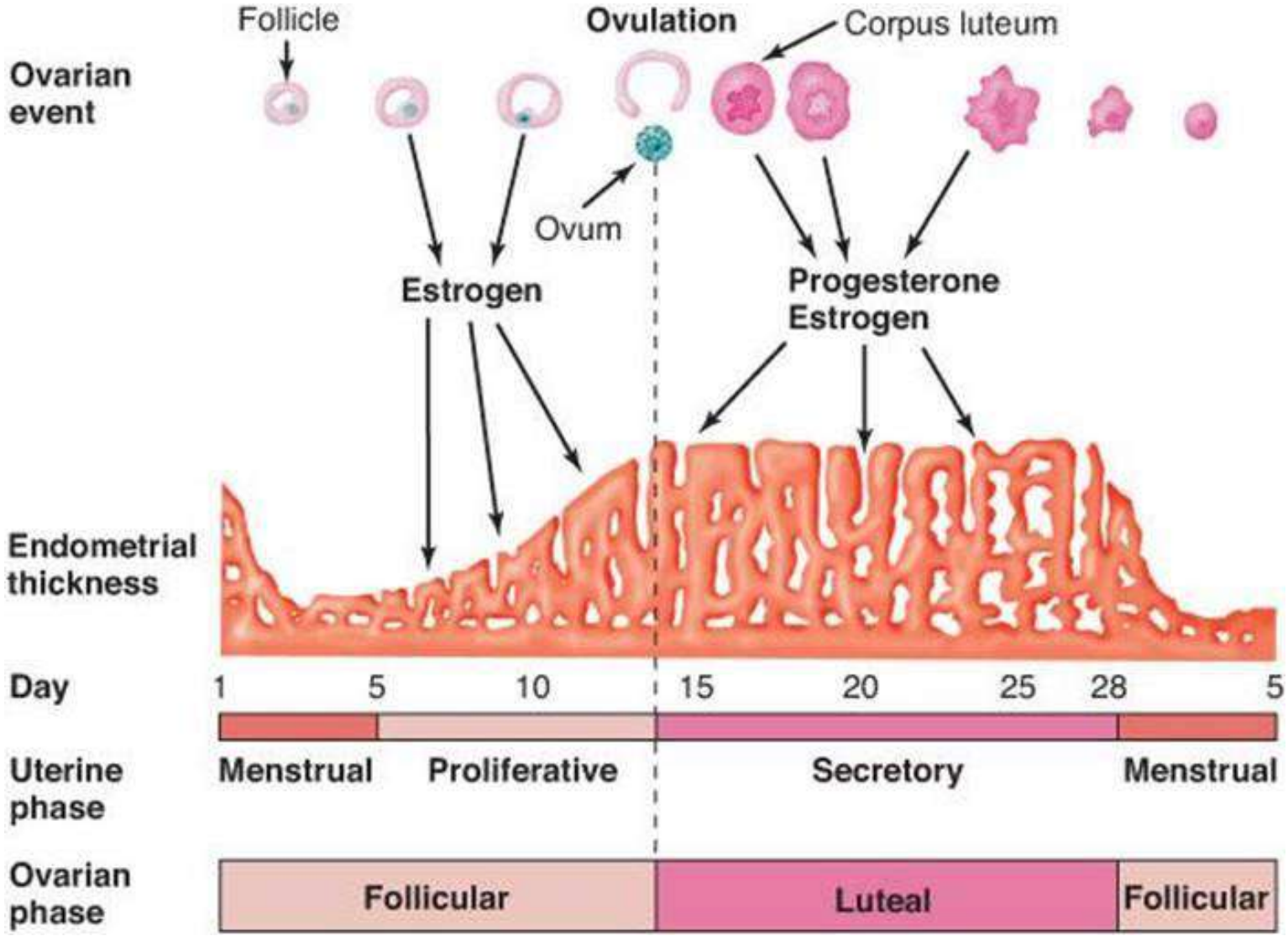
- During the proliferative phase, a rising plasma estrogen level stimulates growth of both the endometrium and the underlying uterine smooth muscle (myometrium). In addition, it induces the synthesis of receptors for progesterone in endometrial cells.
- Then, following ovulation and formation of the corpus luteum, during the secretory phase, progesterone acts upon this estrogen primed endometrium to convert it to an actively secreting tissue: Its glands become coiled and filled with glycogen, the blood vessels become more numerous, and various enzymes accumulate in the glands and connective tissue. These changes are essential to make the endometrium a hospitable environment for an embryo.

- Progesterone also inhibits myometrial contractions, in large part by opposing the stimulatory actions of estrogen and locally generated prostaglandins. This is very important to ensure that a fertilized egg, once it arrives in the uterus, will not be swept out by uterine contractions before it can implant in the wall. Uterine quiescence is maintained by progesterone throughout pregnancy and is essential to prevent premature delivery.

- Estrogen and progesterone also have important effects on the secretion of mucus by the cervix. Under the influence of estrogen alone, this mucus is abundant, clear, and no viscous.
- All these characteristics are most pronounced at the time of ovulation and allow sperm deposited in the vagina to move easily through the mucus on their way to the uterus and uterine tubes. In contrast, progesterone, present in significant concentrations only after ovulation, causes the mucus to become thick and sticky—in essence a “plug” that prevents bacteria from entering the uterus from the vagina. The antibacterial blockage protects the fetus if conception has occurred.

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

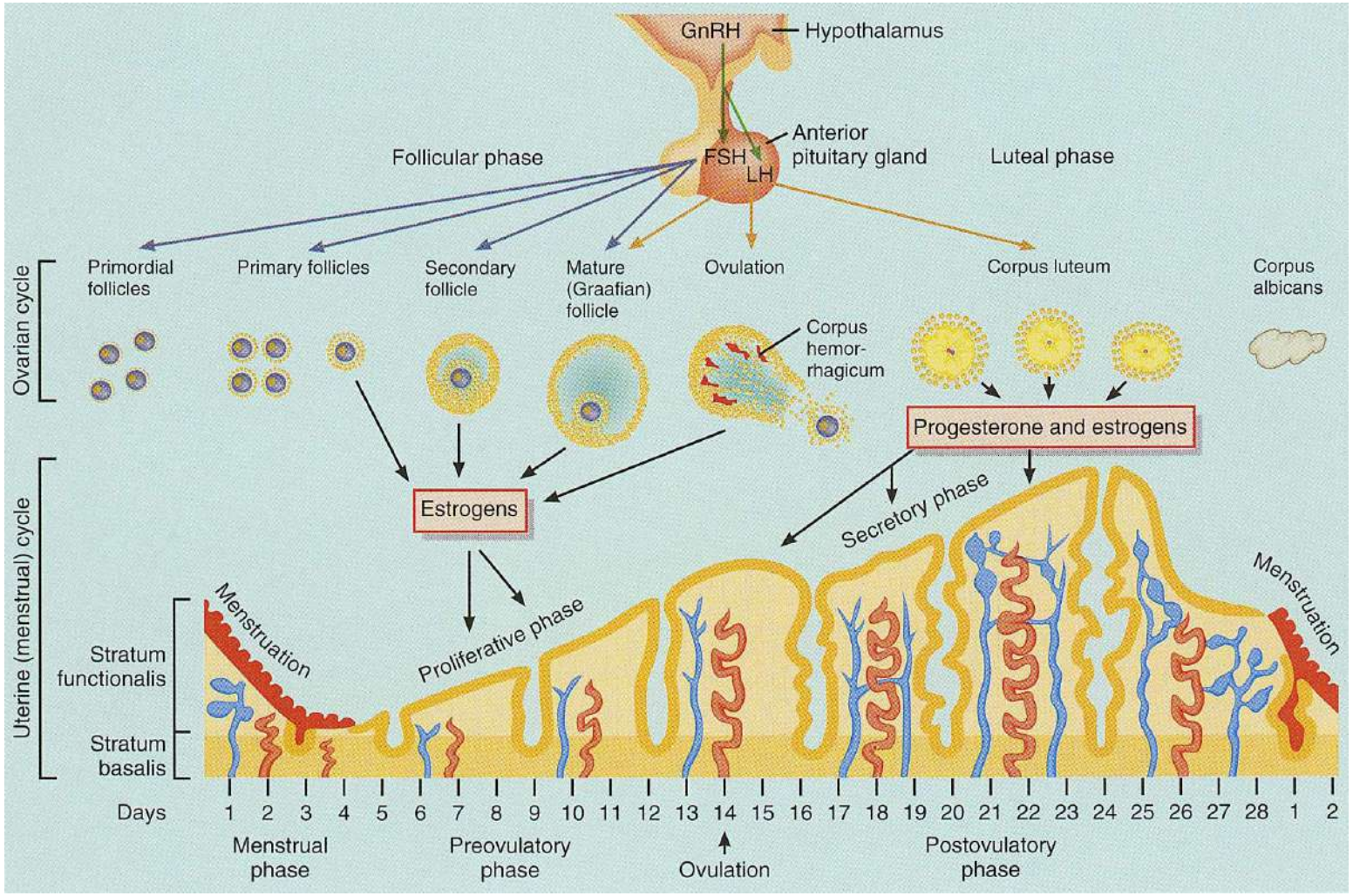
- Both the vasoconstriction and uterine contractions are mediated by prostaglandins produced by the endometrium in response to the drop in plasma estrogen and progesterone. The major cause of menstrual cramps, dysmenorrhea, is overproduction of these prostaglandins, leading to excessive uterine contractions. The prostaglandins also affect smooth muscle in the body, which accounts for the systemic symptoms (nausea, vomiting, and headache) that sometimes accompany the cramps.
- After the initial period of vascular constriction, the endometrial arterioles dilate, resulting in hemorrhage through the weakened capillary walls. The menstrual flow consists of this blood mixed with endometrial debris. Typical blood loss per menstrual period is about 50 to 150 ml.


Follicle
Ovulation
Corpus luteum
Ovarian event
Ovum
Estrogen
Progesterone
Estrogen
Endometrial thickness
Day
1
5
10
15
20
25
28
5
Uterine phase
Menstrual
Proliferative
Secretory
Menstrual
Ovarian phase
Follicular
Luteal
Follicular

Other effects of estrogen and progesterone

- Circulating estrogen provides some protection against atherosclerosis and osteoporosis.
- Progesterone inhibits proliferation of the cells lining the vagina. Further, there is a small rise (approximately 0.5°C) in body temperature that usually occurs after ovulation and persists throughout the luteal phase; this change is probably due to an action of progesterone on temperature regulatory centers in the brain.
- Progesterone exerts an “antiestrogen effect,” by decreasing the number of estrogen receptors. In contrast, the synthesis of progesterone receptors is stimulated by estrogen in many tissues (for example, the endometrium), and so responsiveness to progesterone usually requires the presence of estrogen.
- Both estrogen and progesterone act in the cell nucleus, and their biochemical mechanism of action is at the level of gene transcription.

Summary of ovarian and menstrual cycle



Lec.5 Pregnancy

Pregnancy For pregnancy to occur, sexual intercourse must occur no more than 5 days before ovulation or on the day of ovulation. This is because the sperm, following their ejaculation into the vagina, remain capable of fertilizing an egg for up to 5 days, and the ovulated egg remains fertile for only a few hours.

(It is also possible that the rapid change in cervical mucus that occurs within a few hours after ovulation prevents entry of new sperm into the uterus.)

Egg Transport

- At ovulation, the egg is extruded onto the surface of the ovary, and its first mission is to gain entry into a uterine tube.
- The fimbriae at the end of the uterine tubes are lined with ciliated epithelium. At ovulation, the smooth muscle of the fimbriae causes them to pass over the ovary while the cilia beat in waves toward the interior of the duct. These ciliary motions sweep the egg into the uterine tube as it emerges onto the ovarian surface.
- Within the uterine tube, egg movement, driven almost entirely by uterine-tube cilia, is so slow that the egg takes about 4 days to reach the uterus. Thus, if fertilization is to occur, it must do so in the uterine tube because of the short life span of the unfertilized egg

Sperm Transport and Capacitation

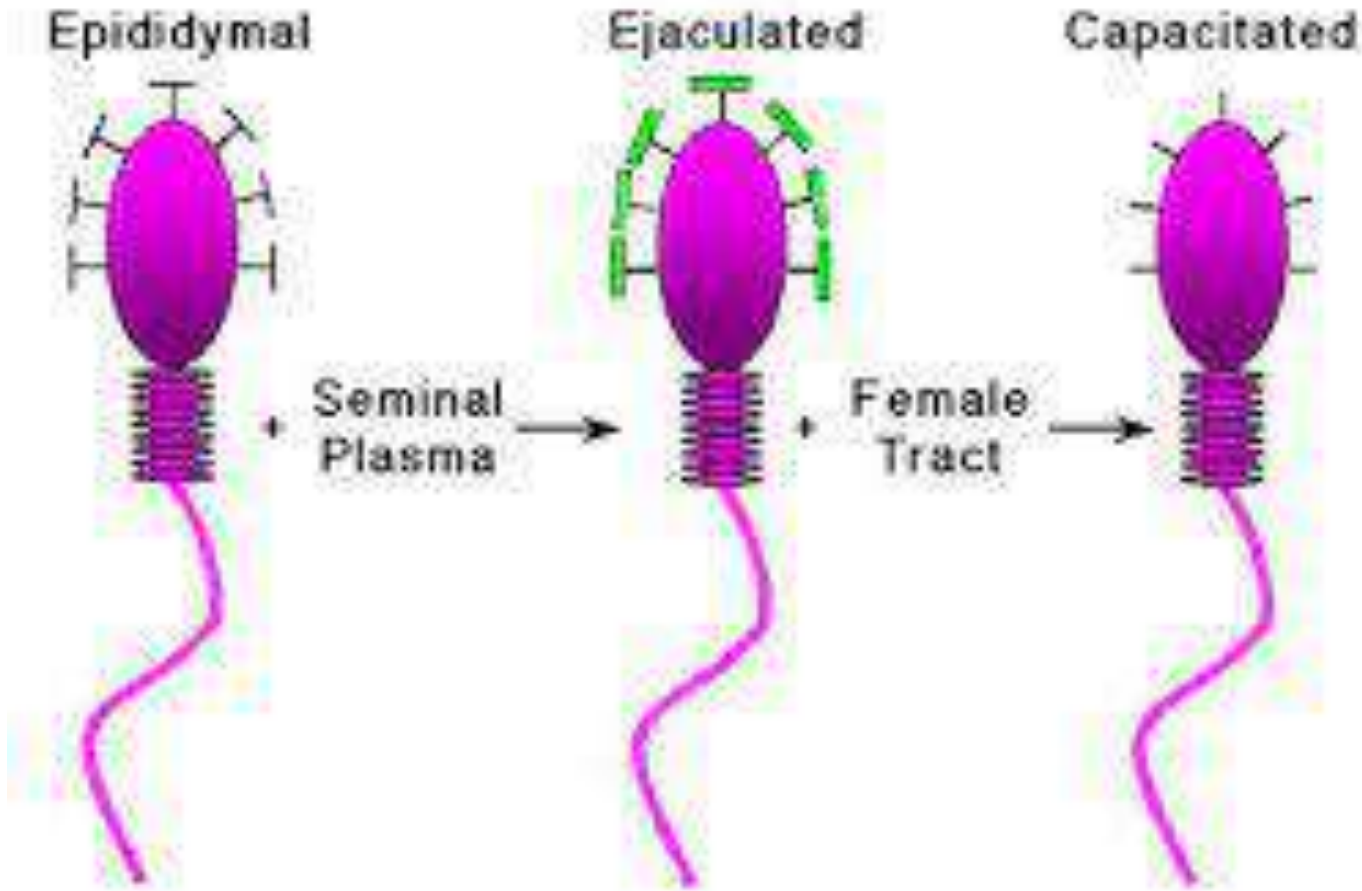
- Within a minute after intercourse, some sperm can be detected in the uterus.
- The act of intercourse itself provides transport of sperm out of the vagina through the cervix and into the uterus because of the fluid pressure of the ejaculate and the pumping action of the penis in the vagina during ejaculation.

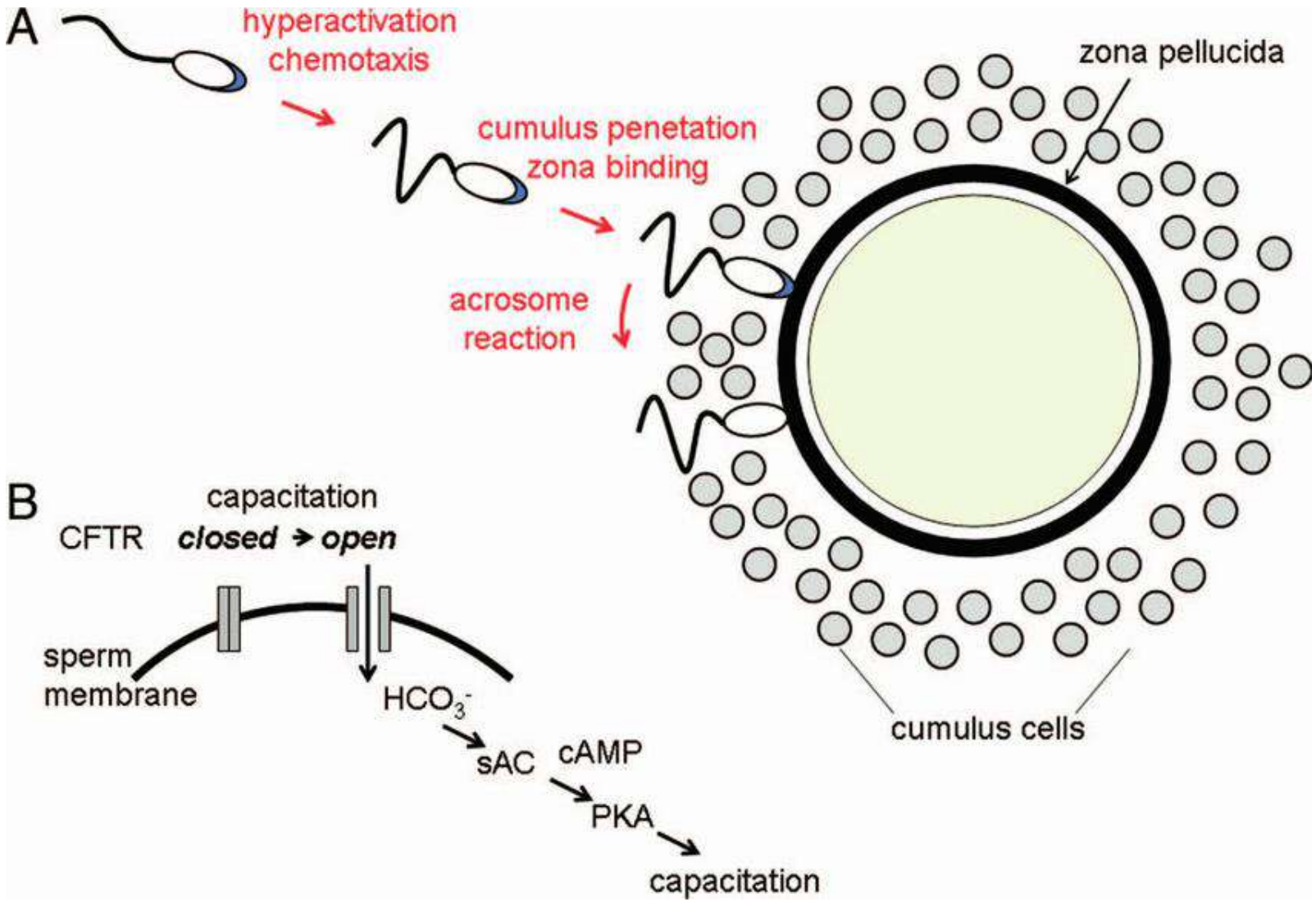
- In addition, beating of the cilia on the inner surface of the cervix probably push the sperm toward the uterus. Passage through the cervical mucus by the swimming sperm is dependent on the estrogen induced changes of the mucus. Transport of the sperm the length of the uterus and into the uterine tube is mainly via the sperm’s own.
- Another possible contributor is the posterior pituitary hormone oxytocin, which is reflexly released during intercourse and causes contraction of the myometrium.

- The mortality rate of sperm during the trip is huge. One reason for this is that the vaginal environment is acidic, a protection against yeast and bacterial infections. Another is the length and energy requirements of the trip.
- Of the several hundred million sperm deposited in the vagina, only a few hundred reach the uterine tube. This is one of the major reasons there must be so many sperm in the ejaculate for fertilization to occur.

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

Effect of Capacitation




A
hyperactivation
chemotaxis
cumulus penetation
zona binding
acrosome
reaction
zona pellucida
cumulus cells
B
capacitation
CFTR
closed → open
sperm
membrane
HCO3-
sAC
cAMP
PKA
capacitation

Lec. 6 Events of Pregnancy

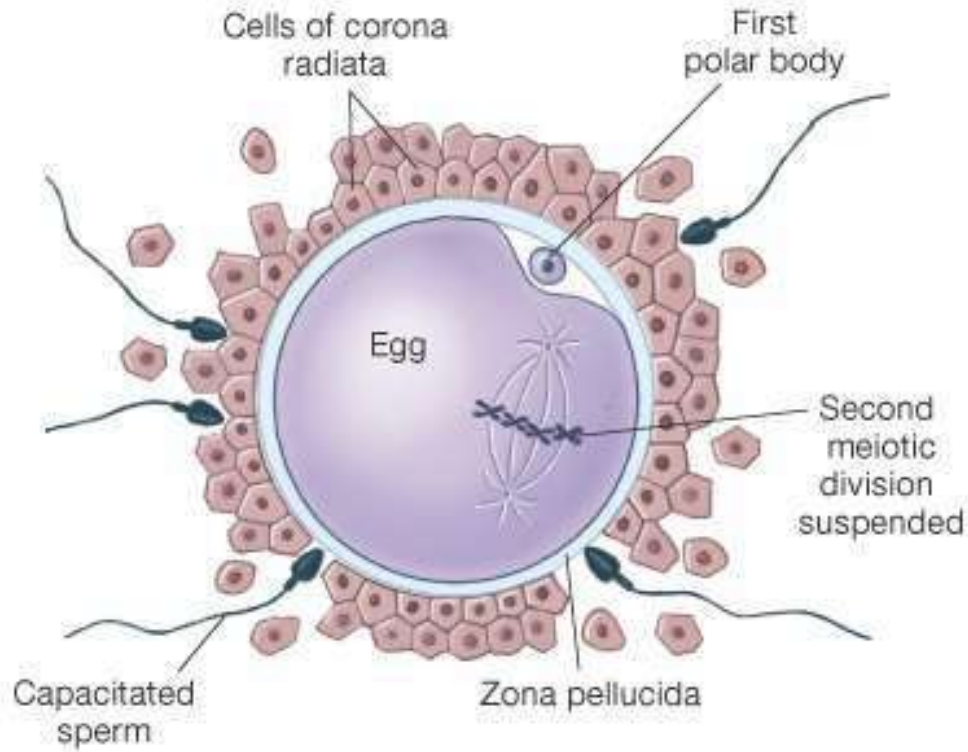
Fertilization

- It is the fusion of a sperm and egg. Many sperm, after moving between the cumulus of granulosa cells still surrounding the egg, bind to the zona pellucida. This is a species-specific binding between a protein (known as ZP3) in the zona pellucida's outer surface and a complementary protein in the plasma membrane of the sperm's head. In other words, the zona pellucida proteins function as receptors for sperm surface proteins.
- This binding triggers what is termed the acrosome reaction in the bound sperm.

- The first sperm to penetrate the entire zona and reach the egg's plasma membrane fuses with this membrane. This sperm then slowly passes into the egg's cytoplasm, penetration achieved not by the sperm's motility but as a result of contractile elements in the egg that draw the sperm in. The newly fertilized egg, now termed a zygote,
- The fertilized egg completes its second meiotic division over the next few hours, and the one daughter cell—the second polar body—is extruded and disintegrates.
- Fertilization also triggers activation of the egg enzymes required for the ensuing cell divisions and embryogenesis.
- Rarely, a fertilized egg remains in a uterine tube and embeds itself in the tube wall. Even more rarely, a fertilized egg may move backwards out of the uterine tube into the abdominal cavity, where implantation can occur. Both kinds of **ectopic pregnancies** cannot succeed, and surgery is necessary to end the pregnancy unless there is a spontaneous abortion—because of the risk of maternal hemorrhage.

(a)

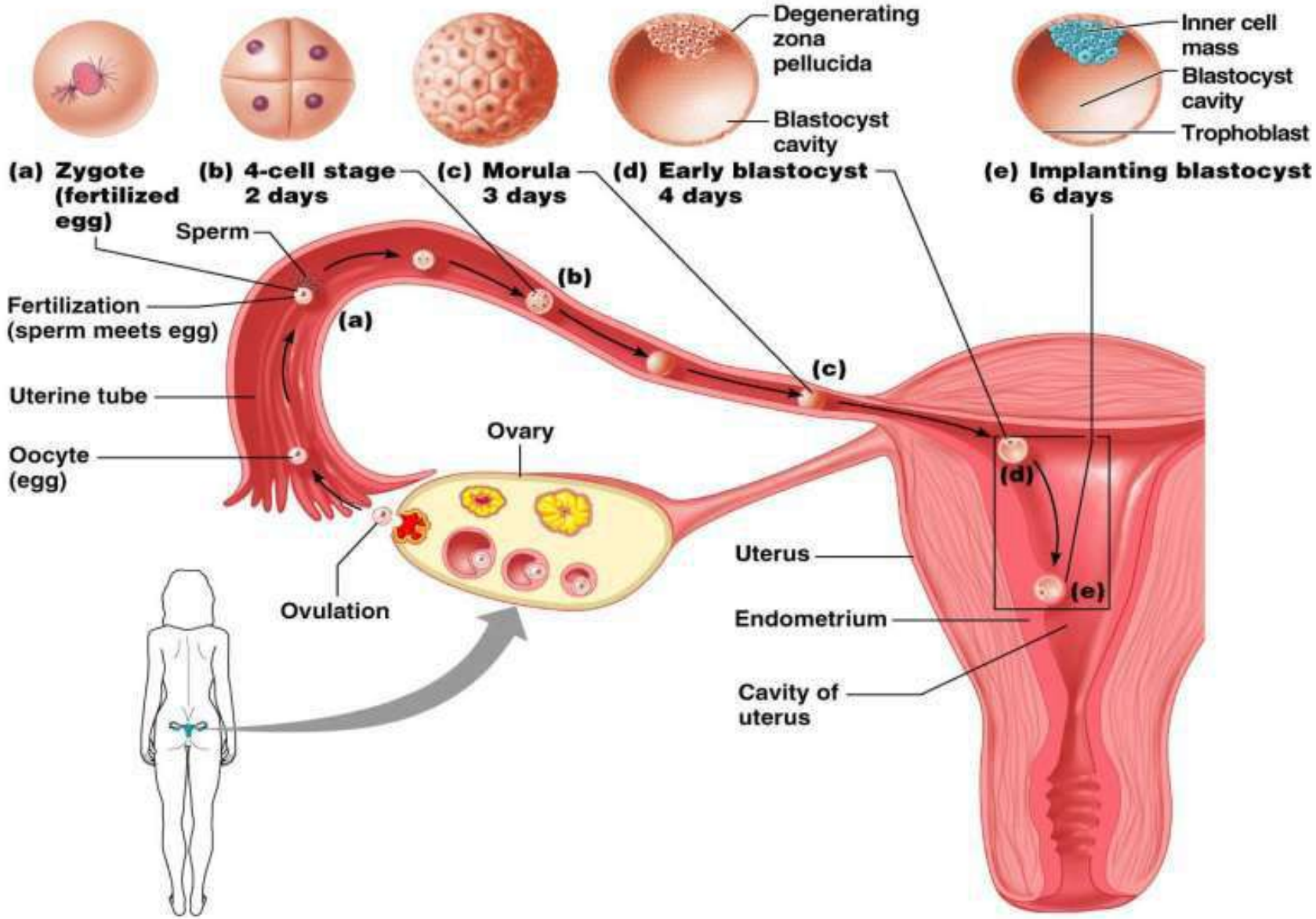
(b) Capacitated sperm release enzymes from their acrosomes in order to penetrate the cells and zona pellucida surrounding the egg.



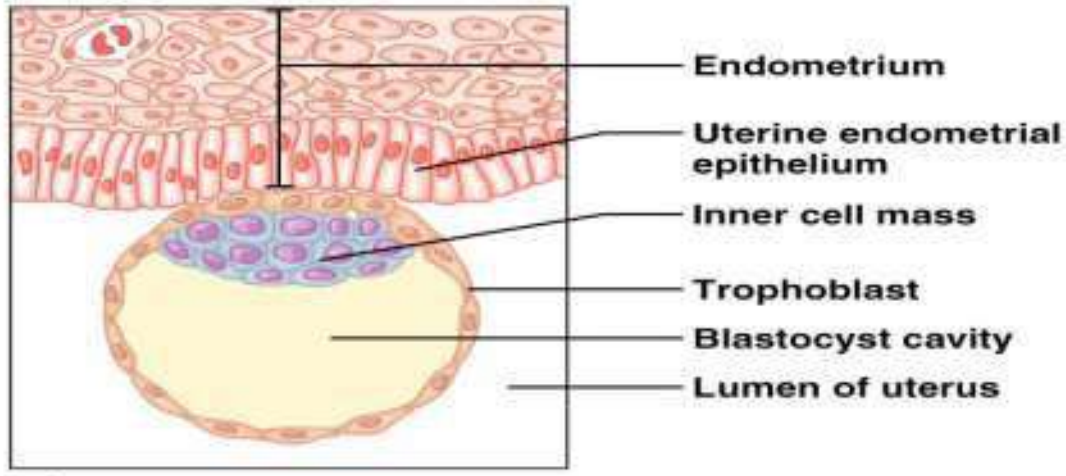
Early Development, Implantation, and Placentation

- The conceptus—a collective term for everything ultimately derived from the original zygote (fertilized egg) throughout the pregnancy—remains in the uterine tube for 3 to 4 days.
- During its stay in the uterine tube, the conceptus undergoes a number of mitotic cell divisions, a process known as cleavage. Thus, the 16- to 32-cell conceptus that reaches the uterus is essentially the same size as the original fertilized egg.
- After reaching the uterus, the conceptus floats free in the intrauterine fluid, from which it receives nutrients, for approximately 3 days, all the while undergoing further cell divisions.
- Soon the conceptus reaches the stage known as a blastocyst, and have begun to differentiate.

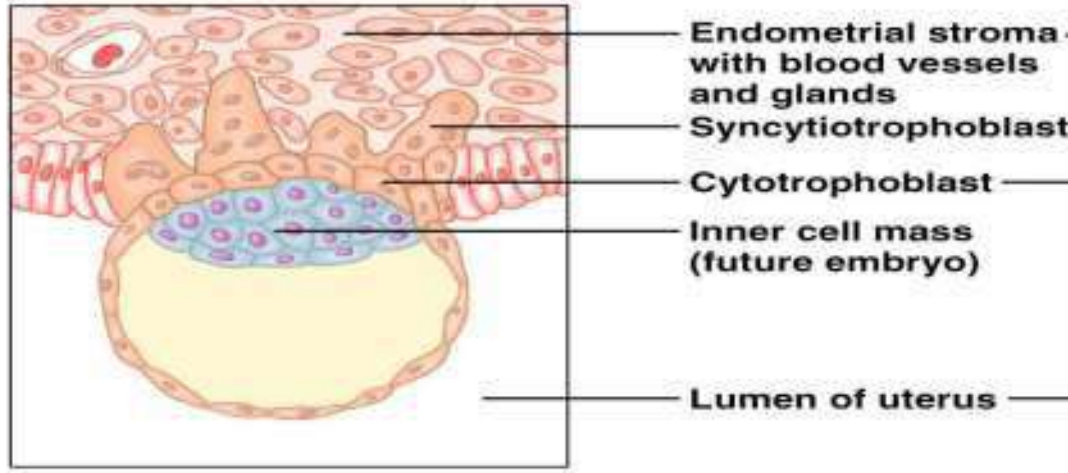
- The blastocyst consists of an outer layer of cells, the **trophoblast**, an inner cell mass, and a central fluid-filled cavity.
- During subsequent development, the inner cell mass will give rise to the developing human—called an **embryo** during the first 2 months and a **fetus** after that—and some of the membranes associated with it.
- The trophoblast will surround the embryo and fetus throughout development and be involved in its nutrition as well as in the secretion of several important hormones.
- The period during which the zygote develops into a blastocyst corresponds with days 14 to 21 of the typical menstrual cycle.
- During this period, the uterine lining is being prepared by progesterone, secreted by the corpus luteum, to receive the blastocyst. By approximately the twenty-first day of the cycle (that is, 7 days after ovulation), implantation—the embedding of the blastocyst in the endometrium—begins.


Degenerating zona pellucida
Blastocyst cavity
Inner cell mass
Blastocyst cavity
Trophoblast
(a) Zygote (fertilized egg)
(b) 4-cell stage 2 days
(c) Morula 3 days
(d) Early blastocyst 4 days
(e) Implanting blastocyst 6 days
Sperm
Fertilization (sperm meets egg)
Uterine tube
Oocyte (egg)
Ovulation
Ovary
(a)
(b)
(c)
(d)
(e)
Uterus
Endometrium
Cavity of uterus

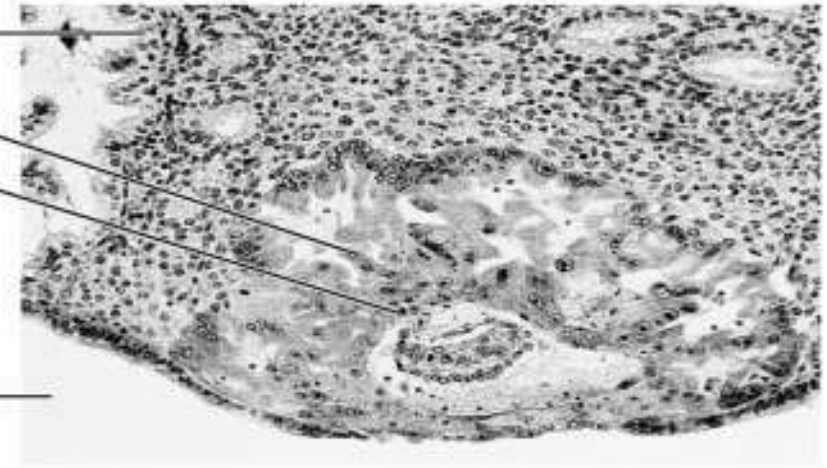
- The initial contact between blastocyst and endometrium induces rapid proliferation of the trophoblast, the cells of which penetrate between endometrial cells. Proteolytic enzymes secreted by trophoblast allow the blastocyst to bury itself in the endometrial layer.
- Implantation is soon completed, and the nutrient-rich endometrial cells provide the metabolic fuel and raw materials required for early growth of the embryo.
- This simple nutritive system, however, is adequate to provide for the embryo only during the first few weeks, when it is very small. The structure taking over this function is the placenta, a combination of interlocking fetal and maternal tissues that serves as the organ of exchange between mother and fetus for the remainder of the pregnancy.



(a)



(b)



(c)

- Throughout pregnancy, plasma concentrations of estrogen and progesterone remain high.
- Estrogen stimulates growth of the uterine muscle mass, which will eventually supply the contractile force needed to deliver the fetus.
- Progesterone inhibits uterine motility so that the fetus is not expelled prematurely.
- During approximately the first 2 months of pregnancy, almost all the estrogen and progesterone are supplied by the extremely active corpus luteum.

- The persistence of the corpus luteum during pregnancy is due to a hormone called **chorionic gonadotropin (CG)**, which starts to be secreted by the trophoblast cells around the time they start their endometrial invasion.
- CG gains entry to the maternal circulation, and the detection of this hormone in the mother's plasma and/or urine is used as a test of pregnancy; it is positive before the next expected menstruation.
- This protein hormone is very similar to LH, and it not only prevents the corpus luteum from degenerating but strongly stimulates steroid secretion by it. Thus, the signal that preserves the corpus luteum comes from the conceptus, not the mother's tissues.

- The secretion of CG reaches a peak 60 to 80 days after the last menstrual period. It then falls just as rapidly, so that by the end of the third month it has reached a low, but still definitely detectable, level that remains relatively constant for the duration of the pregnancy.
- Associated with this falloff of CG secretion, the placenta begins to secrete large quantities of estrogen and progesterone. The very marked increases in plasma concentrations of estrogen and progesterone during the last 6 months of pregnancy are due entirely to their secretion by the trophoblast cells of the placenta, and the corpus luteum regresses after 3 months.

- An important aspect of placental steroid secretion is that the placenta has the enzymes required for the synthesis of progesterone but not those for the formation of androgens, which are the precursors of estrogen. The placenta is supplied, via the fetal circulation, with these androgens, produced by the fetal adrenal glands and liver. The placenta converts the androgens into estrogen.
- Since both these steroid hormones are present in high concentrations throughout pregnancy, the secretion of the pituitary gonadotropins remains extremely low.

- The trophoblast cells of the placenta produce not only CG and steroids, but inhibin and many other hormones as well.
- Some of these (for example, thyroid-stimulating hormone) are identical to hormones normally produced by other endocrine glands, whereas some are unique. One unique hormone that is secreted in very large amounts has effects similar to those of both prolactin and growth hormone. This protein hormone, **placental lactogen** (also called **chorionic somatomammotropin**), plays several roles in the mother—mobilizing fat for energy and stabilizing plasma glucose at relatively high levels (growth hormone–like effects) and facilitating development of the breasts (a prolactin-like effect). In the fetus, this hormone exerts growth-promoting effects, probably by stimulating the secretion of insulin-like growth factor II.
- In addition to all these messengers produced by the trophoblast, the endometrium also secretes a variety of hormones and growth factors important for maintaining the pregnancy.

- Concerning fluid balance and blood pressure during pregnancy, approximately 5–10 percent of pregnant women retain abnormally large amounts of fluid and manifest edema, protein in the urine, and hypertension. These are the symptoms of **preeclampsia**; when convulsions also occur, the condition is termed **eclampsia**. The fetus is also affected, sometimes resulting in intrauterine growth retardation and death.
- The factors responsible for eclampsia are unknown, but the evidence strongly implicates abnormal vasoconstriction of the maternal blood vessels and inadequate invasion of the endometrium by trophoblast cells, resulting in poor blood perfusion of the placenta.

Pregnancy Sickness

- The majority of women suffer from (popularly called morning sickness)—nausea, vomiting, changes in the perception of food palatability, and the presence of taste aversions—during the first three months (first trimester) of pregnancy.
- The exact cause is unknown, but high concentrations of estrogen, progesterone, and other substances secreted at this time are thought to act on the vomiting center in the brain.
- It has been hypothesized that pregnancy sickness is a beneficial process, one that minimizes the mother's intake of potentially toxic chemicals during the first trimester, when the embryo and fetus are particularly susceptible.

Human Reproductive Physiology Dr. Suha Al-Jowari
Lec. 8 Parturition

- A normal human pregnancy lasts approximately 40 weeks, counting from the first day of the last menstrual cycle, or approximately 38 weeks from the day of ovulation and conception. Safe survival of premature infants is now possible at about the twenty-fourth week of pregnancy.
- During the last few weeks of pregnancy, a variety of events occur in the uterus, culminating in the delivery of the infant, followed by the placenta. All these events, including delivery, are termed parturition.
- Throughout most of pregnancy, the smooth-muscle cells of the myometrium are relatively disconnected from each other, and the uterus is sealed at its outlet by the firm, inflexible collagen fibers that constitute the cervix. These features are maintained mainly by progesterone.
- During the last few weeks of pregnancy, as a result of ever-increasing levels of estrogen, the smooth muscle cells synthesize **connexin**, proteins that form gap junctions between the cells, which allows the myometrium to undergo coordinated contractions.

- Simultaneously, the cervix becomes soft and flexible, a process termed "**ripening**," due to an enzymatically mediated breakup of its collagen fibers. The synthesis of the enzymes is mediated by a variety of messengers, including estrogen and placental prostaglandins, the synthesis of which is stimulated by estrogen. (The peptide hormone **relaxin** secreted by the ovaries may also be involved.)
- Estrogen has yet another important effect on the myometrium during this period: It induces the synthesis of receptors for the posterior pituitary hormone **oxytocin**, which is a powerful stimulator of uterine smooth-muscle contraction.
- Delivery is produced by strong rhythmical contractions of the myometrium. Actually, weak and infrequent uterine contractions begin at approximately 30 weeks and gradually increase in both strength and frequency. During the last month, the entire uterine contents shift downward so that the baby is brought into contact with the cervix. In over 90 percent of births, the baby's head is downward and acts as the wedge to dilate the cervical canal when labor begins.

- At the onset of labor or before, the amniotic sac ruptures, and the amniotic fluid escapes through the vagina. When labor begins in earnest, the uterine contractions become coordinated and quite strong (although usually painless at first) and occur at approximately 10- to 15-min intervals. The contractions begin in the upper portion of the uterus and sweep downward
- As the contractions increase in intensity and frequency, the cervix is gradually forced open to a maximum diameter of approximately 10 cm (4 in). Until this point, the contractions have not moved the fetus out of the uterus. At this time the mother, by bearing down to increase abdominal pressure, can help the uterine contractions to deliver the baby. The umbilical vessels and placenta are still functioning, so that the baby is not yet on its own, but within minutes of delivery both the umbilical vessels and the placental vessels completely constrict, stopping blood flow to the placenta. The entire placenta becomes separated from the underlying uterine wall, and a wave of uterine contractions delivers the placenta as the afterbirth.

- Ordinarily, parturition proceeds automatically from beginning to end and requires no significant medical intervention. In a small percentage of cases, however, the position of the baby or some maternal defect can interfere with normal delivery. The headfirst position of the fetus is important for several reasons: (1) If the baby is not oriented headfirst, another portion of its body is in contact with the cervix and is generally a far less effective wedge. (2) Because of the head's large diameter compared with the rest of the body, if the body were to go through the cervical canal first, the canal might obstruct the passage of the head, leading to problems when the partially delivered baby attempts to breathe. (3) If the umbilical cord becomes caught between the canal wall and the baby's head or chest, mechanical compression of the umbilical vessels can result. Despite these potential problems, however, many babies who are not oriented headfirst are born normally.

Mechanisms control the events of parturition

1. The autonomic neurons to the uterus are of little importance since anesthetizing them does not interfere with delivery.

2. The smooth-muscle cells of the myometrium have inherent rhythmicity and are capable of autonomous contractions, which are facilitated as the muscle is stretched by the growing fetus.

3. The pregnant uterus near term and during labor secretes several prostaglandins (PGE2 and PGF2) that are profound stimulators of uterine smooth-muscle contraction.

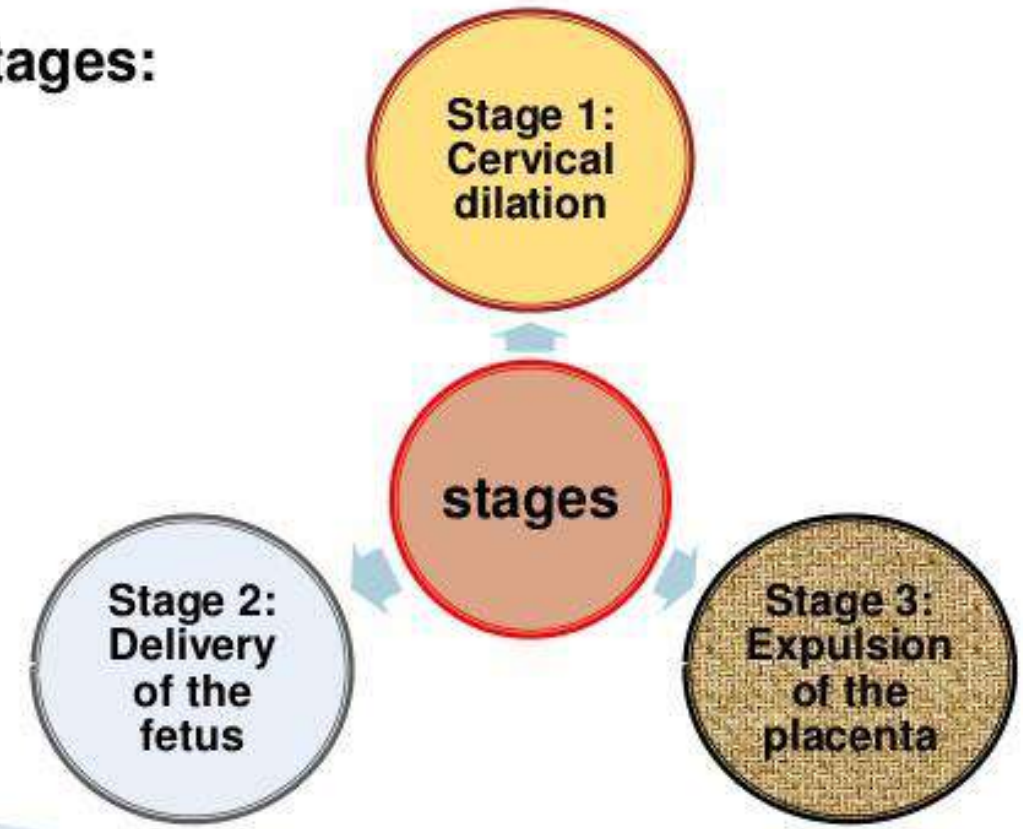
4. Oxytocin, one of the hormones released from the posterior pituitary, is an extremely potent uterine muscle stimulant. It not only acts directly on uterine smooth muscle but also stimulates it to synthesize the prostaglandins mentioned above. Oxytocin is reflexly secreted from the posterior pituitary as a result of neural input to the hypothalamus, originating from receptors in the uterus, particularly the cervix. Also, the number of oxytocin receptors in the uterus increases during the last few weeks of pregnancy; thus, the contractile response to any given plasma concentration of oxytocin is greatly increased at parturition.

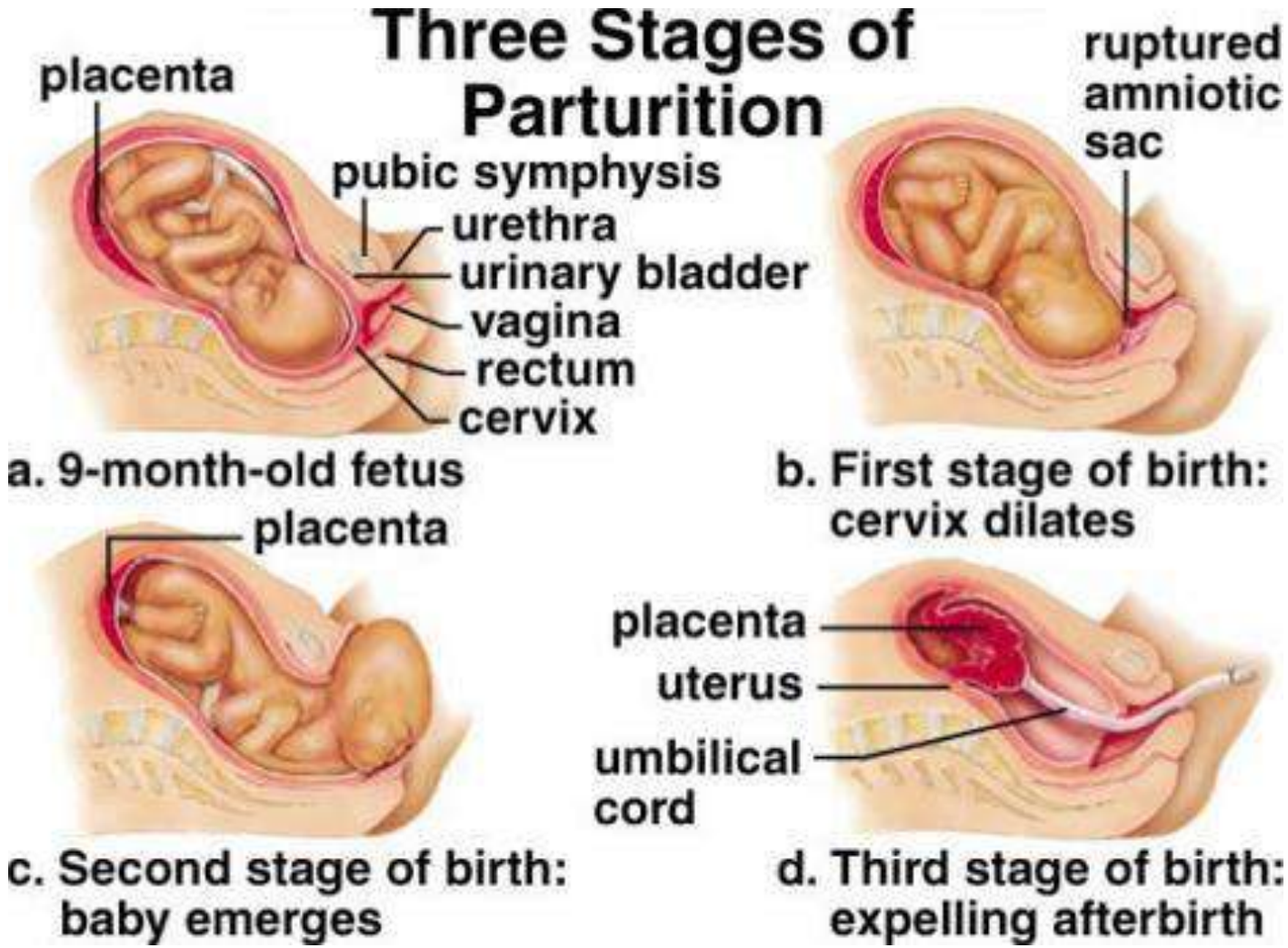
5. Throughout pregnancy, progesterone exerts an essential powerful inhibitory effect upon uterine contractions by decreasing the sensitivity of the myometrium to estrogen, oxytocin, and prostaglandins. Unlike the situation in many other species, however, the rate of progesterone secretion does not decrease before or during parturition in women (until after delivery of the placenta, the source of the progesterone); therefore, progesterone withdrawal does not play a role in parturition.

- The uterine contractions exert a positive-feedback effect upon themselves via both local facilitation of inherent uterine contractions and reflex stimulation of oxytocin secretion. But precisely what the relative importance of all these factors is in initiating labor remains unclear.
- Because of the central role of increasing estrogen levels in parturition, one of the main candidates for the timing of delivery is a hormone from the placenta that stimulates the fetal adrenal cortex to produce androgens, which then are converted into estrogen by the placenta. [This candidate hormone is identical to the hypophysiotropic hormone, corticotropin releasing hormone (CRH).]
- The action of prostaglandins on parturition is the last in a series of prostaglandin effects on the female reproductive system.

Stages

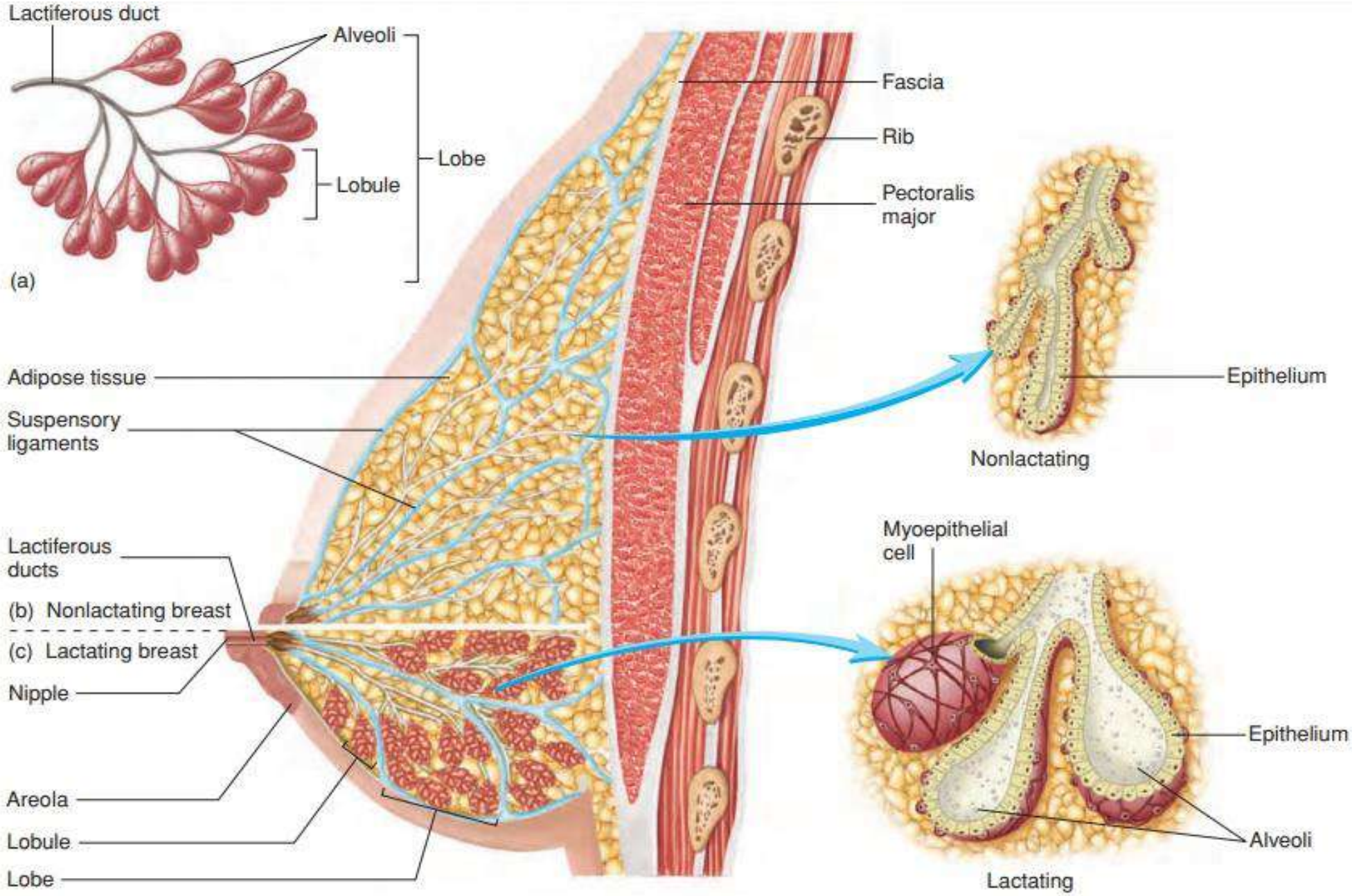
- 3 stages:




Three Stages of Parturition
placenta
pubic symphysis
urethra
urinary bladder
vagina
rectum
cervix
a. 9-month-old fetus
ruptured amniotic sac
b. First stage of birth: cervix dilates
placenta
c. Second stage of birth: baby emerges
placenta
uterus
umbilical cord
d. Third stage of birth: expelling afterbirth

Lec.9 Lactation

- The secretion of milk by the breasts, or **mammary glands**, is termed **lactation.** The breasts contain ducts that branch all through the tissue and converge at the nipples.
- These ducts arise in saclike glands called **alveoli**. The breast alveoli, which are the sites of milk secretion, look like bunches of grapes with stems terminating in the ducts.
- The alveoli and the ducts immediately adjacent to them are surrounded by specialized contractile cells called **myoepithelial cells**.


Lactiferous duct
Alveoli
Lobule
Lobe
(a)
Fascia
Rib
Pectoralis major
Adipose tissue
Suspensory ligaments
Lactiferous ducts
(b) Nonlactating breast
(c) Lactating breast
Nipple
Areola
Lobule
Lobe
Epithelium
Nonlactating
Myoepithelial cell
Epithelium
Alveoli
Lactating

- During each **menstrual cycle**, the breasts undergo fluctuations in association with the changing concentrations of **estrogen** and **progesterone**, but these changes are small compared with the marked breast enlargement during pregnancy as a result of the stimulatory effects of high plasma concentrations of **estrogen, progesterone, prolactin, and placental lactogen**.
- Under the influence of these hormones, both the **ductal and the alveolar structures** become fully developed.

- The **anterior pituitary cells** that secrete **prolactin** are influenced by many hormones.
- They are **inhibited** by **dopamine,** which is secreted by the **hypothalamus**.
- They are probably **stimulated** by **prolactin releasing factor (PRF),** secreted by the **hypothalamus**.
- The **dopamine and PRF** secreted by the hypothalamus are **hypophysiotropic hormones** in that they reach the anterior pituitary by way of the hypothalamo-pituitary portal vessels.
- **Estrogen** also acts on the anterior pituitary to stimulate **prolactin** secretion.
- Under the dominant **inhibitory influence** of **dopamine**, prolactin secretion is low before puberty. It increases at puberty in girls but not in boys, stimulated by the increased plasma estrogen concentration that occurs at this time.
- During **pregnancy**, there is a marked further increase in prolactin secretion due to stimulation by **estrogen**.

- Prolactin is the major hormone stimulating the production of milk.

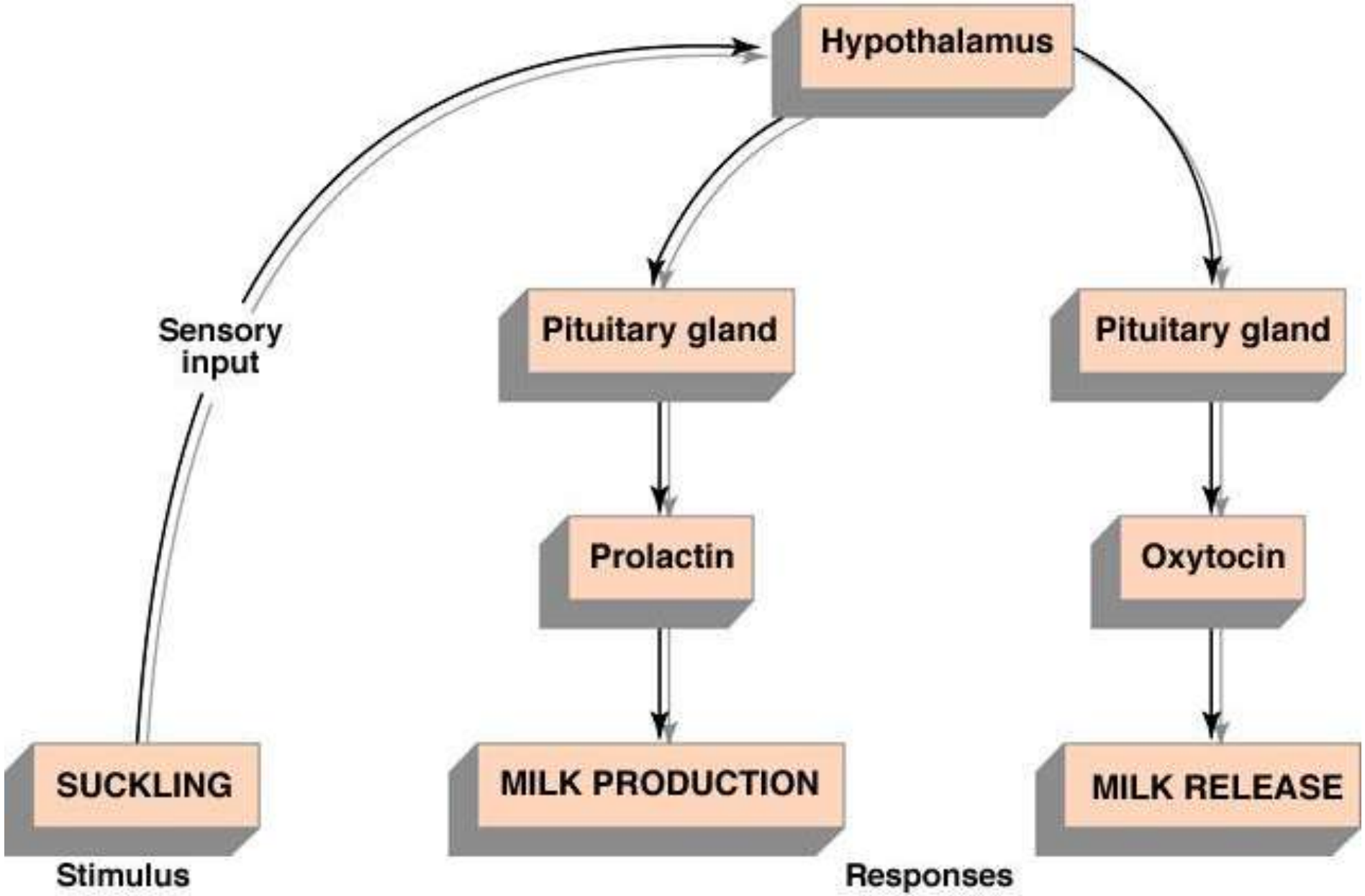
❖despite the fact that prolactin is elevated and the breasts are enlarged and fully developed as pregnancy progresses, there is no secretion of milk. **Why?**

- This is because **estrogen and progesterone**, in large concentrations, prevent milk production by inhibiting this particular action of prolactin on the breasts.
- Thus, although estrogen causes an increase in the secretion of prolactin and acts with prolactin in promoting breast growth and differentiation, it, along with **progesterone**, is **antagonistic to prolactin's ability** to induce milk secretion.
- Delivery removes the source—**the placenta**—of the large amounts of estrogen and progesterone and, thereby, the inhibition of milk production.

- The drop in estrogen following parturition also causes basal prolactin secretion to decrease from its peak late-pregnancy levels and after several months to return toward prepregnancy levels even though the mother continues to nurse. Superimposed upon this basal level, however, are large secretory bursts of prolactin during each nursing period. The episodic pulses of prolactin are signals to the breasts for maintenance of milk production, which ceases several days after the mother completely stops nursing her infant but continues uninterrupted for years if nursing is continued.
- The reflexes mediating the prolactin bursts are initiated by afferent input to the hypothalamus from nipple receptors stimulated by suckling. This input's major effect is to inhibit the hypothalamic neurons that release dopamine and, possibly, also to stimulate the neurons that secrete PRF.

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

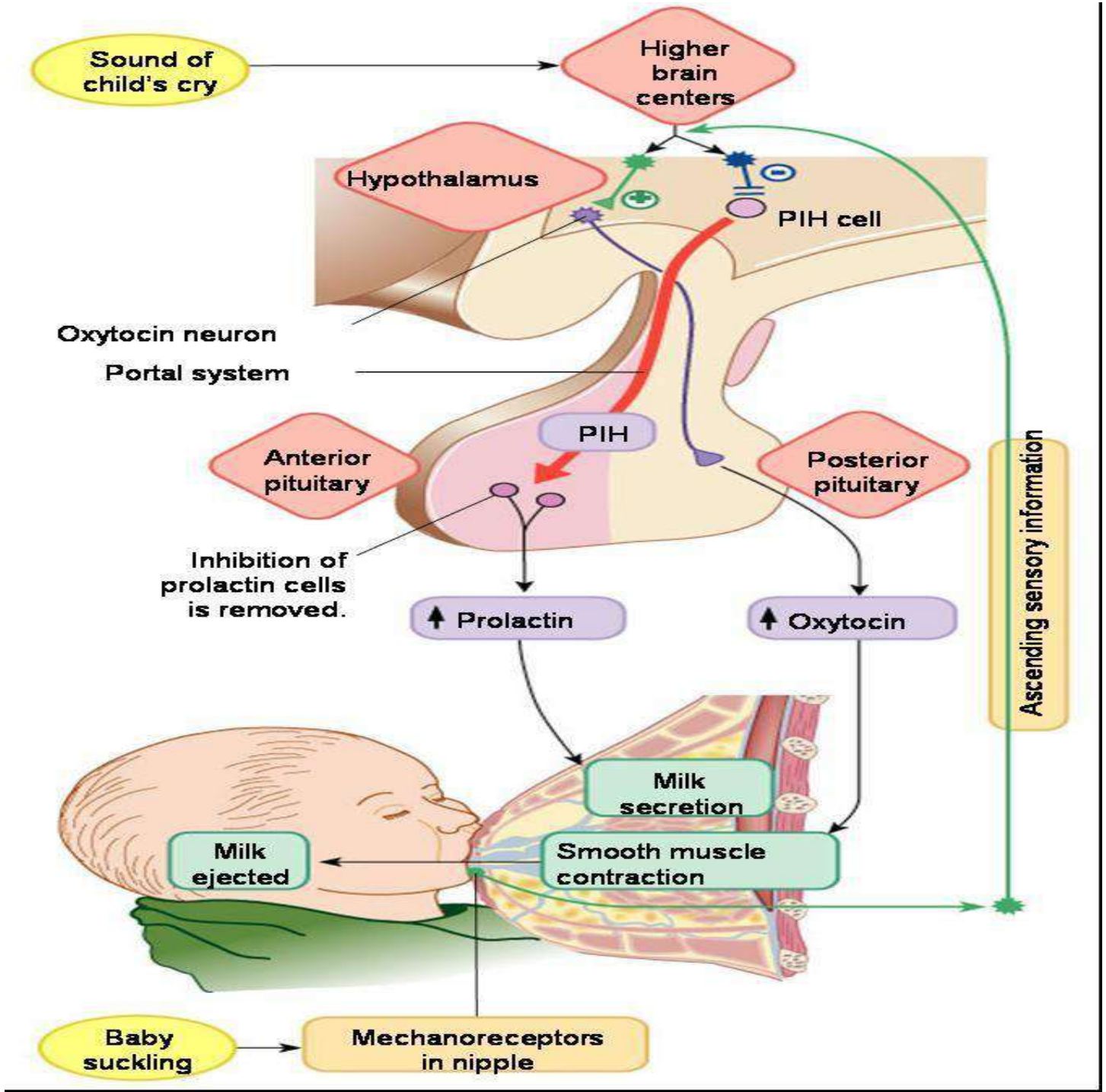
Control of Lactation



- Another **neuroendocrine reflex** triggered by suckling is inhibition of the **hypothalamopituitary- ovarian chain** at a variety of steps, with a resultant block of ovulation. If suckling is continued at high frequency, ovulation can be delayed for years.
- When **supplements are added to the baby's diet** and the **frequency of suckling is decreased**, however, most women will resume ovulation even though they continue to nurse. Failure to recognize this fact may result in an unplanned pregnancy.

Colostrum & Milk Components

- Initially after delivery the breasts secrete only a watery fluid called **colostrum**, which is rich in **protein** but poor in other nutrients.
- After about 24 to 48 hours the secretion of milk, itself, begins.
- Milk contains four major nutrient constituents: **water, protein, fat, and the carbohydrate lactose (milk sugar).**
- Milk also contains **antibodies** and other **messengers of the immune system** which are important for the protection of the newborn, as well as for longer-term activation of the child's own immune system.
- It also contains many **growth factors and hormones** thought to help in tissue development and maturation.
- Some of these substances are synthesized by the breasts themselves, not transported from blood to milk.


Sound of child's cry
Higher brain centers
Hypothalamus
PIH cell
Oxytocin neuron
Portal system
PIH
Anterior pituitary
Posterior pituitary
Inhibition of prolactin cells is removed.
Prolactin
Oxytocin
Ascending sensory information
Milk secretion
Milk ejected
Smooth muscle contraction
Baby suckling
Mechanoreceptors in nipple

Human Reproductive Physiology **Dr. Suha Al-Jowari**

Lec. 10 Contraception & Menopause

Contraception

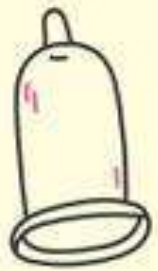
- Some couples use method of contraception. Precise terminology is particularly important in this area. Physiologically, pregnancy is said to begin not at fertilization but after implantation is complete, approximately one week after fertilization.
- Accordingly, procedures that work prior to implantation are termed contraceptives. Procedures that cause death of the embryo or fetus after implantation are termed abortifacients.
- Some forms of contraception—vasectomy, tubal ligation, vaginal diaphragms, vaginal caps, spermicides, and condoms—prevent sperm from reaching the egg. [In addition, condoms significantly reduce the risk of sexually transmitted diseases (STDs) such as AIDS, syphilis, gonorrhea, chlamydia, and herpes.]
- Oral contraceptives are based on the fact that estrogen and progesterone can inhibit pituitary gonadotropin release, thereby preventing ovulation.

- One type of oral contraceptive is a combination of a synthetic estrogen and a progesterone-like substance (a progestogen or progestin).
- Another type is the so called minipill, which contains only the progesterone like substance.
- In actuality, the oral contraceptives, particularly the minipill, do not always prevent ovulation, but they are still effective because they have other contraceptive effects. For example, progestogens affect the composition of the cervical mucus, preventing passage of sperm through the cervix, and they also inhibit the estrogen-induced proliferation of the endometrium, making it inhospitable for implantation.
- Another method of delivering a contraceptive progestogen is via tiny capsules (Norplant) that are implanted beneath the skin and last for 5 years.
- Still another method is the intramuscular injection of a different progestagen substance (Depo-Provera) every 3 months.

- The intrauterine device (IUD) works beyond the point of fertilization but before implantation has begun or is complete. The presence of one of these small objects in the uterus somehow interferes with the endometrial preparation for acceptance of the blastocyst.
- In addition to the methods used before intercourse (precoital contraception), there are a variety of drugs used within 72 h after intercourse (postcoital contraception).
- These most commonly interfere with ovulation, transport of the conceptus to the uterus, or implantation.
- One approach is a high dose of estrogen, or two large doses (12 h apart) of a combined estrogen-progestin oral contraceptive.
- More effective and having fewer side effects is the drug RU 486 (mifeprestone), which has antiprogesterone activity because it binds competitively to progesterone receptors in the uterus but does not activate them.

- Antagonism of progesterone’s effects causes the endometrium to erode and the contractions of the uterine tubes and myometrium to increase.
- RU 486 can also be used later in pregnancy as an abortifacient. The rhythm method uses abstention from sexual intercourse near the time of ovulation.
- Unfortunately, it is difficult to time ovulation precisely, even with laboratory techniques. For example, the small rise in body temperature or change in cervical mucus and vaginal epithelium, all of which are indicators of ovulation, occur only after ovulation.
- This problem, combined with the marked variability of the time of ovulation in many women—from day 5 to day 15 of the cycle—explains why the rhythm method has a high failure rate (19 percent). There are still no effective chemical agents for male contraception.

CONTRACEPTION METHODS



CONDOM

FEMALE CONDOM

DIAPHRAGM

HORMONAL RING

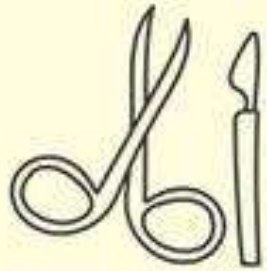
UID

CONTRACEPTIVE INJECTION

IMPLANT

CONTRACEPTIVE PATCH

ORAL CONTRACEPTION



SURGICAL STERILIZATION

Menopause

- Around the age of 50, on the average, menstrual cycles become less regular. Ultimately they cease entirely, and this cessation is known as the menopause.
- The phase of life beginning with menstrual irregularity and including the first year after cessation of menstrual flow is termed the perimenopause, the counterpart of puberty.
- It involves numerous physical and emotional changes as sexual maturity gives way to cessation of reproductive function.
- Menopause and the irregular function leading to it are caused primarily by ovarian failure. The ovaries lose their ability to respond to the gonadotropins, mainly because most, if not all, ovarian follicles and eggs have disappeared by this time through atresia.
- That the hypothalamus and anterior pituitary are functioning relatively normally is evidenced by the fact that the gonadotropins are secreted in greater amounts. The main reason for this is that the decreased plasma estrogen does not exert as much negative feedback on gonadotropin secretion.

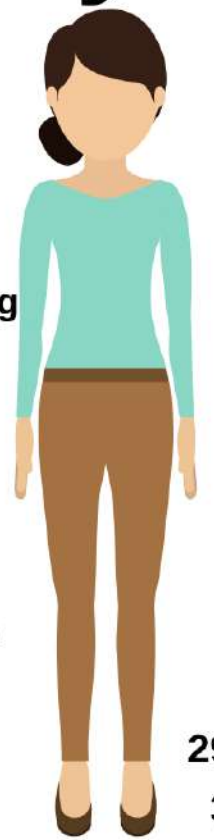
- A small amount of estrogen usually persists in plasma beyond the menopause, mainly from peripheral conversion of adrenal androgens to estrogen, but the level is inadequate to maintain estrogen-dependent tissues.
- The breasts and genital organs gradually atrophy to a large degree. Thinning and dryness of the vaginal epithelium can cause sexual intercourse to be painful.
- Marked decreases in bone mass and strength, termed osteoporosis, may occur because of net bone resorption and can result in bone fractures.
- Sex drive frequently stays the same and may even increase. The hot flashes so typical of menopause are caused by periodic sudden increases in body temperature, which induces a feeling of warmth, dilation of the skin arterioles, and marked sweating; how estrogen deficiency causes this is unknown.

- Another aspect of menopause is its relationship to cardiovascular diseases. Women have much less coronary artery disease than men until after menopause, when the incidence becomes similar in both sexes, a pattern that is due to the protective effects of estrogen: Estrogen exerts beneficial actions on plasma cholesterol, and also exerts multiple direct protective actions on vessel walls.
- Another symptom of menopause in some women is emotional instability.
- Most of the symptoms associated with menopause, as well as the increases in and death from coronary artery disease and osteoporosis, can be reduced by the administration of estrogen.
- Recent studies also indicate that estrogen use may reduce the risk of developing Alzheimer's disease and may also be useful in the treatment of this disease; evaluation of these possibilities must await the completion of larger studies presently in progress.
- The desirability of administering estrogen to postmenopausal women is controversial, however, because of the fact that long-term estrogen administration (more than 5 years) increases the risk of developing uterine endometrial cancer and, possibly, breast cancer as well.
- The increased risk of endometrial cancer can be virtually eliminated by administration of a progestogen along with estrogen, but the progestogen does not influence the risk of breast cancer. The progestogen only slightly lessens estrogen's protective effect against coronary artery disease.

- In conclusion, numerous studies have shown that, overall, hormone replacement therapy definitely decreases mortality in postmenopausal women, principally through estrogen's protective effects against heart disease.
- That is, in the average postmenopausal woman the protection against heart disease (and osteoporosis) far outweighs the negative effect of increased cancer.
- However, this may not be the case for individual women who have a family history of breast or endometrial cancer, or who have another known risk factor for these diseases.
- Relevant to the question of hormone-replacement therapy (as well as to the hormonal treatment of breast and uterine cancer) is the development of substances (for example, tamoxifen) that exert some pro-estrogenic and some anti-estrogenic effects.
- These drugs are collectively termed selective estrogen receptor modulators (SERMs) because they activate estrogen receptors in certain tissues but not in others; moreover, in these latter tissues SERMs act as estrogen antagonists.
- Obviously, the ideal would be to have a SERM that has the pro-estrogenic effects of protecting against osteoporosis, heart attacks, and Alzheimer's disease, but opposes the development of breast and uterine cancers. What makes SERMs possible? One important contributor is that there exist two distinct forms of estrogen receptors, which are affected differentially by different SERMs.

- Changes in the male reproductive system with aging are less drastic than those in women.
- Once testosterone and pituitary gonadotropin secretions are initiated at puberty, they continue, at least to some extent, throughout adult life. There is a steady decrease, however, in testosterone secretion, beginning at about the age of 40, which apparently reflects slow deterioration of testicular function and, as in the female, failure of the gonads to respond to the pituitary gonadotropins.
- Along with the decreasing testosterone levels, both sex drive and capacity diminish, and sperm become much less motile. Despite these events, many men continue to be fertile in their seventies and eighties.
- With aging, some men manifest increased emotional problems, such as depression, and this is sometimes referred to as “male menopause” (or male climacteric). It is not clear, however, what role hormone changes play in this phenomenon.

34 Menopause Symptoms



1.Mood Swings
2.Brain Fog
3.Lack of Motivation
4.Difficulty in Focusing
5.Headaches
6.Night Sweats
7.Hot Flashes
8.Breast Tenderness
9.Digestive Problems
10.Quick Weight Gain
11. Loss of Libido
12.Vaginal Dryness
13.Periods Stop
14.Osteoporosis
15.Joint Stiffness
16.Muscle Aches
17.Decreased Confidence
18.Hair Thins
19.Dry Skin
20.Acne
21.Dry Eyes
22.Wrinkles
23.Dry Mouth
24.Bloating
25.Fatigue
26.Insomnia
27.Anxiety
28.Urinary Pain
29.Clammy Feeling
30.Burning Mouth
31.Facial Hair
32.Dizziness
33.Lack of Focus
34.Depression

The 4 Stages of Menopause

1

Premenopause
Starts when a woman enters her reproductive years and ends with the first signs of menopause. The beginning of premenopause can be defined as the first menstrual cycle.

2

Perimenopause
Estrogen levels begin to decline and fluctuate, causing unpredictable periods. It can last several years and common symptoms are hot flashes, dry skin and irregular periods.

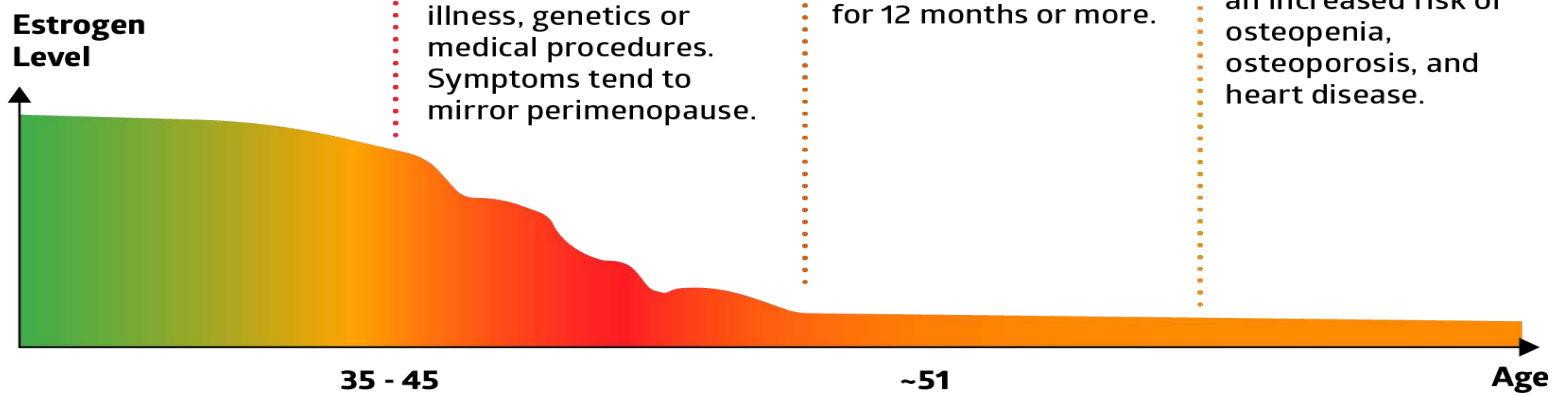
Premature Menopause
Some women may experience early menopause due to illness, genetics or medical procedures. Symptoms tend to mirror perimenopause.

3

Menopause
Represents the end stage of a natural transition in a woman's reproductive life. The ovaries stop producing eggs and a woman can no longer get pregnant naturally. It is marked by the total cessation of the menstrual cycle for 12 months or more.

4

Postmenopause
Refers to the stage after menopause occurs and lasts the remainder of your life. Due to decreases in estrogen, there's an increased risk of osteopenia, osteoporosis, and heart disease.



Symptom Experience: Mild Strong