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Questions

Briefly discuss the cyclic changes in any two of the following

a. cervix

b. vagina

c. breasts

Explicate any one of the following

a. menstrual cycle

b. Hormonal regulation of the menstrual cycle.

ANSWERS

B. VAGINA

The **vagina** is well innervated and has a rich blood supply. It is lined by several layers of epithelium that change histologically during the menstrual cycle. When estradiol levels are low, as during the prepubertal and postmenopausal periods, the vaginal epithelium is thin and the secretions are scanty, resulting in a dry and infection-susceptible area. Estradiol induces proliferation and **cornifi cation (keratinization)** of the vaginal epithelium, whereas progesterone opposes those actions and induces the influxof polymorphonuclear leukocytes into

the vaginal fluids. Estradiol also activates vaginal glands that produce lubricating fluid during coitus.

Oocyte- These mature oocytes develop only once every menstrual cycle. Most follicles in the ovary undergo atresia. However, some develop into mature follicles, produce steroids, and ovulate. As follicles mature, oocytes also mature by entering meiosis, which produces the proper number of chromosomes in preparation for fertilization. After rupturing, the follicle becomes a **corpus luteum.**

The vagina has mucosal, muscular, and adventitial layers. There are no secretory glands, but the cells of the thick, nonkeratinized stratified squamous epithelium become filled with glycogen before desquamation and thin-walled veins of the mucosa and muscular layers exude fluid into the epithelium.The laminapropria is highly cellular and extends narrow papillae into the epithelium The papillae and entire lamina propria are very rich in protective lymphocytes and neutrophils. The muscular layer has bundles of smooth muscle arranged in a circular manner near the mucosa and longitudinally near the adventitia.

The lamina propria of the mucosa is rich in elastic fibers and has numerous narrow papillae projecting into the epithelial layer. The vaginal connective tissue normally contains lymphocytes and neutrophils in relatively large quantities. During the premenstrual and menstrual phases of the cycle, leukocytes are particularly numerous throughout the mucosa and in the lumen of the vagina. The vaginal mucosa itself has few sensory nerve endings.

The muscular layer of the vagina is composed mainly of two indistinct layers of smooth muscle, disposed as circular bundles next to the mucosa and as thicker longitudinal bundles near the adventitial layer. The dense connective tissue of the adventitia is rich in elastic fibers, making the vaginal wall strong and elastic while binding it the surrounding tissues. This outer layer also contains an extensive venous plexus, lymphatics, and nerves.

The wall of the **vagina** lacks glands and consists of three layers: a **mucosa,** a **muscular layer,** and an **adventitia.** Mucus covering the lumen of the vagina is produced by the glands of the uterine cervix. During intercourse additional, lubricating mucus is provided by a pair of large and many small **vestibular glands** opening into the vestibule, a space enclosed within the labia minora that also contains the vaginal and urethral orifices and the anterior erectile tissue of the

clitoris. The stratified squamous epithelium covering these various components of the vestibule, which together make up the **external genitalia**, merges with epidermis of the surrounding skin.

The mucosa of these structures is abundantly supplied with sensory nerves and the range of tactile receptors normally found in skin, which are important in the physiology of sexual arousal.

The epithelium of the vaginal mucosa is stratified squamous, with a thickness of 150–200 m in adults. Its cells contain a small amount of keratohyaline, but do undergo keratinization to form keratin plates as in the epidermis. Stimulated by estrogens, the epithelial cells synthesize and accumulate glycogen. When the cells desquamate, bacteria metabolize glycogen to lactic acid, causing a relatively low pH within the vagina which helps provide protection against pathogenic microorganisms. The vaginal mucosa itself has few sensory nerve endings.The muscular layer of the vagina is composed mainly of two indistinct layers of smooth muscle, disposed as circular bundles next to the mucosa and as thickerlongitudinal bundles near the adventitial layer. The dense connective tissue of the adventitia is rich in elastic fibers, making the vaginal wall strong and elasticwhile binding it the surrounding tissues. This outer layer also contains an extensive venous plexus, lymphatics, and nerves.

C. MAMMARY GLANDS

The **mammary glands** of the breasts develop embryologically as invaginations of surface ectoderm along two ventral lines, the milk lines, from the axillae tothe groin. In humans one set of glands resembling highly modified apocrine sweat glands persists on each side of the chest. Each mammary gland consists of15–25 **lobes** of the compound tubuloalveolar type whose function is to secrete milk to nourish newborns.

Each lobe, separated from the others by denseconnective tissue with much adipose tissue, is a separate gland with its own excretory **lactiferous duct** . These ducts, each 2–4.5 cm long,emergeindependently in the **nipple,** which has 15–25 pore-like openings, each about 0.5 mm in diameter. The structure of the mammary glandsvaries according to sex, age, and physiologic status.

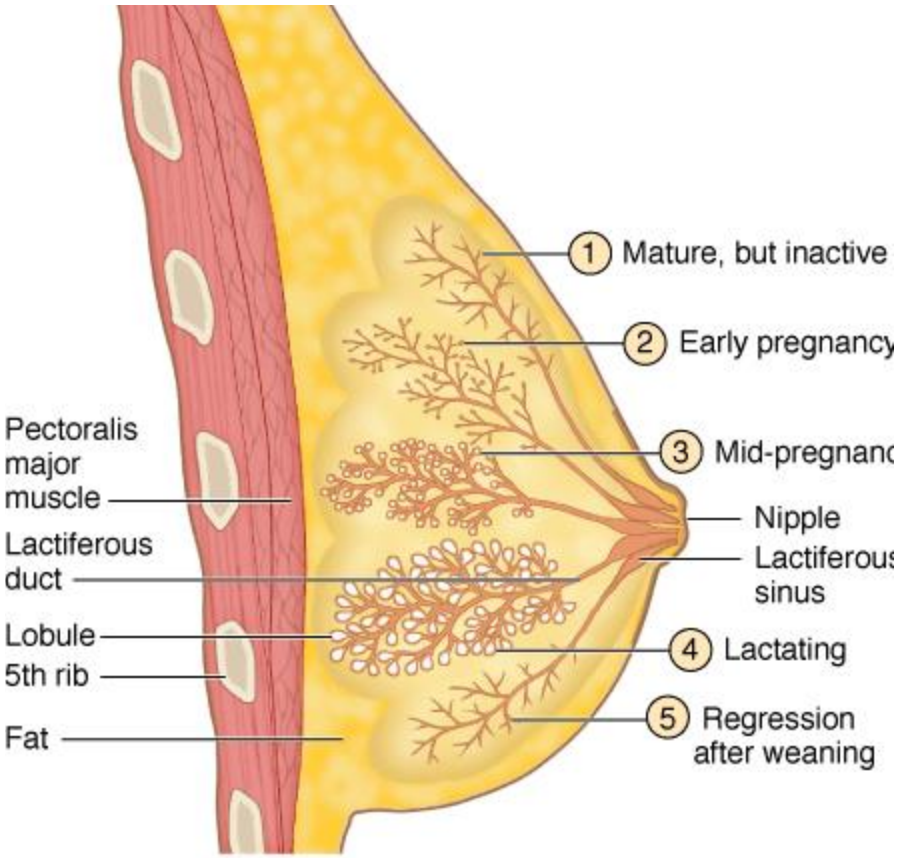


Diagram of the breast

Breast Development during Puberty

Before puberty, the mammary glands in both sexes are composed only of **lactiferous sinuses** near the nipple, with small, branching ducts emerging fromthese sinuses. In girls undergoing puberty and having higher levels of circulating estrogens, the breasts increase in size as a result of adipocyte accumulation in the connective tissue and increased growth and branching of the duct system. The nipple enlarges with growth of the lactiferous sinuses.

In nonpregnant adult women the characteristic parenchymal structure of the gland, the lobe, consists of many **lobules**, sometimes called **terminal ductlobular units** (**TDLU**). Each lobule has several small, branching ducts, but the attached secretory units are small and rudimentary . The ductsystem is embedded in loose, vascular connective tissue and a denser, less cellular connective tissue separates the lobes.

The lactiferous sinuses are lined with stratified cuboidal epithelium and the lining of the lactiferous ducts and terminal ducts is simple cuboidal epithelium covered by closely packed myoepithelial cells. Sparse fibers of smooth muscle also encircle the larger ducts. Epithelial cells of the ducts become slightly morecolumnar at the time of peak estrogen levels around ovulation and in the premenstrual phase of the cycle connective tissue of the breast becomes some what edematous, making the breasts slightly larger.

Skin covering the nipple constituted the **areola** and is fairly typical thin skin with sebaceous glands The epidermis is continuous with the lining of the lactiferous sinuses. The areola contains more melanin than skin elsewhere on the breast and darkens further during pregnancy. Skin of the nipple isabundantly supplied with sensory nerve endings. Connective tissue of the nipple is rich in smooth muscle fibers that run parallel to the lactiferous sinuses and
produce nipple erection when they contract.

Breasts during Pregnancy & Lactation

The mammary glands undergo growth during pregnancy as a result of the synergistic action of several hormones, mainly estrogen, progesterone, prolactin, andhuman placental lactogen. One result of these hormones is the proliferation of secretory **alveoli** at the ends of the intralobularducts.

Alveolar development in the breast during pregnancy

The mammary glands of adult, nonpregnant women are inactive, with small ducts and few lobules having secretory alveoli which are not well-developed. The structure with the large lumen in each lobule is part of the duct; the smaller structures are the small, undeveloped alveoli. The breasts are composed largely of connective tissue, having considerable fat.

The glands become active during pregnancy, with the duct system growing rapidly and the secretory units of each lobule becoming much larger and more extensively branched. In this micrograph adipocytes are included but these are only a small fraction of those present.

During lactation, the lobules are greatly enlarged and the lumens of both the numerous glandular alveoli and the excretory ducts are filled with milk. The protein content of milk makes it

eosinophilic in histological sections. At this time the intralobular connective tissue is more sparse and difficult to see, except for small septa.

Active versus lactating alveoli.

Glandular alveoli develop completely only during pregnancy and begin milk production near the end of pregnancy**.** alveoli develop asspherical structures composed of cuboidal epithelial cells surrounded by the contractile processes of myoepithelial cells . Development occurs at different rates throughout the breast. Late in pregnancy lymphocytes leavevenules, accumulate in the intralobular connective tissue and differentiate as plasma cells .

IgA secreted by these cells is transferred into milk and helps confer passive immunity from the mother to the nursing infant. A small amount of milk is beginning to accumulate in the lumen of the duct .

While alveoli and the system of ducts grow and develop during pregnancy in preparation for lactation, the stroma becomes less prominent. The loose connective tissue within lobules is infiltrated in lymphocytes and plasma cells, the latter becoming more numerous late in pregnancy when they begin to produce immunoglobulins (secretory IgA).

Late in pregnancy the glandular alveoli and ducts are dilated by an accumulation of **colostrum**, a fluid rich in proteins, vitamin A, and certain electrolytes that is produced under the influence of prolactin. Antibodies are synthesized abundantly by plasma cells and transferred into colostrum, from which passive acquired immunity is conferred on the breast-fed newborn.

Following parturition levels of circulating estrogens and progesterone decline and the glandular alveoli of the breasts become very active in milk production, primarily influenced by prolactin from the anterior pituitary. Epithelial cells of the alveoli enlarge and engage actively in synthesis of proteins and lipids for secretion. Large amounts of protein are made on rough ER, processed through the Golgi apparatus and packaged into secretory vesicles, which undergo exocytosis during **merocrine secretion** into the lumen. Spherical lipid droplets, containing primarily neutral triglycerides and cholesterol, form in the cytoplasm of the alveolar cells, grow greatly in size by accretion of more lipids, and eventually pass out of the cells into the lumen by

the process of **apocrine secretion**, during which the droplets become enveloped with a portion of the apical cell membrane

Secretion in the mammary gland

Alveolar cells of the lactating mammary gland are highly active in protein synthesis on rough ER and lipid synthesis. Most proteins are packaged into secretory vesicles in the Golgi apparatus and secreted at the apical end of the cells by typical exocytosis or merocrine secretion. Lipids coalesce as free cytoplasmic droplets.

These grow in size and eventually undergo aprcrine secretion, in which they are extruded from the cell along a portion of the apical cell membrane (and often a small amount of attached cytoplasm.) Both types of secretion are shown here in a sequence moving from left to right.

Throughout lactation secretion of proteins, membrane-bound lipid droplets, and other components is on-going, with the products accumulating as milk in the lumens of the duct system . Proteins normally constitute approximately 1.5% of human milk and include mainly various caseins, which aggregate as micelles, as well as soluble -lactoglobulin and -lactoalbumin, all of which are digested as a source of amino acids by the infant. Less abundant proteins in milk include many which assist digestion and use of other milk nutrients, immunoglobulins and several proteins with antimicrobial activity, and various mitogenic growth factors. Lipids normally constitute about 4% of milk in humans, while the major sugar, lactose, makes up as much as 7–8% and is a major source of energy. Lactose is synthesized in the Golgi apparatus and also serves to help draw water osmotically into the protein secretory vesicles, which adds greatly to the volume of milk.

During lactation

When a woman is breast-feeding, the nursing action of the child stimulates tactile receptors in the nipple, resulting in liberation of the posterior pituitary hormone **oxytocin**. This hormone causes contraction of the smooth muscle of the lactiferous sinuses and ducts, as well as the myoepithelial cells of alveoli, resulting in the **milk-ejection reflex**. Negative emotional stimuli, such as frustration, anxiety, or anger, can inhibit the liberation of oxytocin and thus prevent the reflex.

Postlactational Regression in the Mammary Glands

When breast-feeding is stopped (weaning), most alveoli that developed secretory properties during pregnancy degenerate. There is apoptosis and sloughing of whole cells, with dead cells and debris removed by macrophages, as well as autophagy in most other epithelial cells. The duct system of the gland returns to its general appearance in the inactive state before pregnancy. After menopause, alveoli and ducts of the mammary glands are reduced further in size and there is some loss of fibro-blasts, collagen, and elastic fibers in the stroma

Apoptosis during postlactational mammary gland regression

After weaning, all glandular alveoli of the breast regress, as shown in this plastic section of a single alveolus. The secretory cells now have a low cuboidal structure and many cells are undergoing apoptosis and have sloughed into the lumen. Milk with lipid droplets is also still present there. The dead cells and other tissue debrisare removed by macrophages.

MENSTRUAL CYCLE

The **menstrual cycle** describes the coordinated monthly changes in the ovary and endometrium (lining of the uterus) in women of reproductive age. The menstrual cycle is physically noted by the onset of menstruation, the flow of blood from the uterus through the vagina, when the lining of the uterus is shed. A woman's first menstruation, termed **menarche**, occurs around age 12 years. Th e end of a woman's reproductive phase is called **menopause**, which commonly occurs between ages 45 and 55 years.

Th e average menstrual cycle length in adult women is 28 days, with a range of 25 to 35 days. Th e interval from ovulation to the onset of menstruation is relatively constant, averaging 14 days in most women, and is dictated by the fixed lifespan of the corpus luteum. In contrast, the interval from the onset of menses to ovulation (the follicular phase) is more variable and accounts for diff erences in cycle lengths among ovulating women. Sexual intercourse may occur at any time

during the cycle, but fertilization occurs only during the postovulatory period. Once pregnancy occurs, ovulation ceases, and after parturition, lactation also inhibits ovulation.

Menstrual cycles become irregular as menopause approaches at around age 50 years, and cycles cease thereafter. During the reproductive years, menstrual cycling is subjected to modulation by physiological, psychological, and social factors.

Puberty marks the start of cyclic reproductive function

During the prepubertal period, the hypothalamic-pituitaryovarian axis becomes activated—an event known as **gonadarche -** and gonadotropins increase in the circulation and stimulate ovarian estrogen secretion. Th e increase in gonadotropins results from increased secretion of GnRH. Factors that stimulate the secretion of GnRH include glutamate, norepinephrine, and neuropeptide Y emanating from synaptic inputs to GnRH-producing neurons. In addition, a decrease in γ-aminobutyric acid (GABA), an inhibitor of GnRH secretion, also occurs at this time. Further, the response of the pituitary to GnRH increases at the time of **puberty**.

Collectively, numerous factors control the rise in ovarian estradiol secretion that triggers the development of physical characteristics of sexual maturation.

Estradiol induces the development of **secondary sex characteristics**, including the breasts and reproductive tractand increased fat on the hips and buttocks. Estrogens alsoregulate the growth spurt at puberty, induce closure of theepiphyses, have a positive eff ect in maintaining bone formation,and can antagonize the degrading actions of parathyroidhormone on bone. Therefore, estrogens have a positive effecton bone maintenance, and later in life, exogenous estrogensoppose the osteoporosis oft en associated with menopause.

As mentioned earlier, the fi rst menstruation is called menarche and occurs around age 11–12 years. The first few menstrual cycles are usually irregular and anovulatory, as the result of delayed maturation of the positive feedback by estradiol on a hypothalamus that fails to secrete significant GnRH. During puberty, LH secretion occurs more during periods of sleep than during periods of wakefulness, resulting in a diurnal cycle.

During the pubertal period, the development of breasts, under the influence of estrogen, is known as **thelarche**. At this time, the appearance of axillary and pubic hair occurs,a development known as **pubarche**, controlled by adrenal androgens. Th e adrenals begin to produce significant

amounts of androgens (dehydroepiandrosterone and androstenedione) 4 to 5 years prior to menarche, and this event is called **adrenarche**. Th e adrenal androgens are responsible in part for pubarche. Adrenarche is independent of gonadarche.

Menstrual cycle comprises four phases and requires synchrony among the ovary, brain, and pituitary

The four phases of the menstrual cycle are illustrated in. The **menstrual phase**, also called **menses** or **menstruation**, is the bleeding phase and lasts about 5 days.

Th e ovarian **follicular phase** lasts about 10 to 16 days; follicle development occurs, estradiol secretion increases, and the uterine endometrium undergoes proliferation in response to rising estrogen levels.

The **ovulatory phase** lasts 24 to 48 hours, and the **luteal phase** lasts 14 days. In the luteal phase, progesterone is produced, and the endometrium secretes numerous proteins in preparation for implantation of an embryo.

The menstrual cycle requires several coordinated elements: hypothalamic control of pituitary function, follicular and luteal changes in the ovary, and positive and negative feedback of ovarian hormones at the hypothalamic-pituitary axis. For this purpose, we use a hypothetical cycle of 28 days, divided into four phases as follows:

menstrual (days 0–5),
follicular (days 0–13),
ovulatory(days 13–14),
luteal (days 14–28).

Menstrual phase

During menstruation, estrogen, progesterone, and inhibin levels are low as a result of the luteal regression that has just occurred and the low estrogen synthesis by immature follicles. The plasma FSH levels are high whereas LH levelsare low in response to the removal of negative feedback by estrogen, progesterone, and inhibin. A few days later, however, LH levels slowly begin to rise. FSH acts on a cohort of follicles recruited 20 to 25 days earlier from a resting pool of smaller follicles. Th e follicles on days 3 to 5 average 4 to 6 mm wide and are stimulated by FSH to grow into the preantral stages. In response to FSH, the granulosa cells proliferate,

aromatase activity increases, and plasma estradiol levels rise slightly between days 3 and 7. The designated dominant follicle is selected between days 5 and 7 and increases in size and steroidogenic activity. Between days 8 and 10, plasma estradiol levels rise sharply, reaching peak levels above 200 pg/mL on day 12, the day before the LH surge.

Follicular phase

During the early follicular phase, LH pulsatility is of low amplitude and high frequency (about every hour). Coinciding pulses of GnRH are released about every hour. As estradiol levels rise, the pulse frequency in GnRH further increases, without a change in amplitude. Th e mean plasma LH level increases and further supports follicular steroidogenesis, especially because FSH has increased the number of LH receptors on growing follicles. During the midfollicular to late follicular phase, rising estradiol and inhibin from the dominant follicle suppress FSH release. Th e decline in FSH, together with an accumulation of nonaromatizable androgens, induces atresia in the nonselected follicles. The dominant follicle is saved by virtue of its high density of FSH receptors, the accumulation of FSH in its follicular fluid, and the acquisition of LH receptors by the granulosa cells.

Ovulatory phase

The midcycle surge of LH is short (24–36 hours) and is an example of positive feedback. For the LH surge to occur, estradiol must be maintained at a critical concentration (about 200 pg/mL) for a sufficient duration (36–48 hours) prior to the surge. Any reduction of the estradiol rise or a rise that is too small or too short eliminates or reduces the LH surge. In addition, in the presence of elevated progesterone, high concentrations of estradiol do not induce an LH surge. Paradoxically, although it exertsnegative feedback on LH release most of the time, positivefeedback by estradiol is required to generate the midcyclesurge.

Estrogen exerts its eff ects directly on the anterior pituitary, with GnRH playing a permissive, albeit mandatory, role. Th is concept is derived from experiments in monkeys, whose medial basal hypothalamus, including the GnRH producing neurons, was destroyed by lesioning, resulting in a marked decrease in plasma LH levels. Th e administration of exogenous GnRH at a fi xed frequency restored LH release.

When estradiol was given at an optimal concentration for an appropriate time, an LH surge was generated, in spite of maintaining steady and unchanging pulses of GnRH.

The mechanism that transforms estradiol from a negative to a positive regulator of LH release is unknown. One factor involves an increase in the number of GnRH receptors on the gonadotrophs, increasing pituitary responsiveness to GnRH.

Another factor is the conversion of a storage pool of LH (perhaps within a subpopulation of gonadotrophs) to a readily releasable pool. Estrogen may also increase GnRH release, serving as a fi ne-tuning or fail–safe mechanism. A small but distinct rise in progesterone occurs before the LH surge. This rise is important for augmenting the LH surge and, together with estradiol, promotes a concomitant surge in FSH. There are indications that the midcycle FSH surge is important for inducing enough LH receptors on granulosa cells for luteinization, stimulating plasminogen activator for follicular rupture and oocyte release, and activating a cohort of follicles destined to develop in the next cycle.

The LH surge reduces the concentration of 17a-hydroxylase and subsequently decreases androstenedione production by the dominant follicle. Estradiol levels decline, 17-hydroxyprogesterone increases, and progesterone levels plateau. The prolonged exposure to high LH levels during the surge down-regulates the ovarian LH receptors, accounting for the immediate postovulatory suppression of estradiol.

As the corpus luteum matures, it increases progesterone production and reinitiates estradiol secretion. Both reach high plasma concentrations on days 20 to 23, about 1 week after ovulation.

Some women experience pain around the time of ovulation. This condition is referred to as **mittelschmerz** or mid cycle pain. Mittelschmerz is characterized by lower abdominal, pelvic, and/or lower back pain that can appear suddenly and usually subsides within hours, although in some cases the pain can last up to 2 to 3 days. It has been suggested that spillage of fluid from the ruptured follicle may irritate the peritoneum.

Luteal phase

During the luteal phase, the elevated steroids suppress circulating FSH levels. The LH pulse frequency is reduced during the early luteal phase, but the amplitude is higher than that during

the follicular phase. LH is important at this time for maintaining corpus luteum function and sustaining steroid production. In the late luteal phase, a progesterone- dependent, opioid-mediated suppression of the GnRH pulse generator reduces both LH pulse frequency and amplitude.

After the demise of the corpus luteum on days 24 to 26, estradiol and progesterone levels plunge, causing the withdrawal of support of the uterine endometrium, culminating within 2 to 3 days in menstruation. Th e reduction in ovarian steroids acts centrally to remove feedback inhibition.

The FSH level begins to rise and a new cycle is initiated.

Estradiol and progesterone influence cyclic changes comprising four phases in the reproductive tract

The female reproductive tract undergoes cyclic alterations in response to the changing levels of ovarian steroids. The most notable changes occur in the function and histology of the oviduct and uterine endometrium, the composition of cervical mucus, and the cytology of the vagina . At the time of ovulation, there is also a small but detectable rise in basal body temperature, caused by progesterone. All of the above parameters are clinically useful for diagnosing menstrual dysfunction and infertility.

The oviduct is a muscular tube lined internally with a ciliated, secretory, columnar epithelium with a deeper stromal tissue. Fertilization occurs in the oviduct, aft er which the zygote enters the uterus; therefore, the oviduct is involved in transport of the gametes and provides a site for fertilization and early embryonic development. Estrogens maintain the ciliated nature of the epithelium, and ovariectomy causes a loss of the cilia. Estrogens also increase the motility of the oviducts. Exogenous estrogen given around the time of fertilization can cause premature expulsion of the fertilized egg,

whereas extremely high doses of estrogen can cause “tube locking”—the entrapment of the fertilized egg and an ectopic pregnancy. Progesterone opposes these actions of estrogen.

The endometrium (also called *uterine mucosa*) is composed of a superficial layer of epithelial cells and an underlying stromal layer. Th e epithelial layer contains glands that penetrate the stromal layer. A secretory columnar epithelium lines the glands.

Th e **endometrial cycle** consists of four phases, which includes

Proliferative phase

Th e **proliferative phase** coincides with the midfollicular to late follicular phase of the menstrual cycle. Under the influence of the rising plasma estradiol concentration, the stromal and epithelial layers of the uterine endometrium undergo hyperplasia and hypertrophy and increase in size and thickness. Th e endometrial glands elongate and are lined with columnar epithelium.

The endometrium becomes vascularized, and more spiral arteries—a rich blood supply to this region—develop.

Estradiol also induces the formation of progesterone receptorsand increases myometrial excitability and contractility.

Secretory phase

Th e **secretory phase** begins on the day of ovulation and coincides with the early to midluteal phase of the menstrual cycle. Th e endometrium contains numerous progesterone receptors. Under the combined action of progesterone and estrogen, the endometrial glands become coiled, store glycogen, and secrete large amounts of carbohydrate-rich mucus. The stroma increases in vascularity and becomes edematous, and the spiral arteries become tortuous. Peak

secretory activity, edema formation, and overall thickness of the endometrium are reached on days 6 to 8 aft er ovulation in preparation for implantation of the blastocyst. Progesterone antagonizes the eff ect of estrogen on the myometrium and reduces spontaneous myometrial contractions.

Ischemic phase

Th e **ischemic phase**, generally not depicted graphically, occurs immediately before the menses and is initiated by the declining levels of progesterone and estradiol caused by regression of the corpus luteum. Necrotic changes and abundant apoptosis occur in the secretory epithelium as it collapses.

The arteries constrict, reducing the blood supply to the superficial endometrium. Leukocytes and macrophages invade the stroma and begin to phagocytose the ischemic

tissue. Leukocytes persist in large numbers throughout menstruation, providing resistance against infection to the denuded endometrial surface.

Menstrual phase

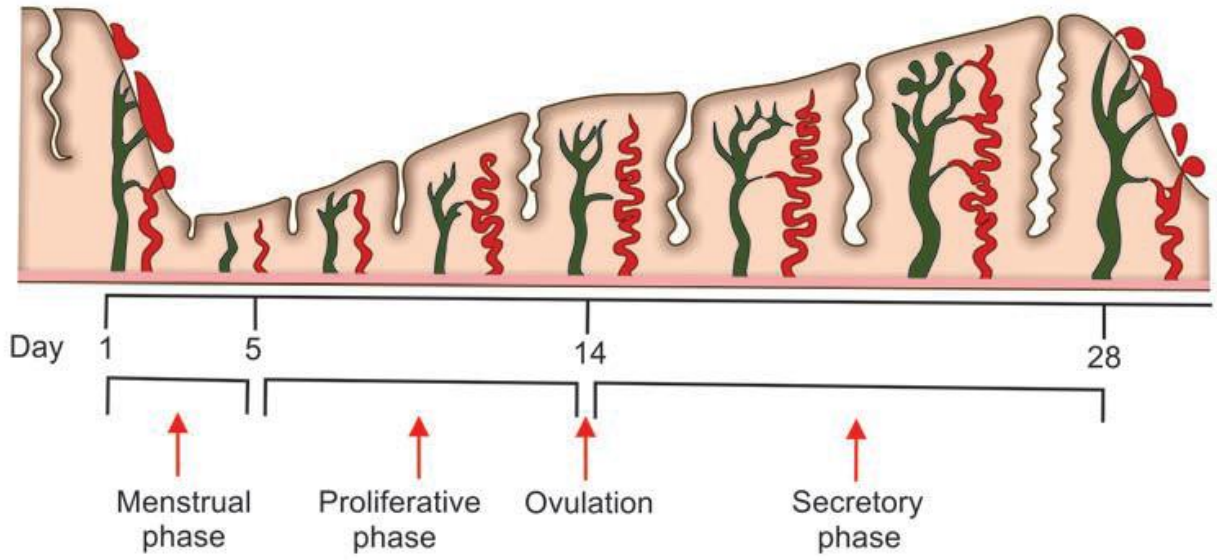
Desquamation and sloughing of the entire functional layerof the endometrium occur during the menstrual phase(*menses*). Th e mechanism leading to necrosis is only partly understood. Th e reduction in steroids destabilizes lysosomal membranes in endometrial cells, resulting in the liberation of proteolytic enzymes and increased production of vasoconstrictor prostaglandins such as prostaglandin F2.

The prostaglandins induce vasospasm of the spiral arteries, and the proteolytic enzymes digest the tissue. Eventually, the blood vessels rupture and blood is released, together with cellular debris. The endometrial tissue is expelled through the cervix and vagina, with blood from the ruptured arteries.

The menstrual flow lasts 4 to 5 days and averages 30 to 50 mL in volume. It does not clot because of the presence of fibrinolysin, but the spiral arteries constrict, resulting in a reduction in bleeding.

Cervical mucus changes

Changes in the properties of the cervical mucus promote the survival and transport of sperm and can thus be important for normal fertility. The cervical mucus undergoes cyclic changes in composition and volume. During the follicular phase, oestrogen increases the quantity, alkalinity, viscosity, and elasticity of the mucus. Th e cervical muscles relax, and the epithelium becomes secretory in response to estrogen. By the time of ovulation, elasticity of the mucus or spinnbarkeit is greatest. Sperm can readily pass through the estrogen-dominated mucus. With progesterone rising either aft er ovulation, during pregnancy, or with low-dose administration of progestogen during the cycle, the quantity and elasticity of the mucus decline;



Uterine changes during menstrual cycle

it becomes thicker (low spinnbarkeit) and does not form a ferning pattern when dried on a microscope slide. With these conditions, the mucus provides better protection against infections and sperm do not easily pass through. The vaginal epithelium proliferates under the influence of estrogen. Basophilic cells predominate early in the follicular phase. The columnar epithelium becomes cornified (keratinized) under the influence of estrogen and reaches its peak in the periovulatory period. During the postovulatory period, progesterone induces the formation of thick mucus, the epithelium becomes infiltrated with leukocytes, and cornification decreases..

Menopause is the cessation of ovarian function and reproductive cycles

The time after which the final menses occurs is termed menopause. Generally, menstrual cycles and bleeding become irregular, and the cycles may become shorter from the lack of follicular development (shortened follicular phases). The ovaries atrophy and are characterized by the presence of few, if any, healthy follicles. The decline in ovarian function is associated with a decrease in estrogen secretion and a concomitant increase in LH and FSH, which is characteristic of menopausal women. It is used as a diagnostic tool. The elevated LH stimulates ovarian stroma cells to continue producing androstenedione. Estrone, derived almost entirely from the peripheral conversion of adrenal and ovarian androstenedione, becomes the dominant estrogen. Because the ratio of estrogens to androgens decreases, some women exhibit hirsutism, which results from androgen excess. The lack of estrogen causes atrophic changes in the breasts and reproductive

tract, accompanied by vaginal dryness, which oft en causes pain and irritation. Similar changes in the urinary tract may give rise to urinary disturbances. The epidermal layer of the skin becomes thinner and less elastic. Hot fl ashes, resulting from the loss of vasomotor tone, osteoporosis, and an increased risk of cardiovascular disease are not uncommon. Hot flashes are associated with episodic increases in upper body and skin temperatures, peripheral vasodilation, and sweating. They occur concurrently with LH pulses, but are not caused by the gonadotropins because they are evident in hypophysectomized women. Hot flashes, consisting of episodes of sudden warmth and sweating, reflect temporary disturbances in the hypothalamic VGnRH pulse generator. Osteoporosis increases the risk of hip fractures, and estrogen replacement therapy reduces the risk. Estrogen antagonizes the eff ects of PTH on bone but enhances its effect on kidney; that is, it stimulates retention of calcium.

Estrogen also promotes the intestinal absorption of calcium through 1,25-dihydroxyvitamin D3.

Menopausal symptoms are oft en treated with hormone replacement therapy, which includes estrogens and progestins

- **ESTROGEN, PROGESTIN, AND ANDROGEN**- Th e principal sex steroids in the female are estrogen, progestin, and androgen. Three **estrogens** are present in significant quantities: estradiol, estrone, and estriol. Estradiol is the most abundant and is 12 and 80 times more potent than estrone and estriol, respectively. Much of estrone is derived from peripheral conversion of either androstenedione or estradiol). During pregnancy, large quantities of estriol.

REGULATION OF MENSTRUAL CYCLE

Regulation of menstrual cycle is a complex process that is carried out by a well organized regulatory system.

The regulatory system is a highly integrated system, which includes hypothalamus, anterior pituitary and ovary with its growing follicle. In the whole scenario, the growing follicle has a vital role to play.