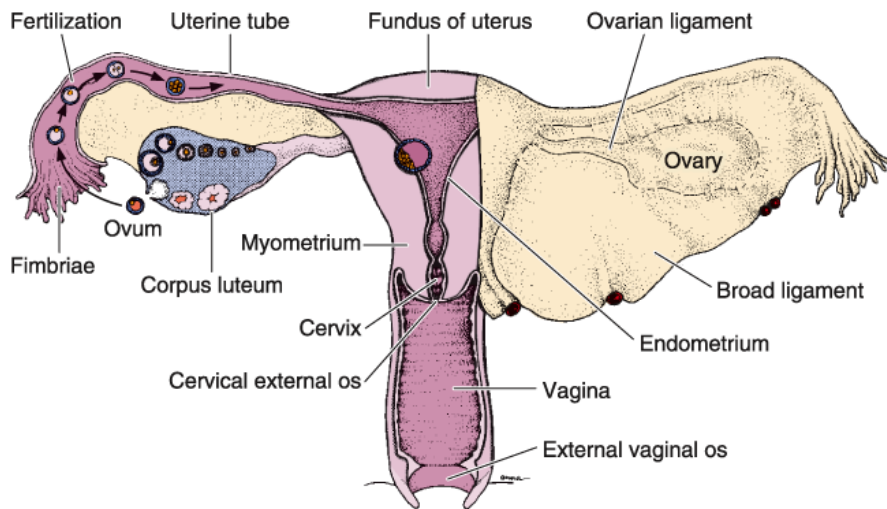


Histology

Female Reproductive System

The female reproductive system consists of 2 **ovaries**, 2 **oviducts** (**uterine tubes**), single **uterus**, **vagina** & **external genitalia**. The functions of female reproductive system are to produce female gametes (**oocytes**), provide the environment for fertilization, & to hold the embryo throughout its development until birth. In addition, the female reproductive system produces the female sexual hormones.

In humans, the female reproductive system starts to function at the age of 12-15 years (the **menarche**), where it undergoes monthly cyclic changes under stimulation of pituitary hormones that end with the liberation of an oocyte from one ovary. This continues until the age of 45-50 years (the **menopause**), when this menstrual cycle stops & the female becomes infertile.



The Ovary

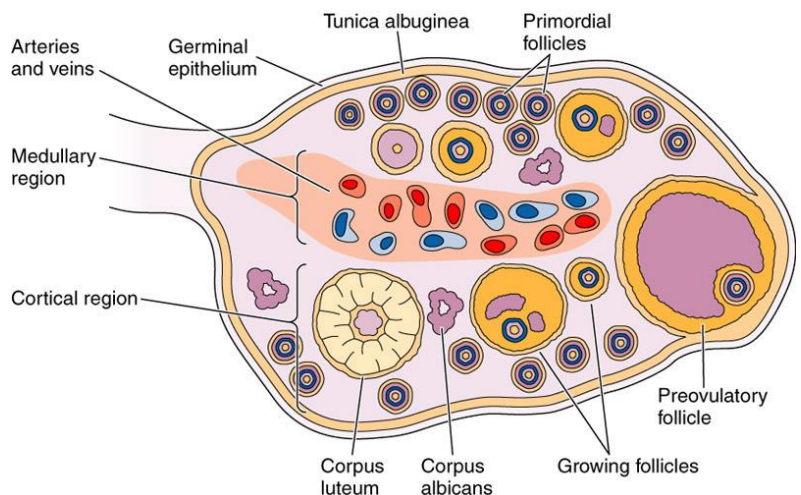
The ovaries are 2 almond-shaped bodies (3x1.5x1 cm) that lie in the true pelvis. Externally, each ovary is covered by a single layer of variable-height cuboidal epithelium (the **germinal epithelium**), which rests on a dense connective tissue layer (the **tunica albuginea**). The ovary is divided into an outer cortex & an inner medulla.

The **ovarian cortex** is a connective tissue (stroma) containing a great number of specialized spindle-shaped fibroblasts (the **stromal cells**) that can respond to certain hormones. In the cortex, the ovarian follicles (structures that contain the oocytes) are seen in different stages of development.

The **ovarian medulla** is a loose connective tissue containing rich vascular bed. The cortico-medullary border is not so clear.

Ovarian Follicular Development:

- **Prenatal events:** after the first month of embryonic life, primordial germ cells (oogonia) are formed in the yolk sac. They divide mitotically several times while migrating to the cortex of the future ovary, where mitotic divisions continue. From the third to the seventh month of



intrauterine life, some of these oogonia enter the prophase of the first meiotic division but stop at the diplotene stage of prophase and become primary oocytes. Each primary oocyte becomes surrounded by a single layer of flattened follicular cells and stays as so till the puberty.

- **Postpubertal events:** the female reaches the puberty with her ovaries containing about 500,000 ova all dormant in the prophase of the first meiotic division. Under hormonal stimuli (discussed later) the ovaries start to have cyclic monthly changes during which some follicles grow and only one of them reaches full maturity and ends with the liberation of its ovum out of the ovary (i.e: ovulation). During each cycle , the following follicular stages are seen:

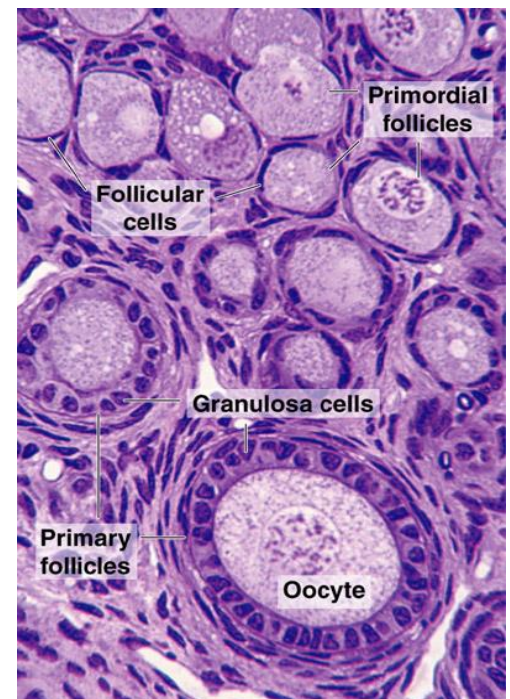
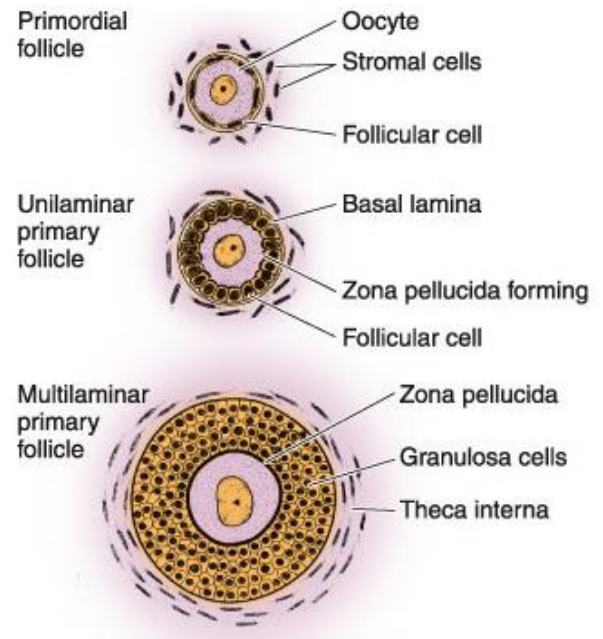
- i. **Primordial follicles:** present in the ovary since intrauterine life, each follicle consists of a single primary oocyte (25 μ m) surrounded by a single layer of flattened follicular cells. Until puberty, they are unresponsive to gonadotropins (resting stage).

- ii. **Growing follicles:** these include :

- a- **Unilaminar primary follicles:** the flattened cells surrounding the primary oocyte in the primordial follicle divide mitotically and become cuboidal cells that form a single layer around the ovum.

- b- **Multilaminar primary follicles:** the cuboidal cells (above) continue to divide forming multiple layers of follicular cells, called "the **granulosa cells**" around the ovum, with gap junctions found between these cells. Simultaneously, a thick glycoprotein coat, the "**zona pellucida**", is formed between the oocyte and granulosa cells. Zona pellucida is penetrated by oocyte microvilli, which meet longer processes (filopodia) from follicular cells, & join them by gap junctions. Separated from granulosa cells by their basement membrane, the stroma immediately around the follicle differentiates to form "**theca folliculi**", which subsequently differentiates into "**theca interna**" and "**theca externa**". Theca interna cells have the features of steroids secreting cells (large rounded cells with cytoplasmic lipid droplets), they synthesize androstenedione, which is converted into estradiol by granulosa cells. Theca externa cells are spindle-shaped with no secretory function.

- c- **Secondary Follicles:** as granulosa cells increase in size and number, they secrete follicular fluid (**liquor folliculi**) that accumulates between the cells. The cavities containing the fluid coalesce to form a larger cavity, the "**antrum**", and the follicle now is called "**secondary**

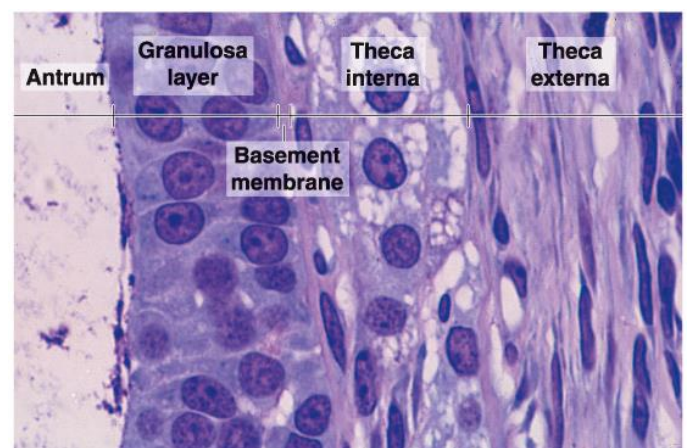
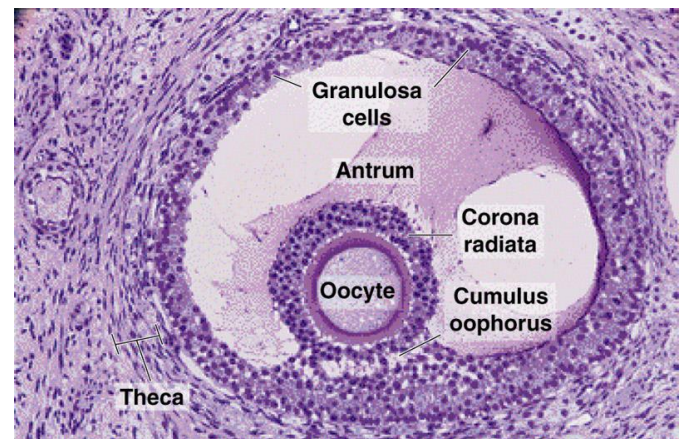
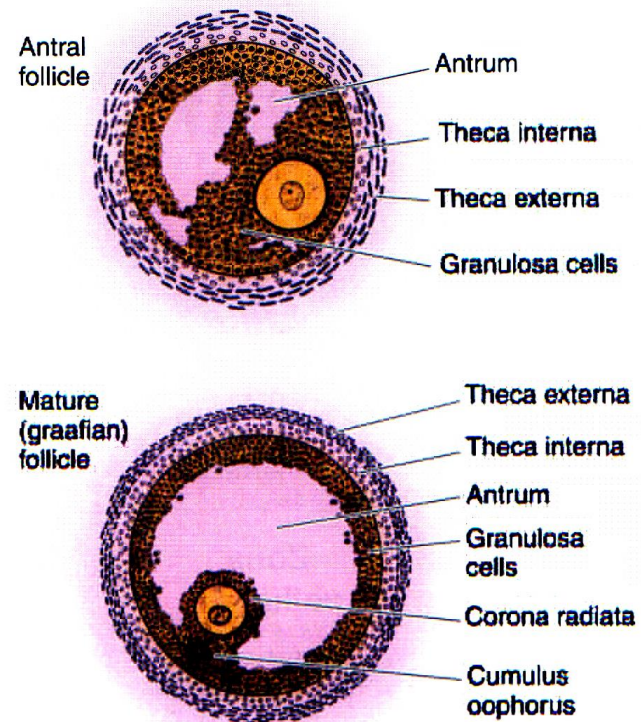


(antral) follicle". Follicular fluid contains proteins (hyaluronate, growth factors, heparin sulfate, etc) & steroids (progesterone, androstenedione and estrogens). As the antrum enlarges, granulosa cells form the wall of the follicle, with a cellular mass containing the oocyte on one side, called the "**cumulus oophorus**". The oocyte grows no more thereafter. Theca interna and theca externa are more prominent than in the primary follicles.

iii. **Mature (Graafian) follicles:** these represent the final stage of follicular development, they result from the increased amount of follicular fluid and number of granulosa cells so that the follicle is about 2.5 cm in diameter before ovulation. Due to faster fluid accumulation, follicular wall becomes thinner, with the oocyte attached to it via the cumulus oophorus. The granulosa cells that form the first layer around the ovum become elongated and form the "**corona radiata**", which accompanies the ovum after ovulation. The primary oocyte completes the first meiotic division by this stage of development producing the "secondary oocyte" and a small **polar body**. At ovulation, the secondary oocyte is in the metaphase of meiosis II. In each ovarian cycle, large number of primordial follicles grow under FSH effect, eventually only one of them reaches full maturity & become a Graafian follicle where ovulation occurs.

Ovulation:

Ovulation is the rupture of the wall of the mature follicle and liberation of the oocyte, which is caught by the oviduct fimbria. It occurs at about the middle of the menstrual cycle. The stimulus for ovulation is a surge of **luteinizing hormone (LH)** secreted by the anterior pituitary gland in response to high levels of estrogen produced by the growing follicles. LH surge causes: (1) an increased blood flow through the ovary causing oedema, (2) an increased collagenase activity causing digestion of collagen fibers of tunica albuginea over the follicle (with the appearance of a whitish translucent area "the **stigma**" on the ovarian surface), (3)



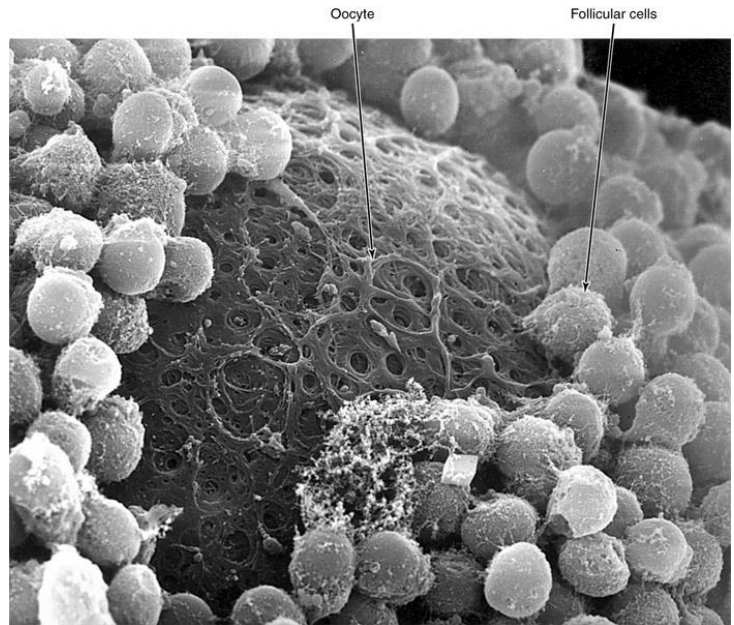
an increase in prostaglandins level that causes local contraction in the ovarian stromal cells. High follicular fluid pressure plus local weakness lead to rupture of follicular wall and ovulation.

The first meiotic division is completed just before ovulation (until this moment the oocyte was in prophase I of meiosis). One of the **secondary oocytes** retains almost all of the cytoplasm, & the other becomes the first **polar body** (a very small cell containing a small nucleus & a minimal amount of cytoplasm). Immediately after that, the secondary oocyte starts the second meiotic division, which stops in metaphase. Meiosis II is completed only if fertilization occurs. If fertilization doesn't occur within 24 hours after ovulation, the secondary oocyte degenerates.

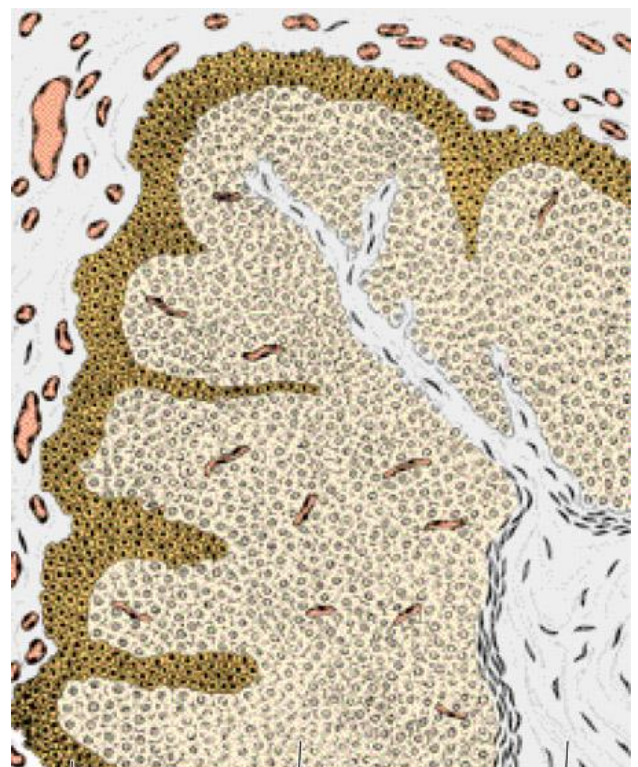
Before leaving the ovary, the oocyte (surrounded by corona radiata & some cumulus cells) may break free from its attachment to the follicular wall and float in the follicular fluid. With rupture of the follicle, antral fluid leaks out, & the congested capillaries in the theca interna decompress & rupture, filling the remaining cavity with blood.

Corpus Luteum:

After ovulation, and under the effect of luteinizing hormone (LH), the granulosa cells and theca interna cells reorganize to form a temporary endocrine gland called the "**corpus luteum**". Release of the follicular fluid results in collapse of the follicle's wall that becomes folded. Blood in the cavity coagulates and later invaded by connective tissue. Although granulosa cells do not divide after ovulation, they increase greatly in size, making up to 80 per cent of the corpus luteum and are now called "**granulosa lutein cells**", having the characteristics of steroid secreting cells (while before ovulation, they appear to be protein secreting cells). Cells of theca interna transform into "**theca lutein cells**". They are similar in structure to granulosa lutein cells but are smaller, darker, and occupy the periphery & folds of corpus luteum. The blood capillaries and lymphatics that were restricted to theca interna now invade the interior of corpus luteum and form the rich vascular network of it.



E.M image showing an oocyte surrounded by granulosa cells. The surface of oocyte is covered by zona pellucida



The cells of corpus luteum begin to secrete **progesterone** and **estrogens**. If pregnancy does not occur, the cells of the corpus luteum degenerate by apoptosis, and phagocytosed by macrophages, then the area is invaded by nearby fibroblasts producing a scar of dense connective tissue called "**corpus albicans**". If pregnancy occurs, the implanting embryo trophoblast secretes **Human Chorionic Gonadotropin (HCG)** whose action is similar to LH, thus keeping corpus luteum, which is now called "**corpus luteum of pregnancy**", active to secrete progesterone. It stays until its role is replaced by the placenta four to five months later.

Follicular Atresia:

Of the huge number of oogonia formed in utero, only 500 to 600 reach full maturity and ovulation in women's life. Some fail to develop, while others undergo a process called "**atresia**", which affects follicles at any stage of development. This process is characterized by cessation of mitosis in the granulosa cells, detachment of granulosa cells from the basal lamina, and the death of the oocyte with collapse of zona pellucida that remains identifiable. After cell death, macrophages invade the follicle to phagocytose the debris. When atresia occurs in small follicles, degeneration takes place leaving no scar. However, larger (mature) follicles undergo gradual disintegration and replacement by hyaline fibrous tissue, which may form a scar "**corpus fibrosum**".

Follicular atresia takes place from before birth until a few years after menopause. It is greatly accentuated just after birth (when the effect of maternal hormones ceases) and during puberty and pregnancy when marked hormonal modifications occur.

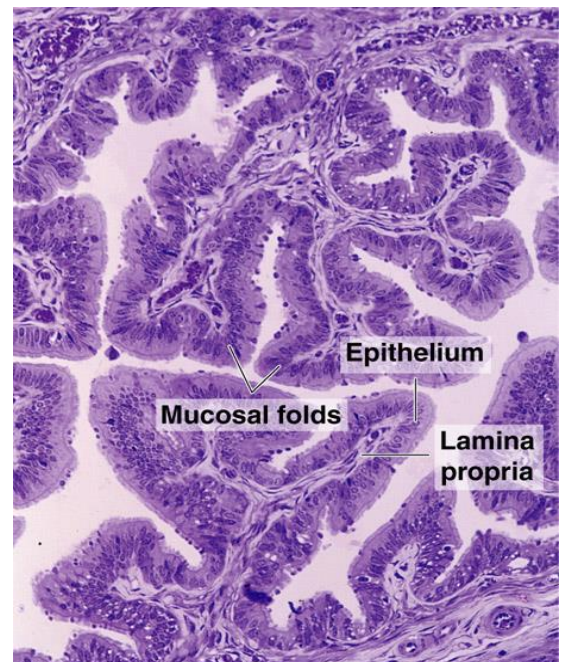
Interstitial Glands:

Although granulosa cells and the ovum undergo degeneration via atresia, theca interna cells frequently persist in isolation (interstitial cells) or in groups (interstitial glands) throughout the cortical stroma. Interstitial cells and/or glands, present from childhood through menopause, are active androgen secretors stimulated by LH.

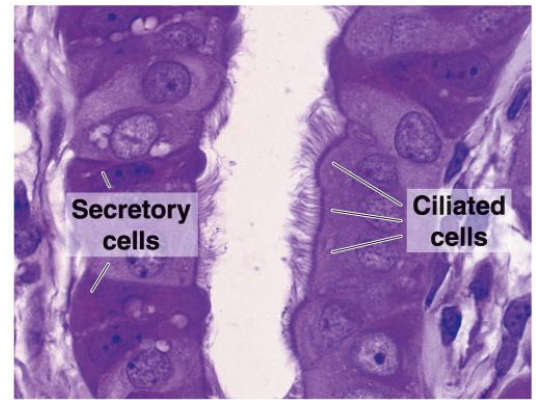
The Oviduct

These are 2 muscular tubes (12 cm long) of great motility, they conduct the liberated ova from the peritoneal cavity near the ovary to the uterine cavity, & facilitate fertilization. From lateral to medial, each tube is divided into 4 parts: the **infundibulum** (the conical region that carries the fimbria), the **ampulla** (the dilated part where fertilization occurs), the **isthmus** (the narrow part that is connected to the uterus) & the **intramural part** (that is embedded in the uterine wall). Histologically, the oviduct shows 3 layers:

1. **The mucosa:** this consists of epithelium & lamina propria, & has longitudinal folds that are most numerous in the ampulla (in cross section, the mucosa of ampulla resembles a labyrinth). Mucosal folds



decrease in height towards the uterus. The lining epithelium is simple columnar epithelium made of 2 types of cells: **ciliated cells**, with long cilia that beat toward the uterus, & darker **secretory (peg) cells** (covered with microvilli) that bulge into the lumen & secrete the fluid layer on the oviduct lumen, which contains nutrients for the oocyte. Under estrogenic effect, cilia elongate & both cell types hypertrophy during the proliferative phase of the cycle, & atrophy with loss of cilia during the luteal phase. During ovulation, the uterine tube moves towards the ovary which becomes partially covered by the fimbria. This ensures the capture of the ovum by the tube, & the fimbrial sweep movement with ciliary activity moves the ovum to the ampulla where fertilization should occur. The transport of zygote to the uterine cavity is normal in females with immotile cilia syndrome, showing that ciliary movement is not essential for transport.



2. **The muscularis:** thick layer of smooth muscle fibers arranged in inner circular (or spiral) & outer longitudinal layers.
3. **The serosa:** single layer of visceral peritoneum (connective tissue & mesothelium).

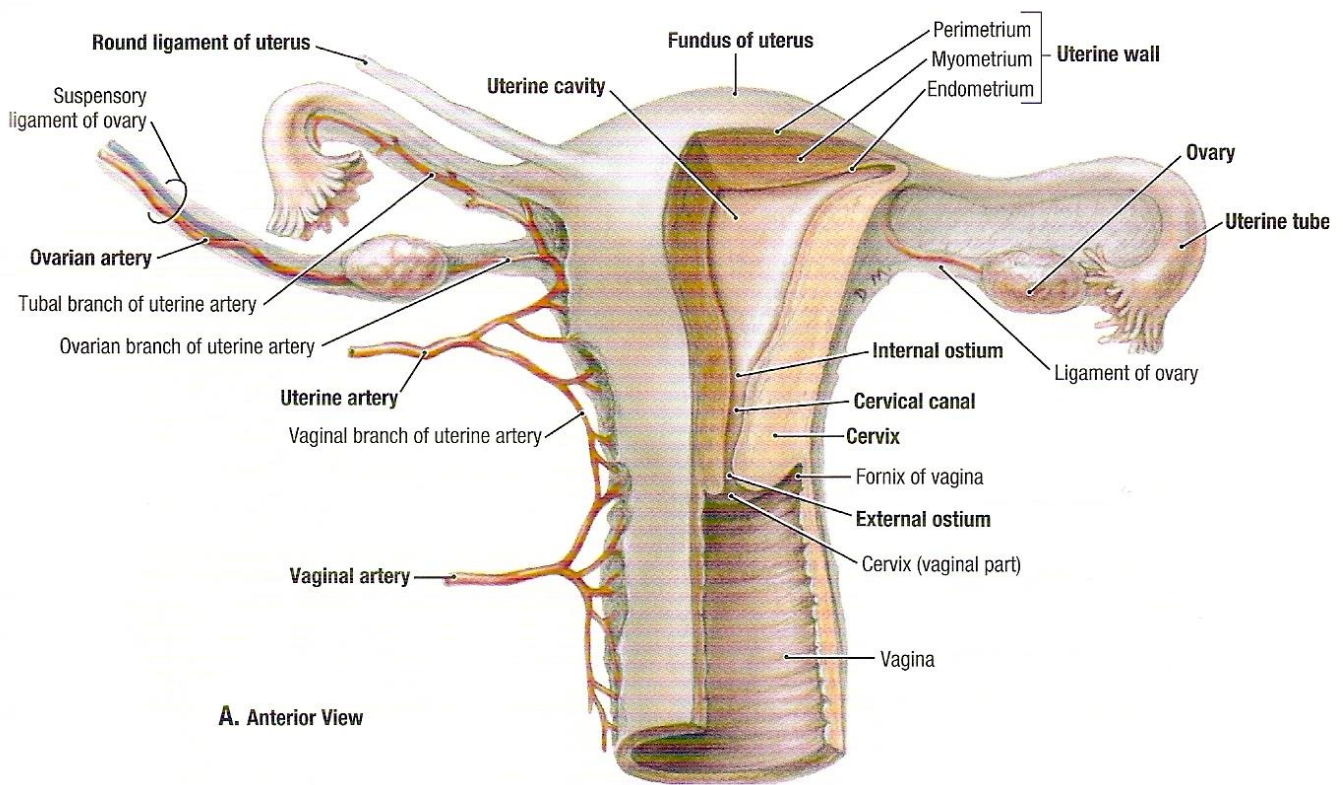
The Uterus

The uterus is a pear-shaped organ with thick muscular wall. It consists of an upper conical **body** (with a dome-shaped fundus) & a lower cylindrical **cervix**. The **cavity** of the uterine body is like an inverted triangle, continuous with the lumens of the oviducts above & with the cylindrical **endocervical canal** below (at the internal os). The uterus is bent anteriorly in the pelvic cavity, & fixed to its lateral walls by the broad ligaments.

Histologically, the uterus consists of 3 layers:

1. The outer layer is the **perimetrium**, made by **serosa** (visceral peritoneum) around the body of the uterus, & **adventitia** around the cervix.
2. The **myometrium** is a layer that forms the majority of uterine wall thickness. It consists of bundles of smooth muscle fibers separated by connective tissue. The myometrium is divided into 4 poorly defined layers: the outer & inner layers are mainly longitudinal, while the intermediate two layers are mainly circular, & contain the larger blood vessels. During pregnancy, the myometrium undergoes both hyperplasia (increase in the number of muscle cells) & hypertrophy (increase in the size of the cells), in addition to the synthesis of large amount of collagen fibers.
3. The **endometrium** is the mucosa of uterus. It consists of a lamina propria lined with simple columnar epithelium that sends simple tubular glands, which may branch in their deep portions. The lining epithelium consists of ciliated & secretory cells, however, ciliated cells are rare in the glands. The connective tissue of lamina propria is rich in fibroblasts, ground substance, & contain mainly type III collagen.

Functionally, the endometrium can be divided into 2 zones:

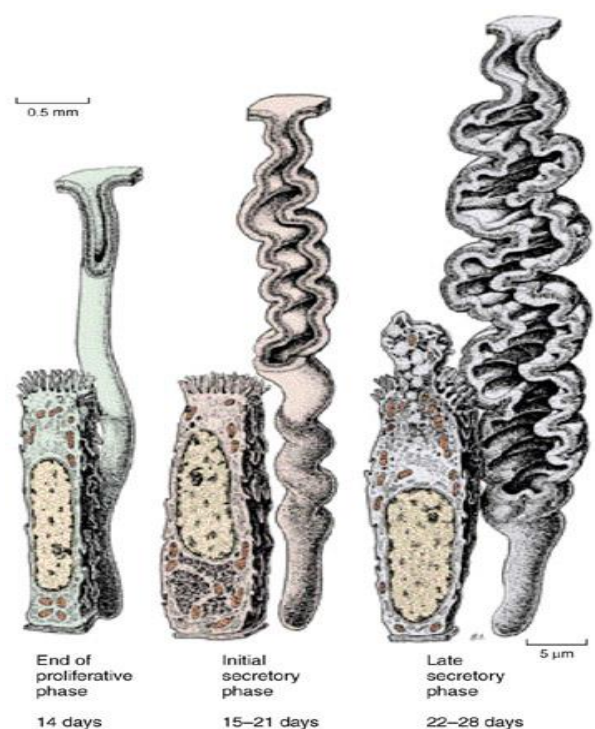


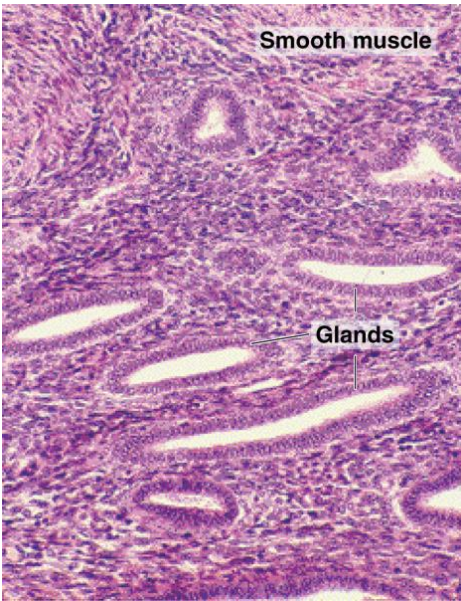
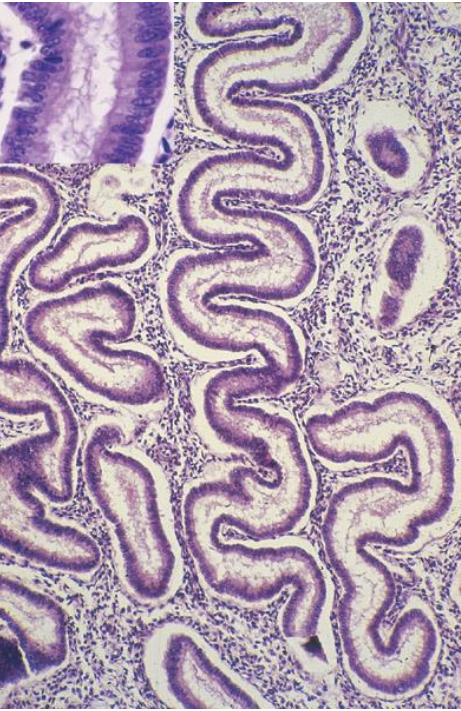
- **Stratum basalis**: the deepest layer adjacent to the myometrium, it contains lamina propria & the closed tips of uterine glands.
- **Stratum functionalis**: the thicker superficial layer, containing the rest of lamina propria & the glands, with the surface epithelium. This layer undergoes profound changes during the menstrual cycle, while st. basalis remains unchanged. Some authors subdivide stratum functionalis into a narrow superficial *stratum compactum* & a deeper *stratum spongiosum*.

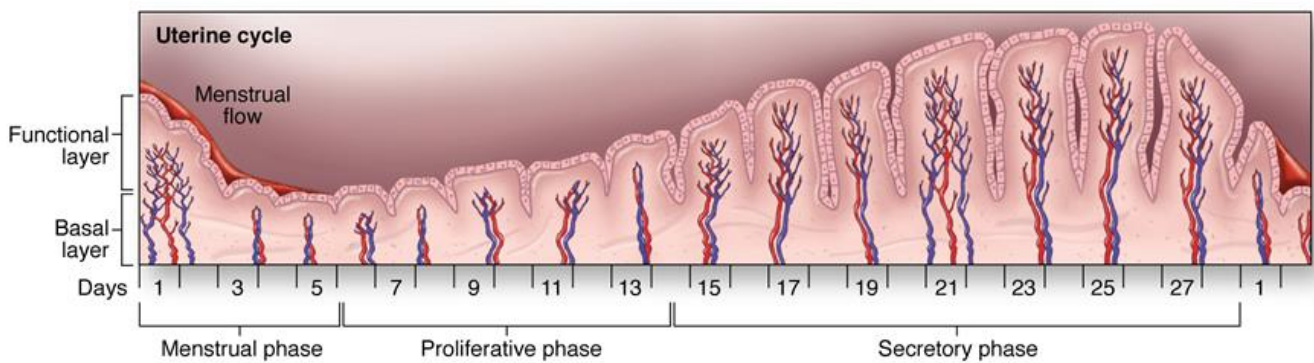
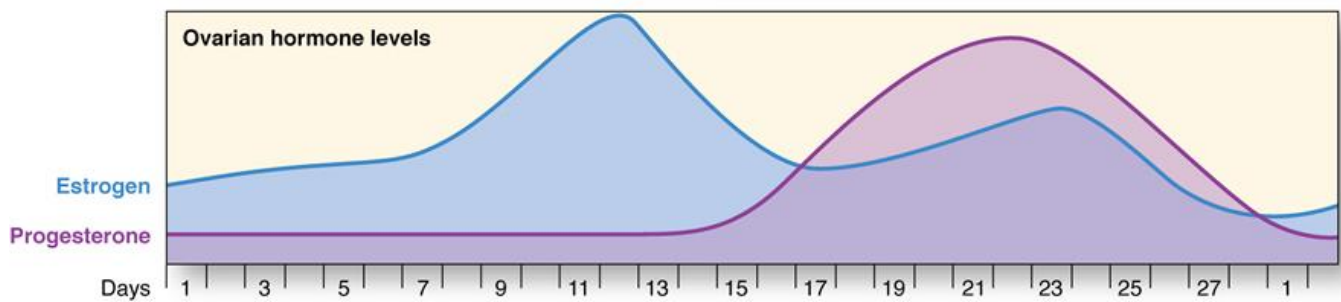
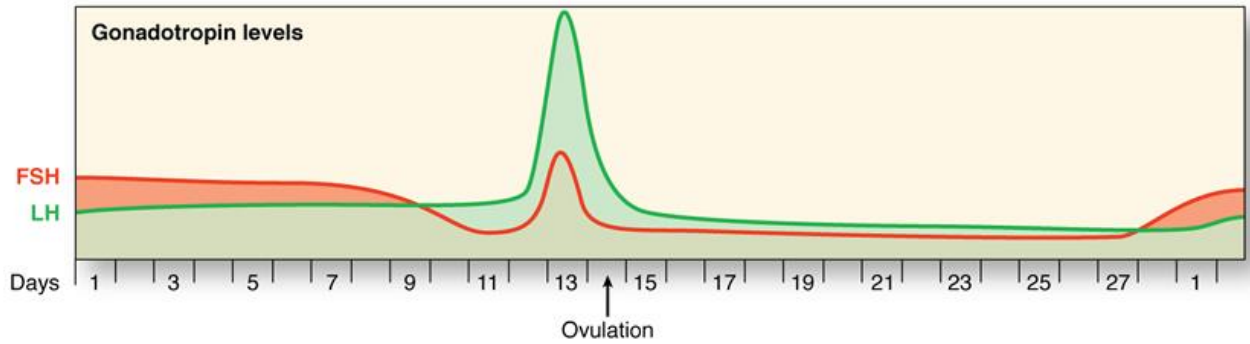
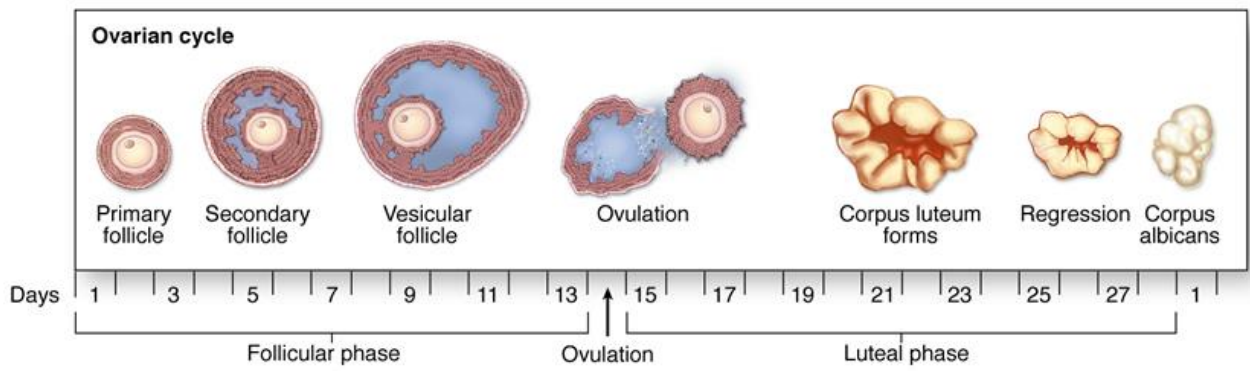
Blood supply of the uterus: The uterus is supplied by the **uterine arteries**. Branches from each uterine artery enter the lateral aspects of the uterus & penetrate the myometrium to form the **arcuate arteries** that run circumferentially in the middle myometrial layers. Arcuate arteries give 2 sets of branches: **straight arteries** to st. basalis & **spiral arteries** to st. functionalis.

The Menstrual Cycle:

During the reproductive life of the female, the reproductive system undergoes cyclic structural and functional changes that result in oocyte production and preparation of the uterus for the implantation of the fertilized ovum (the zygote) if fertilization occurs. This cycle lasts about 28 days in humans. The cycle is divided into a proliferative phase and a secretory phase, with the ovulation occurring between them. A menstrual phase represents the end of each cycle.



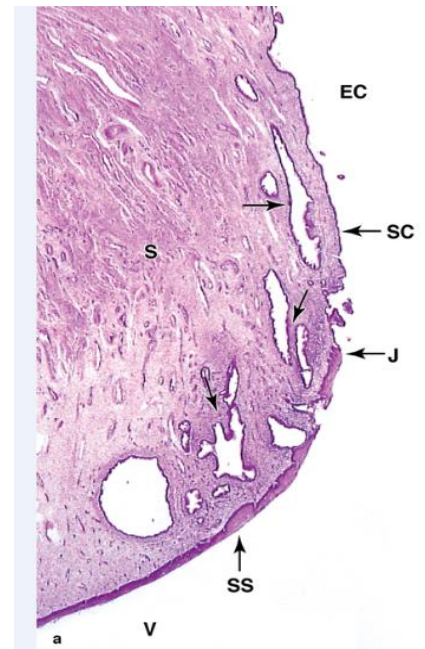
1. **The Proliferative (follicular, estrogenic) Phase (days 6-14):** Here, pituitary FSH stimulates follicular growth in the ovary, & when developed enough, these follicles start to secrete estrogens. Estrogen acts on the endometrium causing proliferation & reconstitution of the endometrium lost in the last cycle. At the beginning of this phase, the endometrial thickness is about 0.5 mm, & the endometrial glands are tubular & straight with empty lumens. At the end of this phase, the endometrial thickness is 2-3 mm, & the cells of the glands accumulate rER & large Golgi complexes in preparation for the secretory phase. Spiral arteries lengthen & establish extensive vasculature near the surface. Higher levels of estrogen (from the growing follicles) causes sudden increase in pituitary LH secretion, this stimulates ovulation & begins the secretory phase.
 
2. **The Secretory (luteal, progesterogenic) Phase (days 15-28):** This phase begins after ovulation. Here, pituitary LH stimulates the formation of corpus luteum from the ruptured follicle, which starts to secrete progesterone (& lesser amounts of estrogen). Progesterone further stimulates uterine glands to accumulate glycogen below their nuclei. Then glycoproteins are secreted into the lumens of the glands dilating them. The glands become highly coiled & the stroma becomes oedematous, resulting in a maximal endometrial thickness (5 mm). The microvasculature now includes thin-walled blood filled lacunae. If fertilization occurs, the embryo is implanted in the endometrium 6-7 days after ovulation, with the uterine glands being the major source of nutrition. Progesterone inhibits uterine muscle contraction & prevents menstruation.
 
3. **The Menstrual Phase (days 1-5):** If fertilization does not occur, corpus luteum degenerates with rapid decrease in progesterone & estrogen levels. This leads to a series of events including: ¹spasm in tunica media of spiral arteries (at the junction between st. basalis & st. functionalis), ²increase prostaglandin synthesis by endothelium causing vasoconstriction (& then arteries rupture above the constrictions). Tissue hypoxia results in stratum functionalis & leukocytes aggregate & secrete collagenase & other enzymes that lead to the shedding of the majority of the endometrium (st. functionalis). Stratum basalis is not affected by these changes because it is supplied by straight arteries. At the end of this phase, the endometrial thickness is 0.5 mm.



The Cervix:

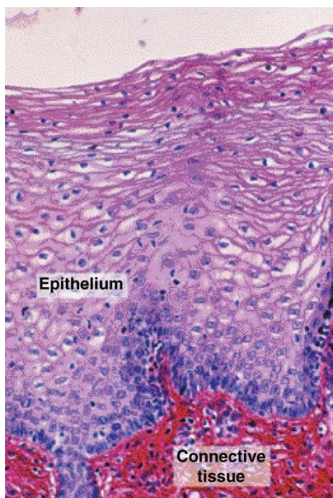
The cervix is the lower cylindrical part of the uterus, it has a dome-shaped lower end that bulges into the upper part of the vagina. The cavity of the cervix is the narrow **endocervical canal** that communicates with the uterine cavity via the **internal os** & with the vaginal lumen via the **external os**. Histologically, the stroma of cervix is made by a fibromuscular tissue formed majorly by dense connective tissue, with few smooth muscle fibers. The lining epithelium of the cervical canal (the endocervix) is mucus secreting simple columnar epithelium with highly branched mucous cervical glands embedded in a thick lamina propria. Externally, the cervix is covered by non-keratinized stratified

squamous epithelium (the exocervix) continuous with the vaginal epithelium. At the external os, there is a **transformation zone** where the columnar epithelium abruptly changes into stratified squamous epithelium. At time of ovulation, cervical mucous secretions are watery & allow sperms to penetrate into the uterus, while during the luteal phase & pregnancy, progesterone causes the cervix to secrete thick viscous secretions (forming a mucous plug) that prevent the passage of sperms & micro-organisms into the uterine cavity. Before parturition (childbirth), there is marked collagenolysis in the cervix, which softens to dilate during the passage of the fetus.



The Vagina:

A muscular tube that connects the uterus to the external genitalia. It extends from the cervix to the external vaginal os. The vagina is flattened anteroposteriorly & bent slightly to the posterior side, forming an angle with the cervix. Histologically, the vagina consists of three layers:



- **Mucosa:** thick layer of stratified squamous epithelium & a lamina propria. Epithelial cells may contain a small amount of keratohyalin. Under estrogen stimulation, vaginal epithelium synthesizes & accumulates glycogen. When the cells desquamate, bacteria metabolize glycogen to lactic acid, which is responsible

for the low vaginal pH necessary to protect against some microorganisms. The lamina propria is a loose connective tissue very rich in elastic fibers. Lymphocytes & neutrophils invade the epithelium & the lumen during the premenstrual & menstrual phases of the cycle. Vaginal mucosa has no glands (the mucus in the lumen comes from the cervix), but contains sensory nerve endings.

- **Muscular layer:** circular smooth muscle bundles next to the mucosa, & thicker longitudinal bundles near the adventitia.
- **Adventitia:** dense connective tissue rich in thick elastic fibers, which are responsible for the great elasticity of the vagina. Adventitia unites the vagina to the surrounding tissues & contains an extensive venous plexus, lymphatics & nerves.

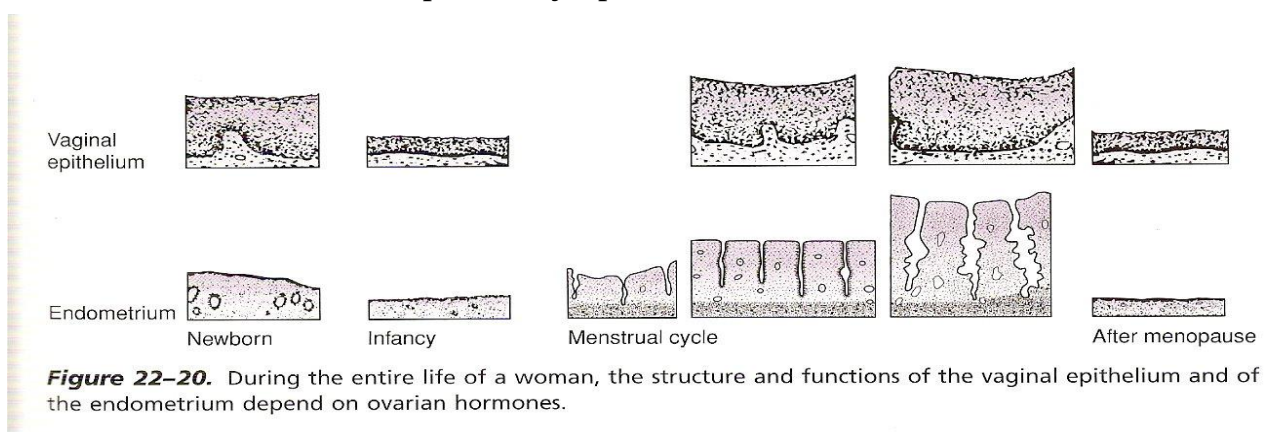


Figure 22-20. During the entire life of a woman, the structure and functions of the vaginal epithelium and of the endometrium depend on ovarian hormones.

External Genitalia (the Vulva)

The vulva consists of the following parts:

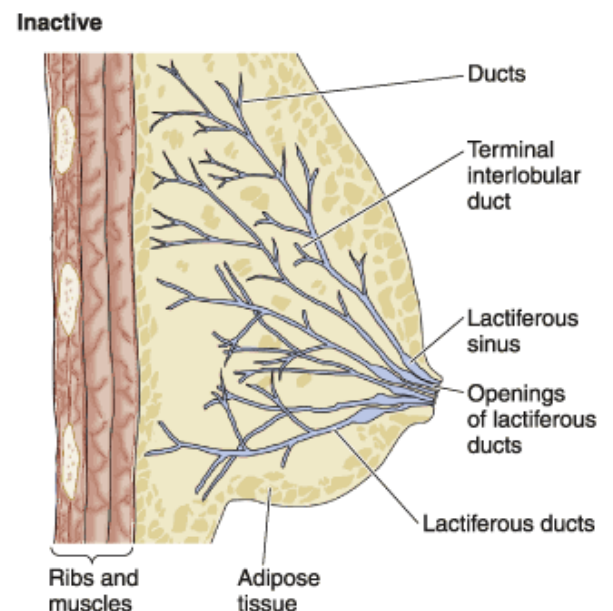
- The **labia majora** are 2 longitudinal skin folds that surround other parts of vulva. Labia majora contain large amount of adipose tissue & a thin layer of smooth muscle. They are covered by thin skin rich with coarse hairs, sweat & sebaceous glands.
- The smaller **labia minora** are 2 longitudinal skin folds that lie medial to labia majora. They are covered by stratified squamous epithelium that has no hairs, only a thin layer of keratinized cells, & contains sebaceous & sweat glands. The core of labia minora is formed by a spongy connective tissue (bulb of vestibule) rich in elastic fibers. Labia minora surround a region called the vestibule.
- The **clitoris** is a small structure homologous to the penis in males. It consists of 2 crura, body & glans, all made from an erectile tissue. Externally, the clitoris is covered by skin similar to that of labia minora.
- The **vestibule** (a longitudinal region extending from the clitoris to the junction of labia minora) contains the urethral orifice anteriorly, the vaginal orifice posteriorly, & the openings of the 2 major vestibular glands on each side of the vaginal orifice. The **major vestibular glands (Bartholin glands)** lie deep in the connective tissue of labia minora. The **minor vestibular glands** are numerous & scattered around the urethra & clitoris. All vestibular glands secrete mucus.

The vulva is very rich in sensory tactile nerve endings, including Meissner's & Pacinian corpuscles, which contribute to the physiology of sexual arousal.

Mammary Glands

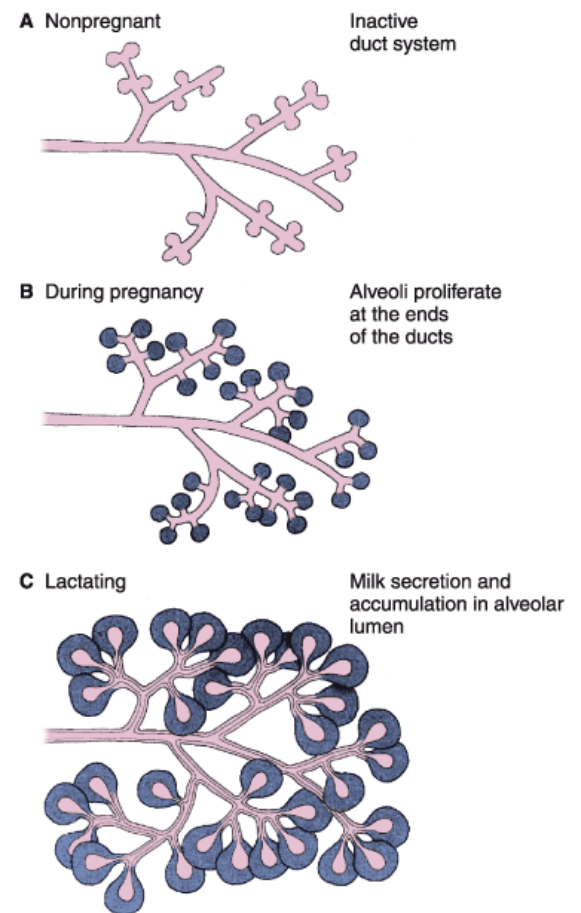
Mammary glands are specialized exocrine glands derived from the surface ectoderm of the skin. The shape, size, & structure of the female breast varies according to the age, pregnancy, & hormonal state, therefore, we shall describe the breast according to the different age/physiological states:

- **Before puberty:** the breast is flattened & the mammary glands are composed of 15-25 lactiferous sinuses that give several branches (the lactiferous & terminal ducts).
- **After puberty:**
 - Size: the breasts enlarge due to (1) accumulation of adipose & connective tissues, (2) the growth & branching of the duct system under ovarian estrogenic effect.
 - Arrangement: mature (inactive) breast contains 15-25 lobes, separated from each other by dense connective tissue septa (called the suspensory ligaments of the breast) & much adipose tissue. Each lobe is made by a single mammary gland with multiple lobules & a single duct (lactiferous duct), all embedded in a



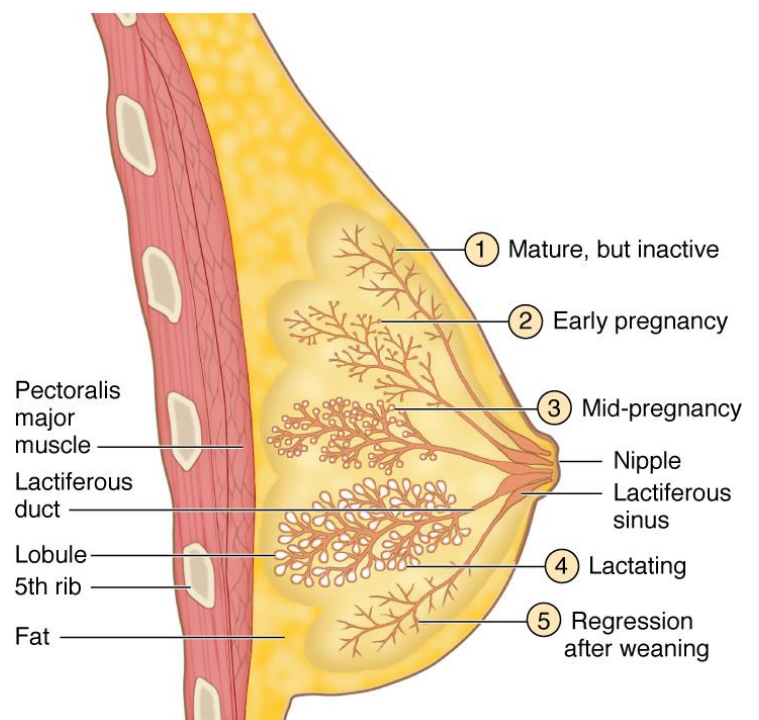
vascular loose connective tissue.

- Mammary glands: each lobule is made by tiny terminal ducts, which unite with each other forming interlobular ducts, that then form a single lactiferous duct. Terminal & interlobular ducts & the beginning of lactiferous duct are lined with simple cuboidal epithelium, that becomes stratified cuboidal in the large lactiferous duct. The whole ductal system is surrounded with a dense layer of myoepithelial cells. Deep to the nipple, each lactiferous duct dilates forming a **lactiferous sinus**, with its stratified cuboidal epithelium changing into (keratinized) stratified squamous epithelium continuous with the skin covering the nipple.
- The nipple: The nipple (& the surrounding areola) are covered by darker skin (due to more melanin) & richer in sebaceous glands. Lactiferous sinuses open separately on the nipple. Deep to the nipple skin, the lactiferous sinuses are surrounded by circular smooth muscle fibers, then longitudinal (radial) layer. These muscle fibers contract in response to cold, or baby suckling, causing nipple erection. The nipple has a rich sensory nerve supply.
- Cyclic changes: During the estrogenic phase of menstrual cycle (about the time of ovulation), the cells lining the duct system become higher, & in the premenstrual phase, the connective tissue becomes oedematous, causing a slight breast enlargement.



- **During early pregnancy:**

The breasts enlarge due to the intense growth of mammary glands, mediated by several hormones (estrogen, progesterone, prolactin, & human placental lactogen). These hormones cause the formation of the secretory **alveoli** at the ends of terminal ducts. Alveoli are spherical collections of cuboidal epithelial cells surrounded by stellate myoepithelial cells found between alveolar cells & their basement membrane. With the growth of the mammary glands, the amount of connective & adipose tissues decreases considerably in relation to the



glandular tissue, but contains increasing numbers of lymphocytes & plasma cells that produce immunoglobulin-A (secretory IgA) that provide the newborn with passive immunity. The nipple & areola darken during pregnancy due to melanin accumulation.

- **During late pregnancy & lactation:** Mammary glands take the typical shape of compound tubuloalveolar glands. Secretory alveoli enlarge & secrete colostrum (a fluid rich in proteins, vitamin A, & electrolytes). It accumulates in their lumens & in the ducts, dilating them, & the breasts reach their maximal size. IgA (from plasma cells) are transferred to the colostrum to protect the infant. After childbirth, estrogens & progesterone levels decline, but the glandular alveoli become very active in milk production by the effect of prolactin. The secretory cells become low cuboidal, & their cytoplasm contains lipid droplets of different sizes that, when released from the cell, become enveloped with a portion of apical cell membrane (apocrine secretion). In addition to lipid droplets, alveolar cells contain membrane-limited vacuoles containing milk proteins, which are released by exocytosis (merocrine secretion). Proteins constitute about 1.5% of human milk, lipids 4%, & sugars (mainly lactose) 7-8%. The areola may become lighter in colour after delivery but rarely returns to its original shade.

- **After lactation:** After weaning the baby, most alveoli undergo degeneration by apoptosis. This includes sloughing of whole cells & autophagic absorption of cellular components, with dead cells & debris removed by macrophages. The duct system returns to its pre-pregnancy state.

- **After menopause:** Involution of mammary glands is characterized by reduction in the size & atrophy the secretory portions & ducts. Atrophic changes involve also the connective tissue, including some loss of fibroblasts, collagen, & elastic fibers.

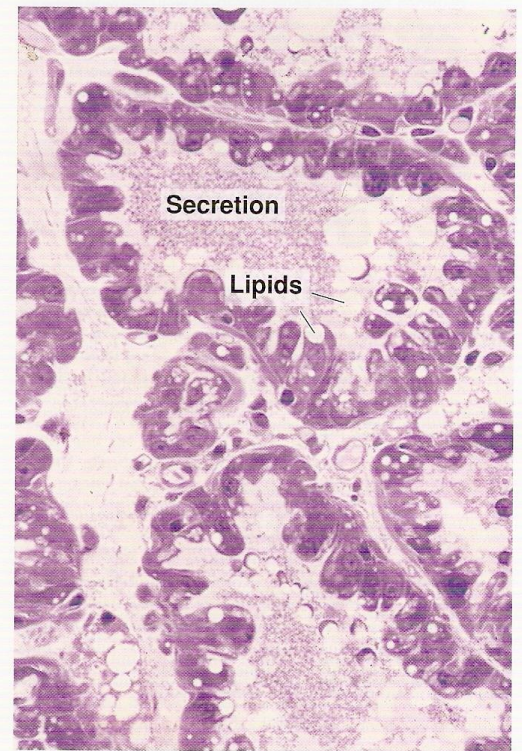
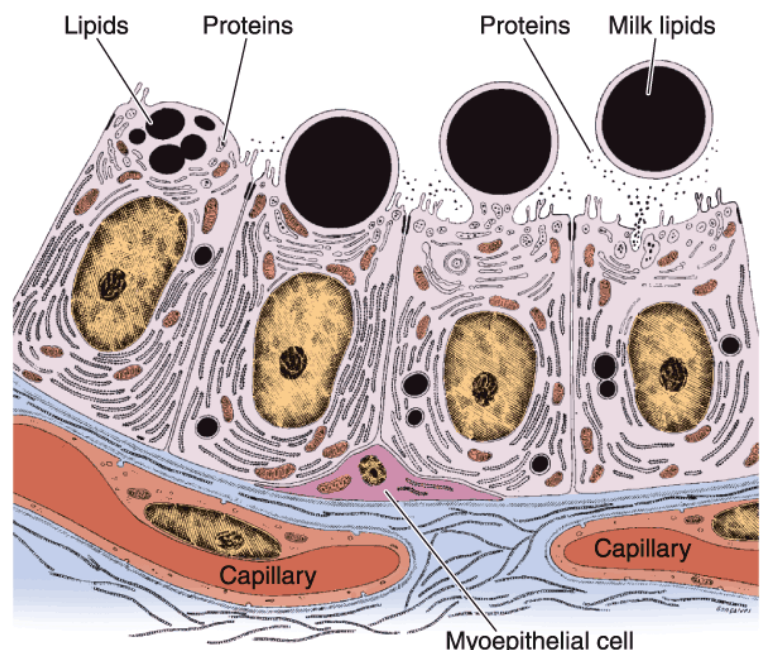
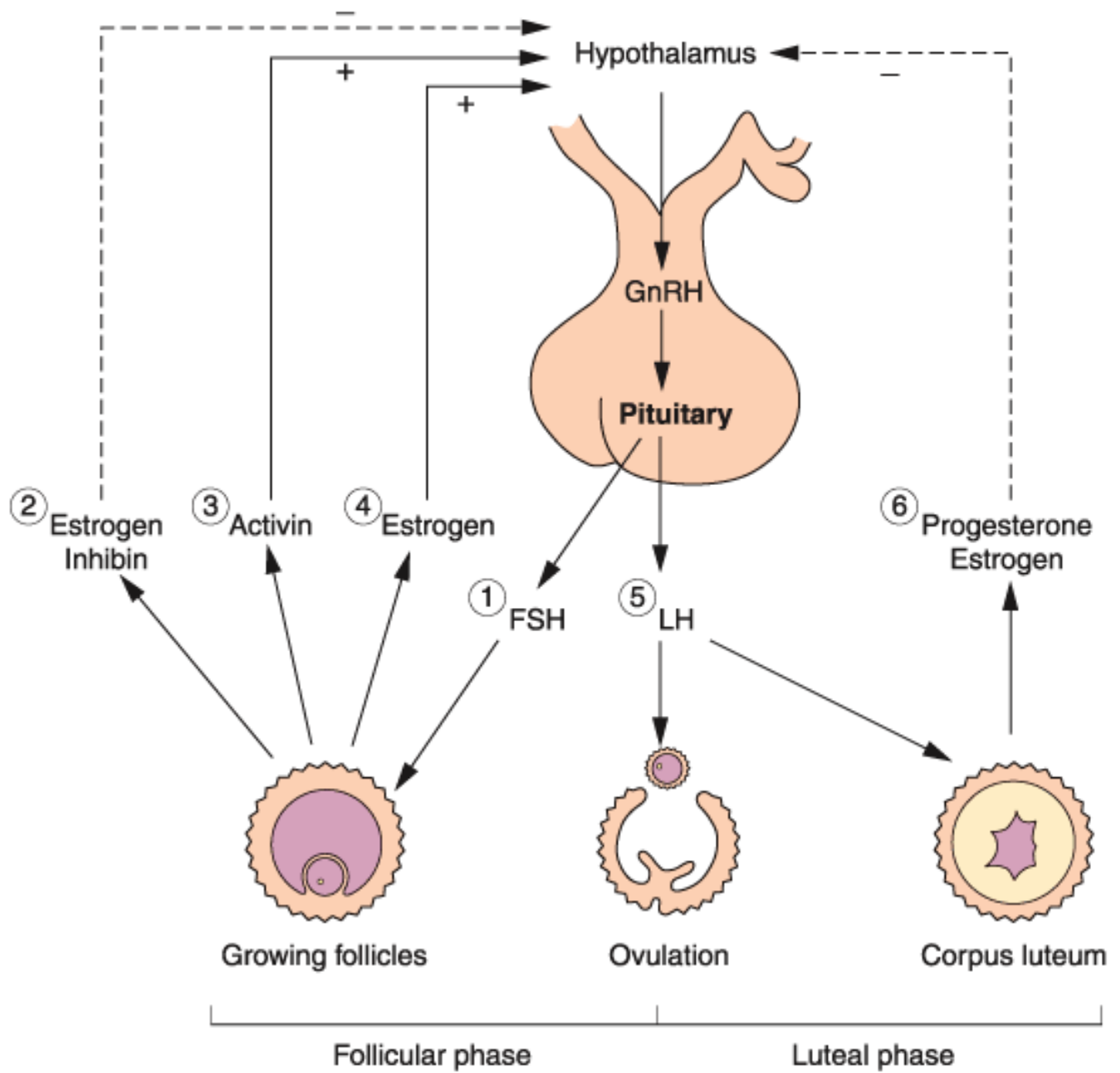


Figure 22-29. Photomicrograph of a lactating mammary gland. Several alveoli are filled with milk, visible as granular material. The vacuoles in the lumen and in the alveolar cell cytoplasm represent the lipid portion of milk. PT stain. Medium magnification.





End