Lecture 5 ESS_3rd semester

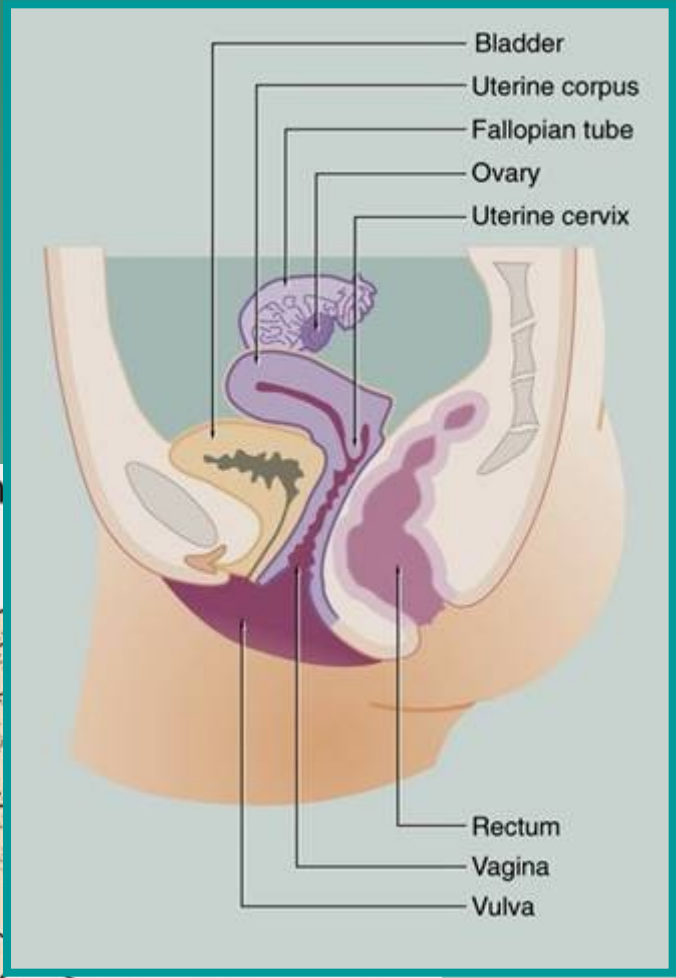
MICROSCOPIC STRUCTURE OF FEMALE REPRODUCTIVE SYSTEM

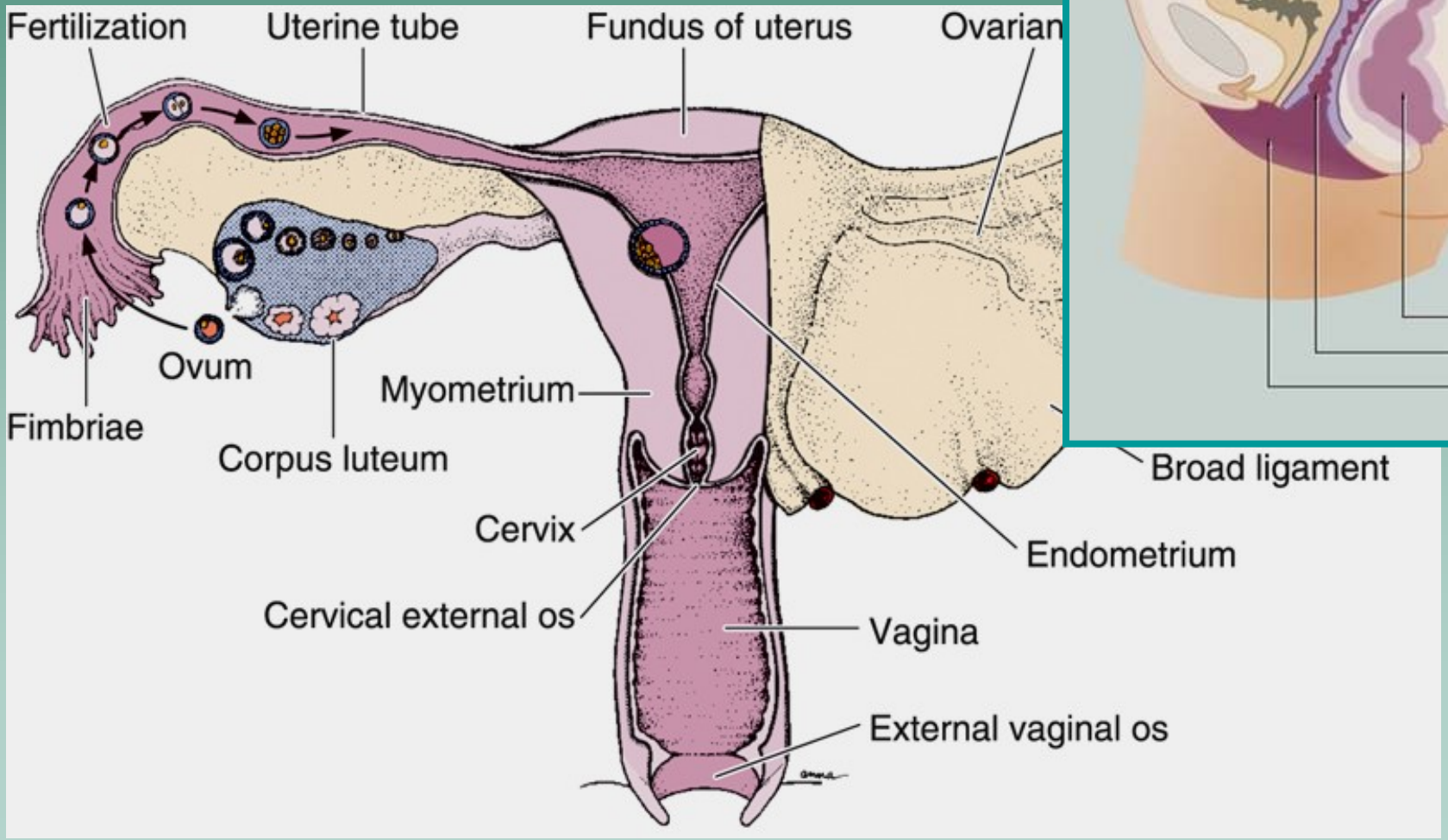
Ovary, oviduct, uterus, vagina, and external genitalia
Ovarian cycle, ovulation, and atresia. Oogenesis
Menstrual cycle - its relations to the ovarian cycle

2 **ovaries**, 2 **oviducts** (uterine tubes), the **uterus**, the **vagina**, and **external genitalia** (clitoris, labia majora et minora pudendi, vestibulum vaginae and hymen)

the **placenta** and **umbilical cord**

a close relation to FRS have **mammary glands**





function of female reproductive system:

- to produce and transport ova
- to support a developing embryo

in sexual mature females, some organs of this system undergoe cyclic changes in their structure and functional activity

the sexual maturity begins

- **menarche** = the time when the first menses occur

and ends

- **menopause** = a period, during which the cyclic changes become irregular or eventually disappear altogether

MICROSCOPIC ANATOMY OF THE OVARY

(lat. ovarium, gr. oophoron)

an almond-shaped body approximately 3 cm long, 1.5 cm wide, and 1 cm thick

it is roughly divided into

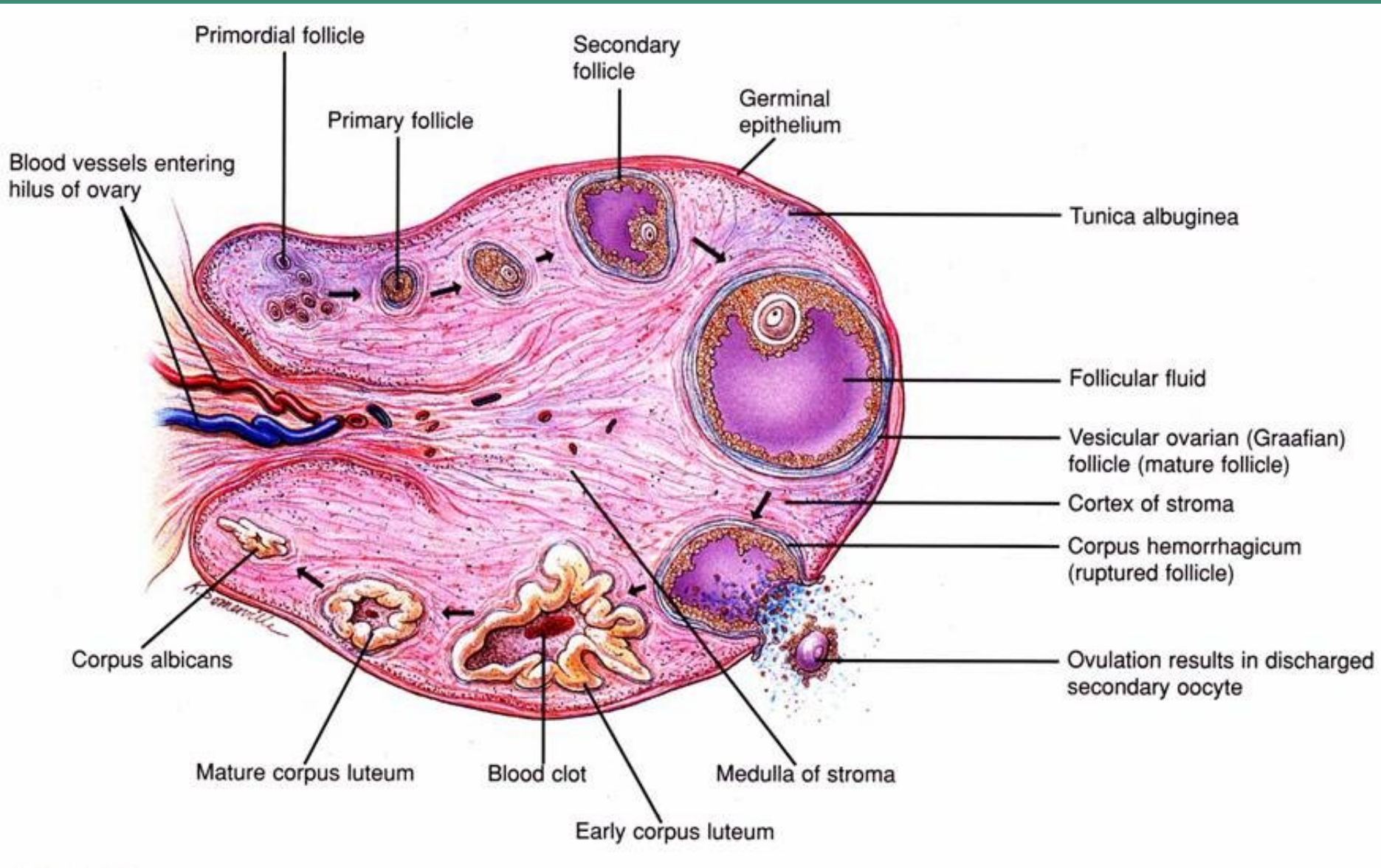
- a central **medulla** that is occupied by a dense connective tissue stroma with a rich vascular bed
- a peripheral **cortex** composed of spindle-shaped form cells = **fibroblasts**

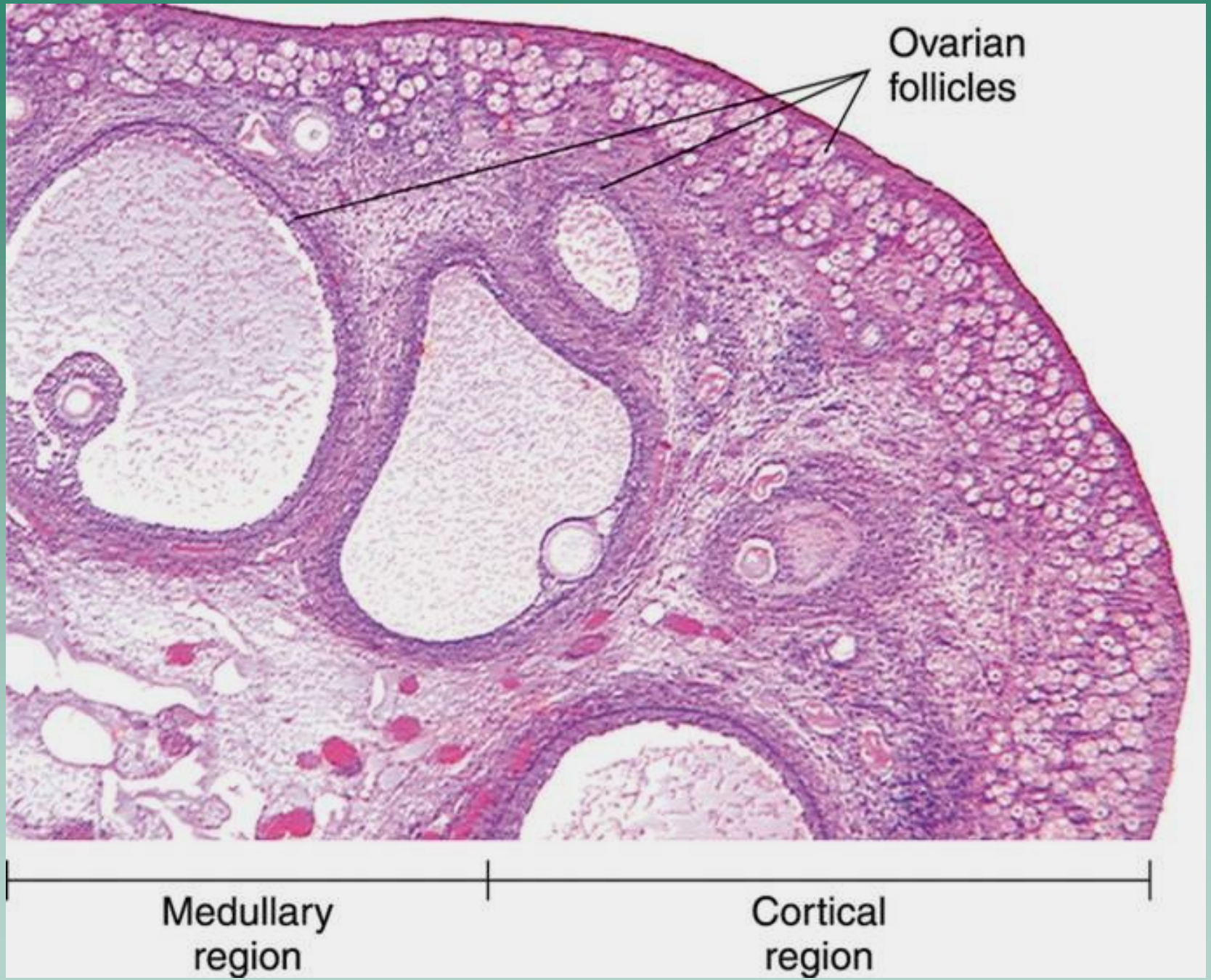
the surface of the organ is covered by simple squamous or cuboidal epithelium called the **germinal epithelium**

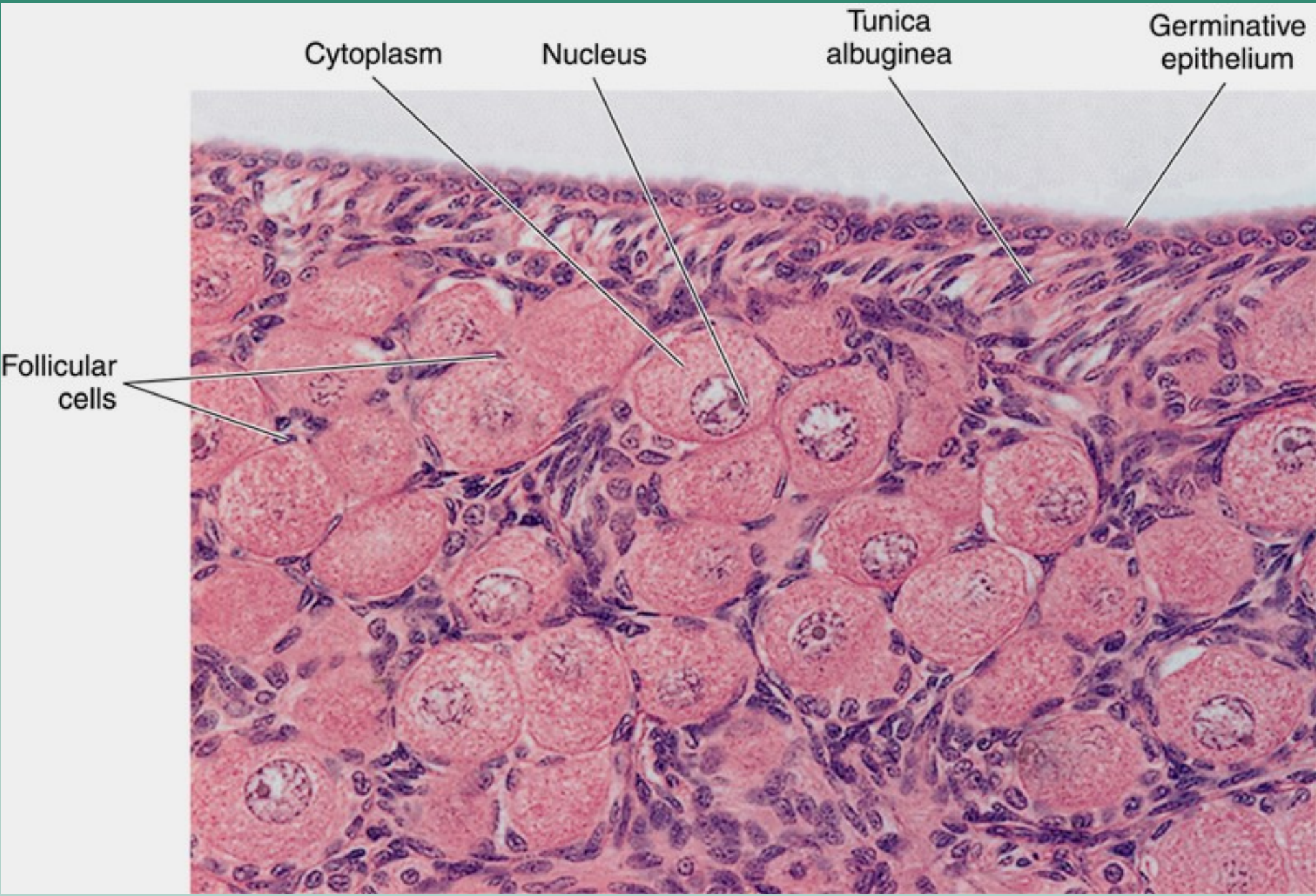
under the germinal epithelium fibroblasts are densely organized to form the capsule of the ovary known as the **tunica albuginea**

the cortex contains **ovarian follicles** and **their derivatives** that are **corpus luteum** and **corpus albicans**

The ovary


Primordial follicle
Secondary follicle
Primary follicle
Germinal epithelium
Blood vessels entering hilus of ovary
Tunica albuginea
Follicular fluid
Vesicular ovarian (Graafian) follicle (mature follicle)
Cortex of stroma
Corpus hemorrhagicum (ruptured follicle)
Corpus albicans
Ovulation results in discharged secondary oocyte
Mature corpus luteum
Blood clot
Medulla of stroma
Early corpus luteum

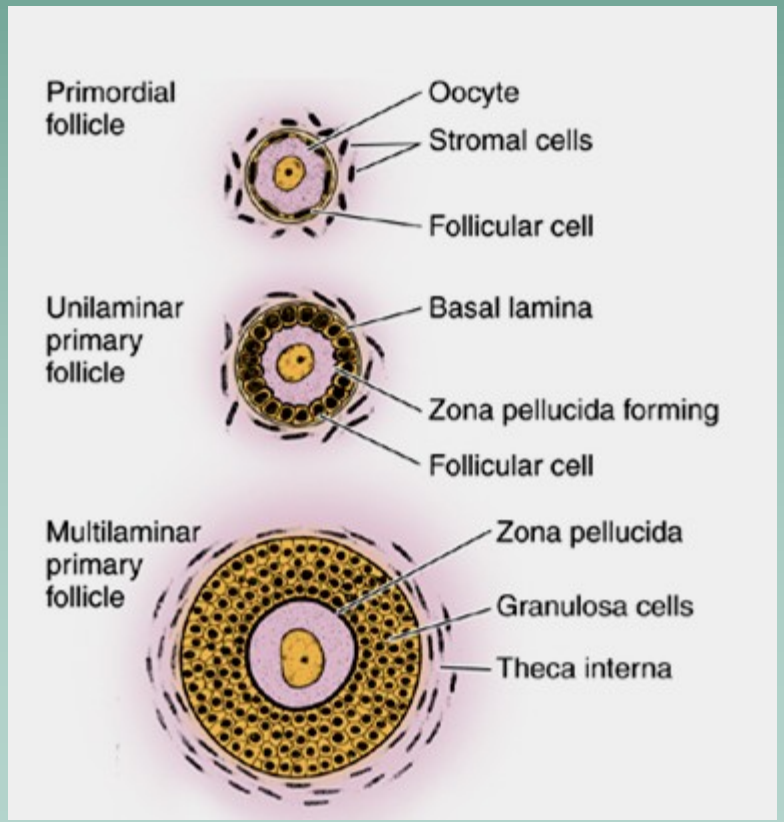

Ovarian follicles
Medullary region
Cortical region

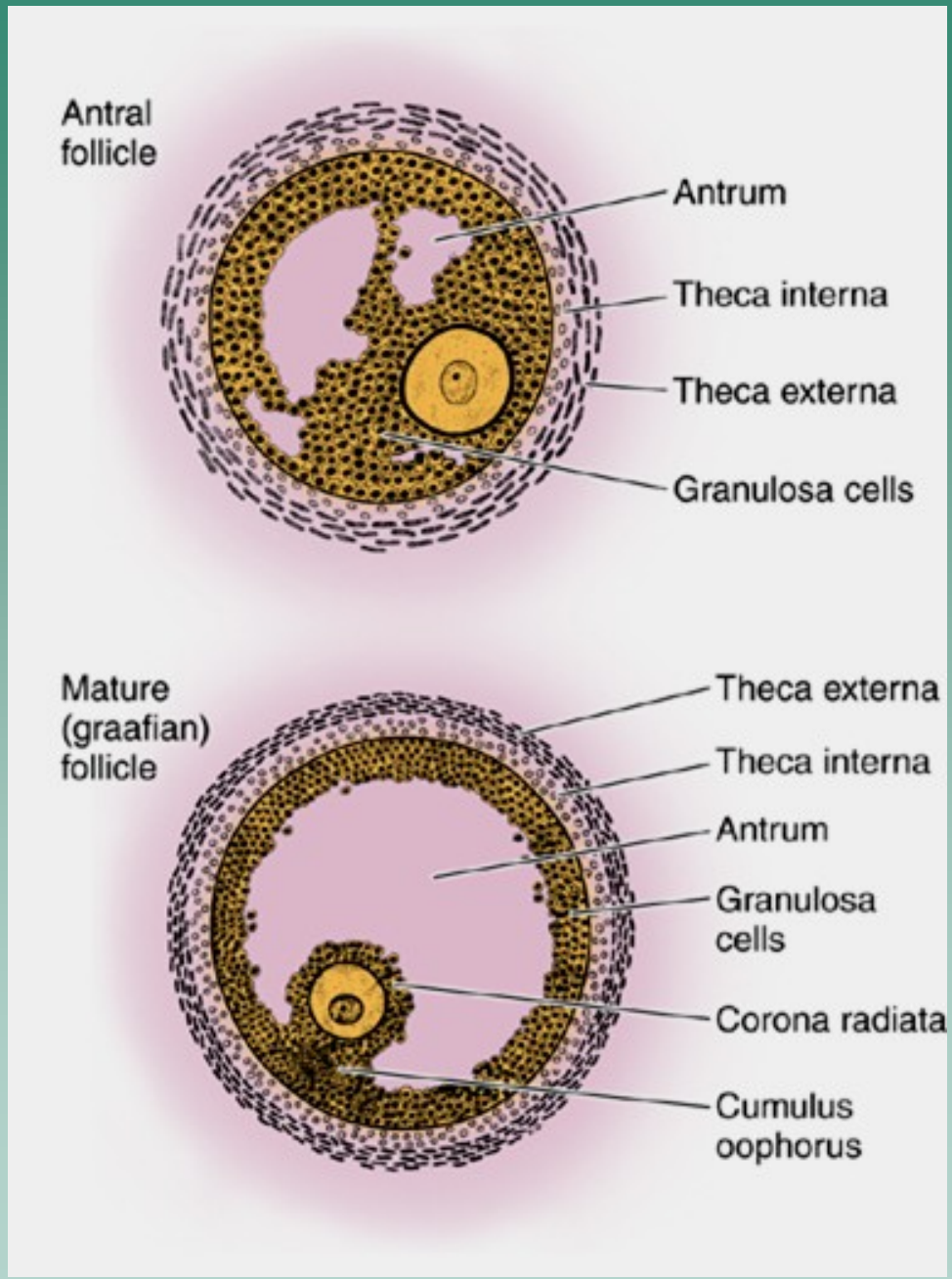

Cytoplasm
Nucleus
Tunica albuginea
Germinative epithelium
Follicular cells

Ovarian follicles and **their derivatives**

Follicles are classified:

- **primordial** follicle
- **unilaminar primary** follicle
- **multilaminar primary** follicle
- **secondary (antral)** follicle
- **mature (graafian)** follicle





Primordial follicle

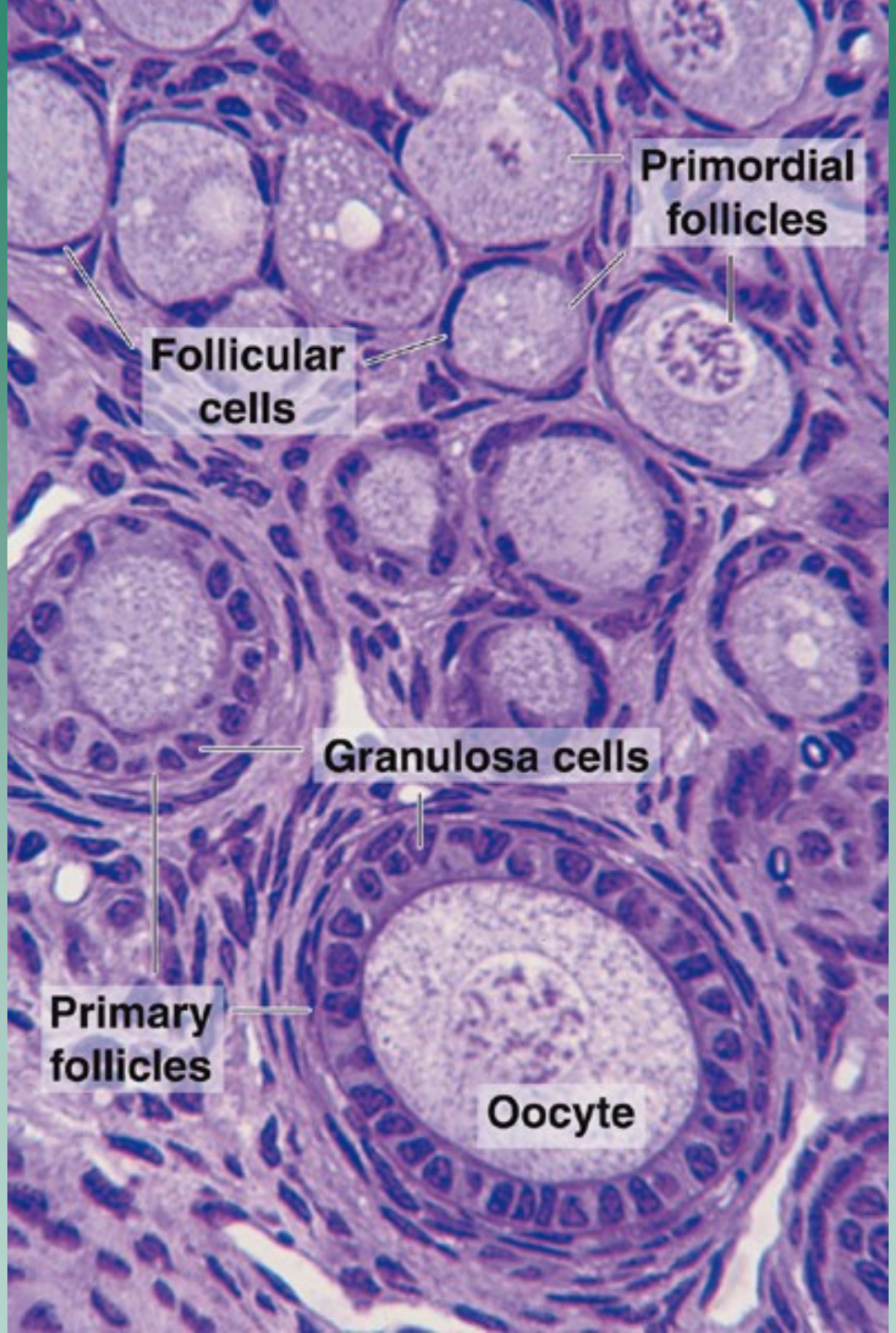
d. 45–50 μm

- a **primary oocyte** enveloped by
- a single layer of flattened **follicular cells** (granulosa cells)
- a basement membrane of the follicular epithelium

Unilaminar primary follicle

d. 60–75 μm

differs from primordial follicle by presence of cuboidal follicular cells

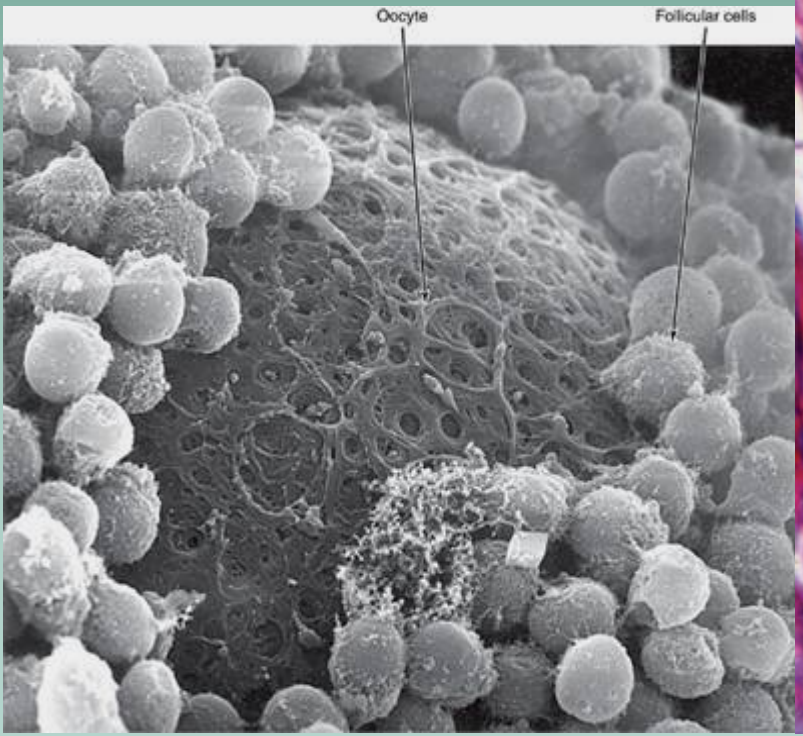


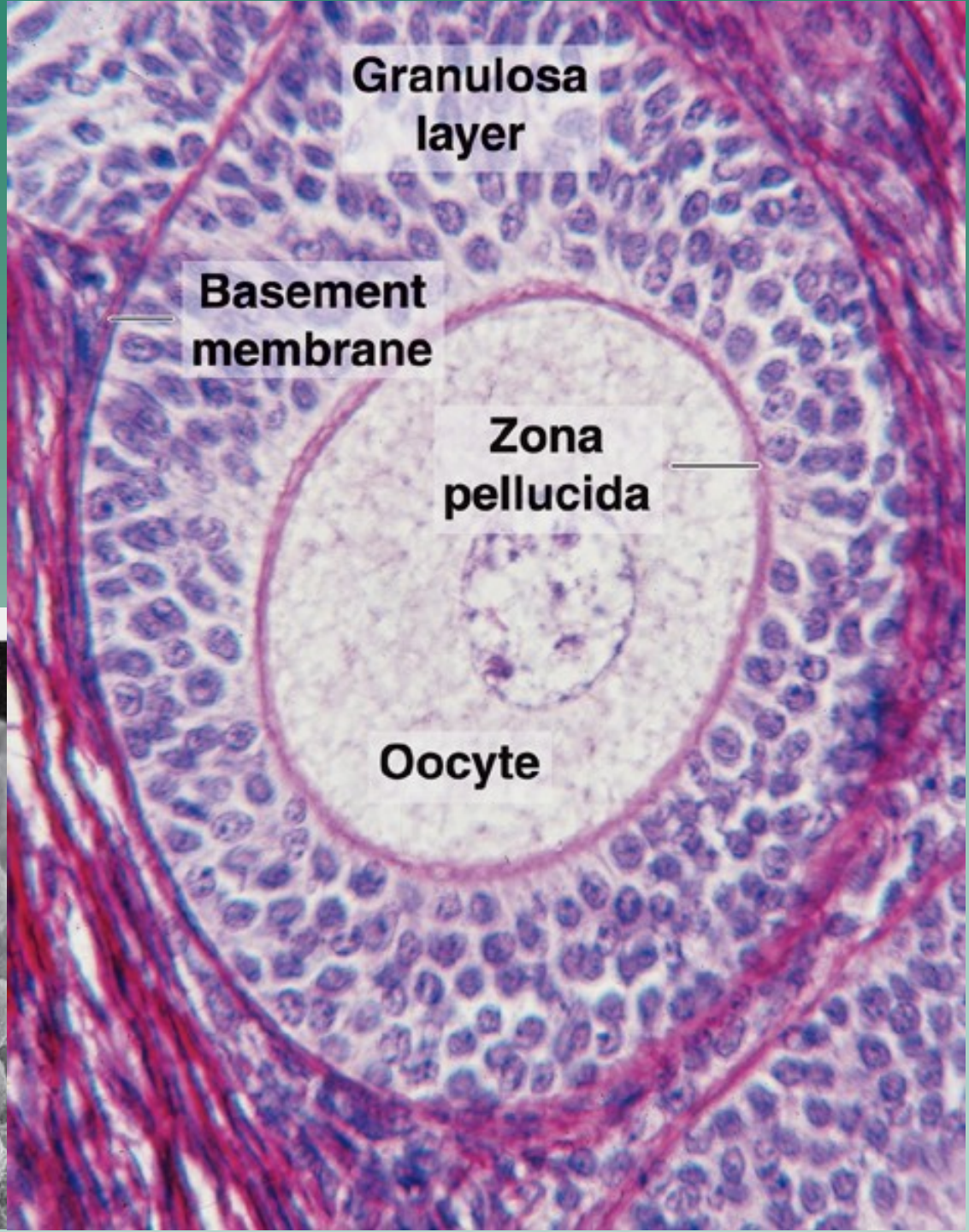
Multilaminar primary follicle

d. 200 až 250 μm

oocyte increases its size and follicular cells proliferate by mitosis and form around it several layers - **zona granulosa**

formation of the **zona pellucida**





the **zona pellucida**

- is composed of glycosaminoglycans
- it is thought that both oocyte and follicular cells take part in its synthesis

with this event, the cortical stroma around the follicle develops to form the **theca folliculi**
it differentiates subsequently into

- the theca **interna** that is highly vascularized and and whose cells enlarge
- the theca **externa** formed by a connective tissue

the cells of the theca interna synthesize androstenedione that is converted into **estradiol** by cells of zona granulosa

Secondary (antral) follicle

is characterized by accumulation of fluid between follicular cells (cells of zona granulosa) and by formation small cavities that gradually become to fuse in the single, eccentrically placed cavity, the **antrum folliculi** filled with **liquor folliculi**

the lining of this single cavity is formed with several layers of follicular cells, the **membrana granulosa**
at the follicle pole adjacent to the medulla, the membrana granulosa thickens into the **cumulus oophorus**, protruding to the interior of the antrum
the oocyte is housed within the cumulus oophorus

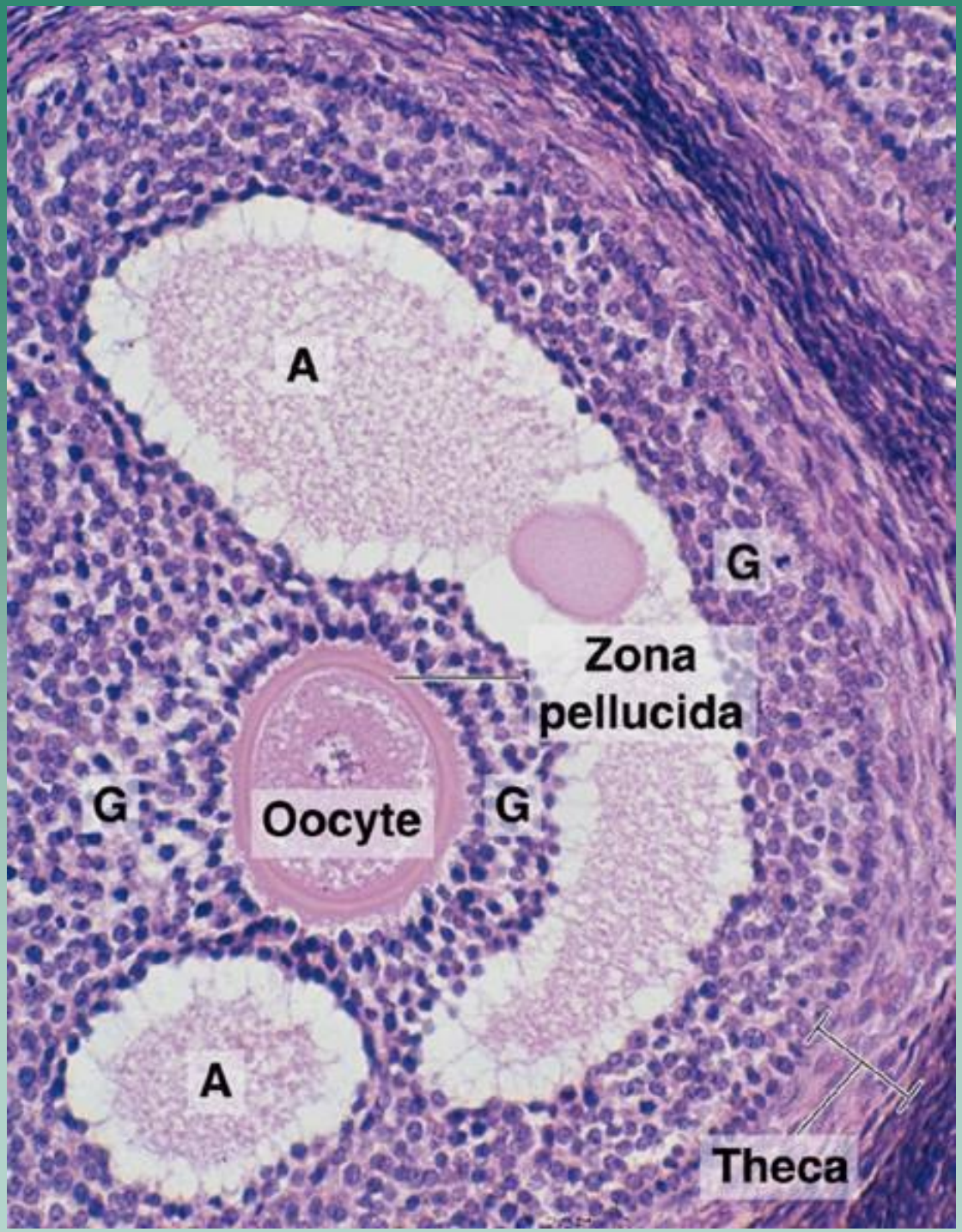
Secondary (antral) **follicle**

antrum folliculi formation in 0,2–0,3 mm large follicles

theca folliculi – t. f. interna
– t. f. externa

membrana granulosa

d. 7 to 9 mm



Mature (graafian or preovulatory) follicle

is about 1.5 - 2.5 cm in diameter and resembles transparent vesicle that bulges from the surface of the ovary

Its wall consists of:

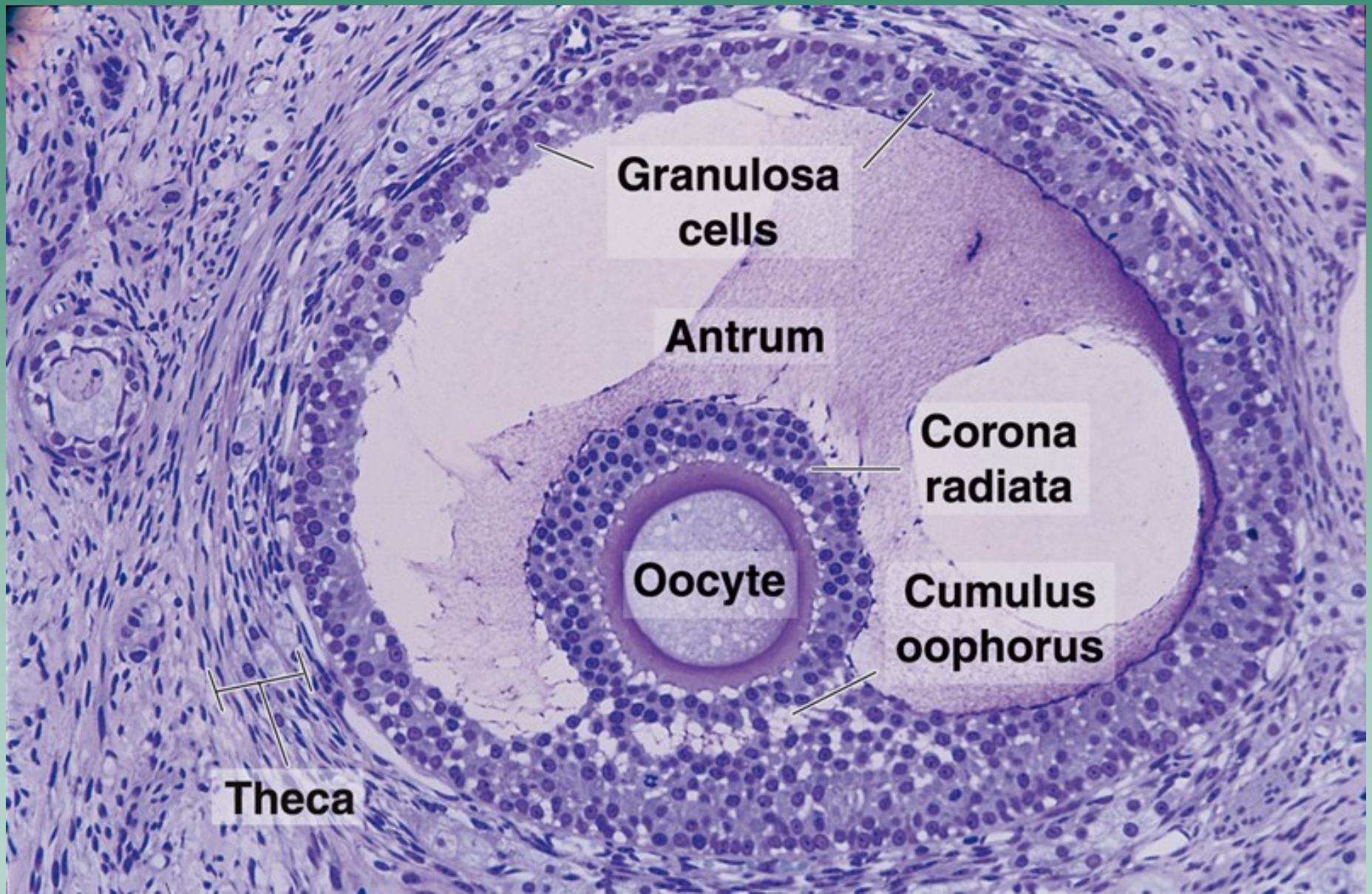
- 4 - 5 layers of follicular cells - there is the membrana granulosa,
- the thickened basement membrane called as the **membrane of Slawjanski** (firstly described by Slawjanski)
- the theca folliculi interna
- the theca folliculi externa

granulosa cells surrounding the oocyte are firmly attached to the zona pellucida and accompany the oocyte during ovulation and its expelling -

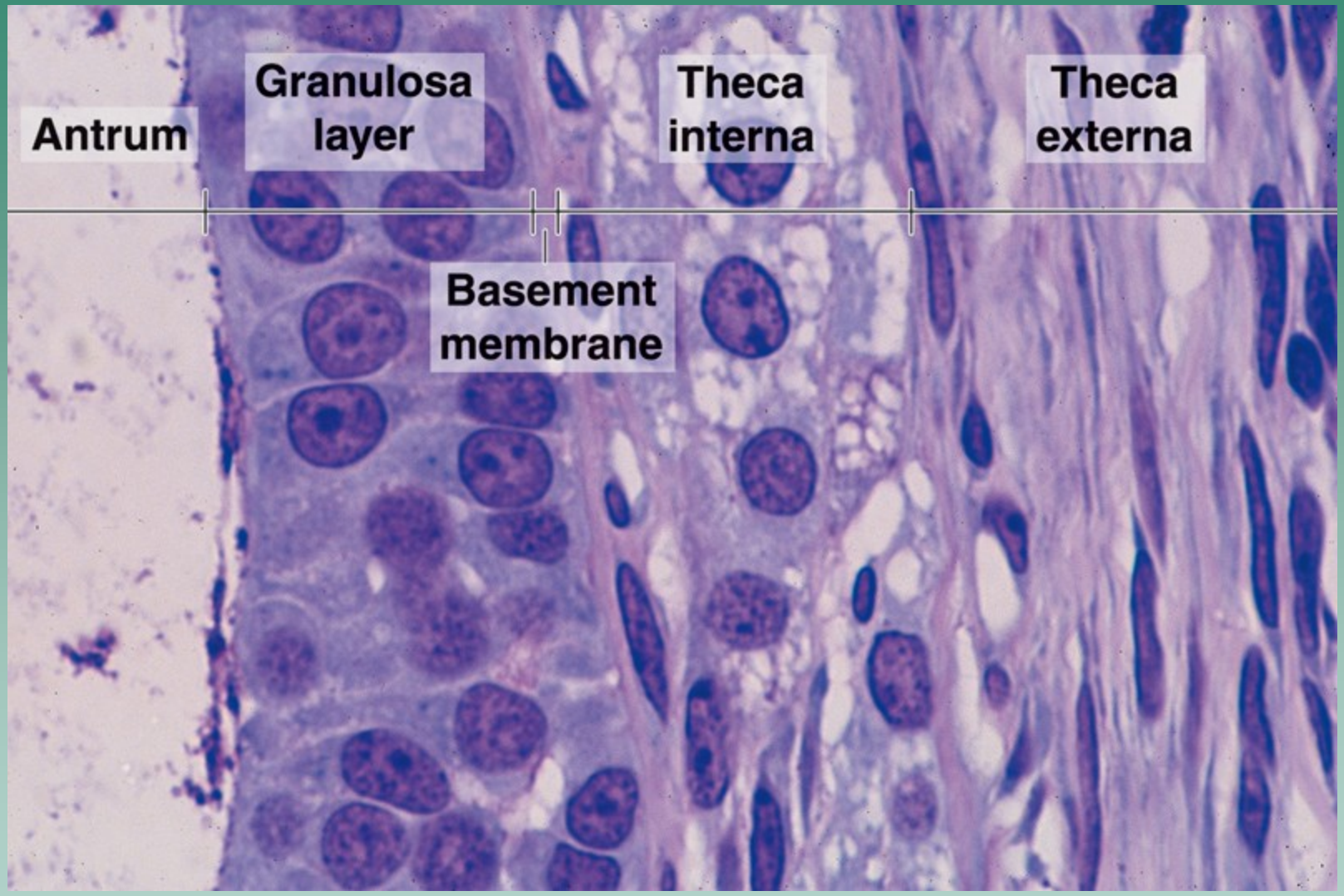
are usually called as the **corona radiata**

Mature (preovulatory or graafien) follicle

diameter 1 to 2 cm



A detail of the wall of mature follicle:



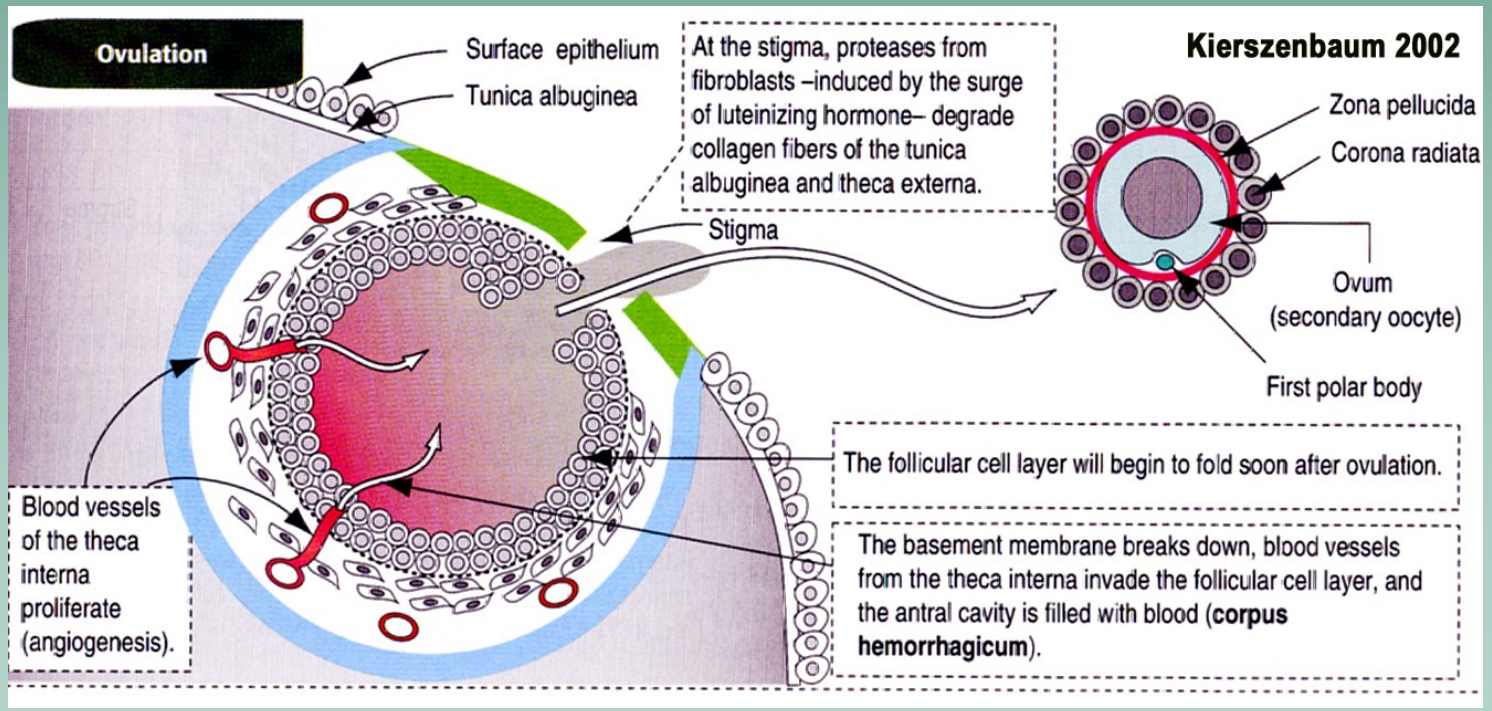
Ovulation

is a process during which mature follicle ruptures
the ovum is liberated and then caught by a dilated end of the oviduct

ovulation takes place in approximately **the middle of menstrual cycle**, ie. around the 14th day of a 28 day cycle

rupture of the folicle is due to increased activity of proteases (collagenase and plasmin) that dissolute connective tissue around the follicle that will ovulate

after ovulation the ruptured follicle is transformed into the **corpus luteum**
the process is known as **luteinization**



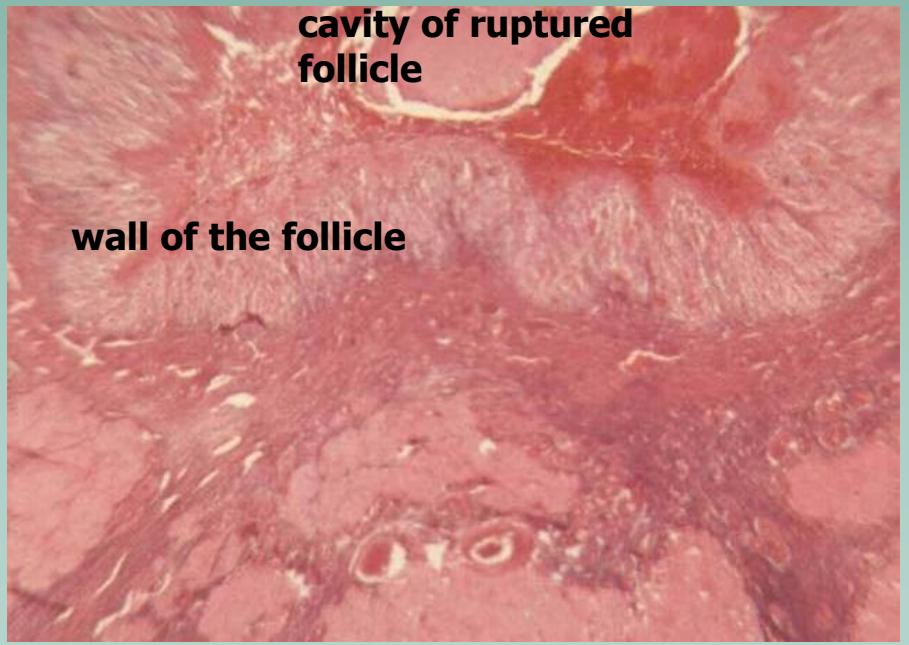
after ovulation the ruptured follicle is transformed into the **corpus luteum** the process is known as **luteinization**

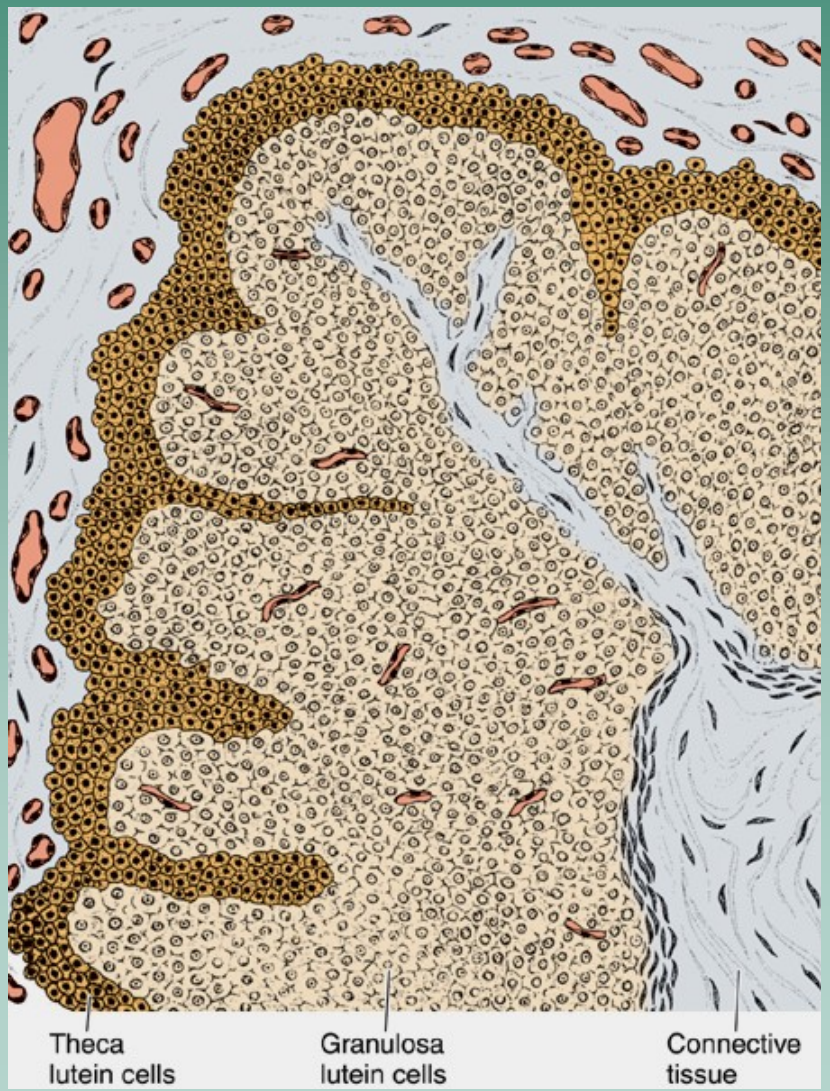
Corpus luteum

release of follicular fluid results in collapse of the follicle wall so that it becomes folded some blood flows into the follicular cavity and forms in it a coagulum

two layers of mature follicle are involved in the development of corpus luteum:

- cells of the membrana granulosa - called now **granulosa lutein cells**
- cells of the theca interna - called now **theca lutein cells**





The **granulosa lutein cells**

are located at luminal border and increase greatly in size (35 μm)

the granulosa lutein cells show characteristics of steroid-secreting cells and produce the **progesterone**

The **theca lutein cells** are located externally or in folds of the wall of then corpus luteum

cells are smaller then granulosa lutein ones and stain more intesively in histological sections

they produce steroids other than progesterone

if the ovum is not fertilized, the corpus luteum functions only 10-12 days, and after this period starts to degenerate and disappear - the **corpus luteum of menstruation**

if pregnancy occurs, chorionic gonadotropin produced by the placenta stimulates the growth of corpus luteum, which becomes larger and is in function for about 3 months - the **corpus luteum of pregnancy**

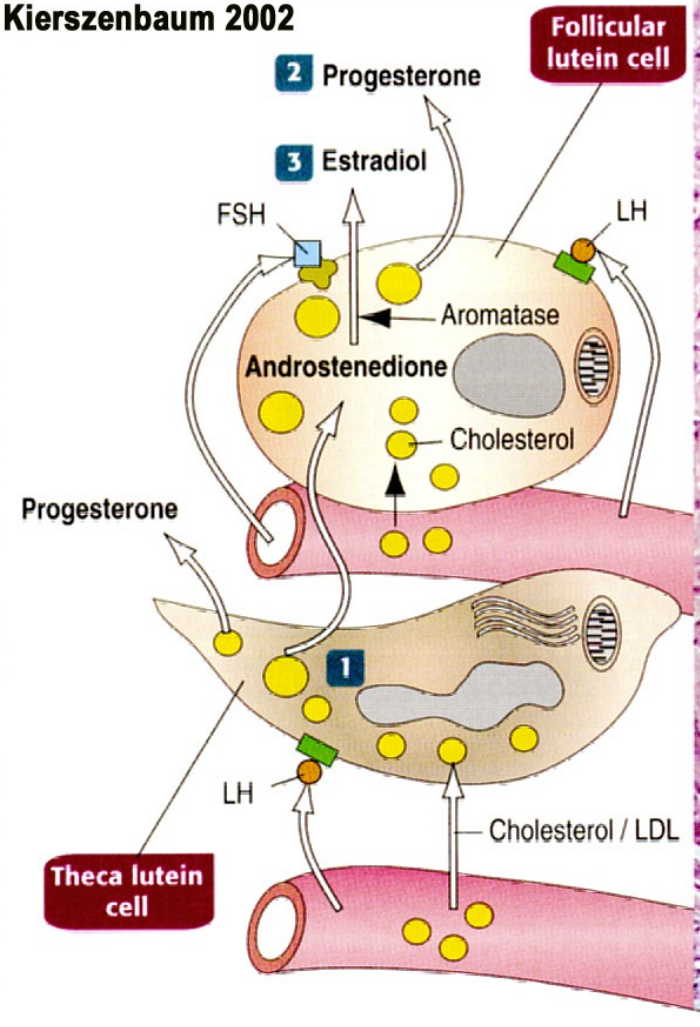
thereafter it gradually declines and definitively disappears after birth (during the childbed)

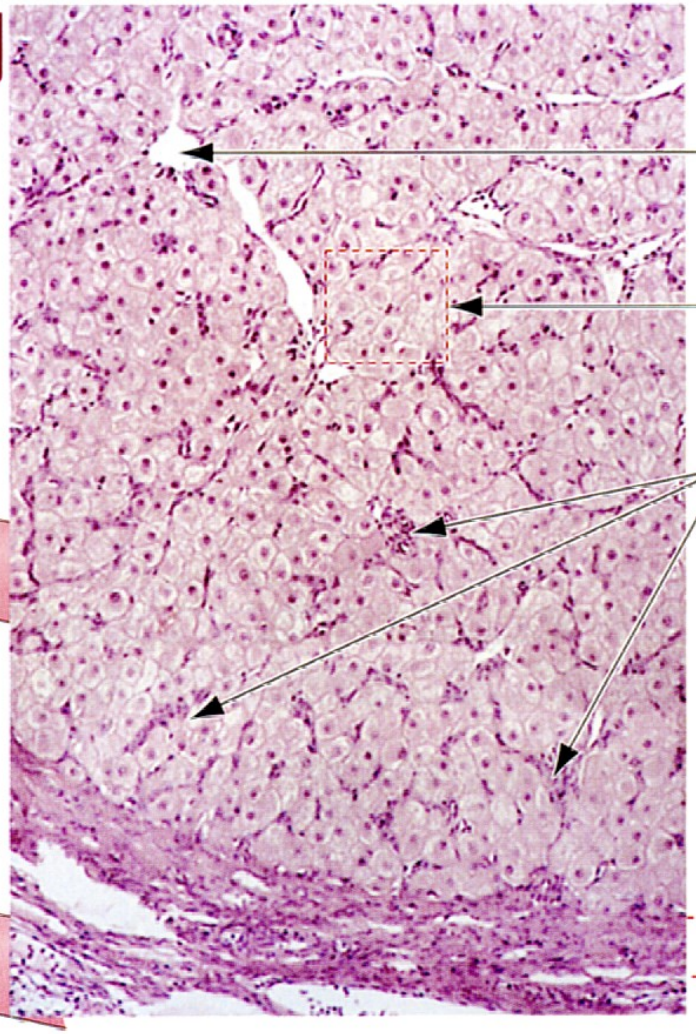
corpus albicans - is a final product occurring as a result of degeneration of corpus luteum

it appears as a region of dense connective tissue, later as a scar

Follicular lutein cell-theca lutein cell cooperation

Kierszenbaum 2002



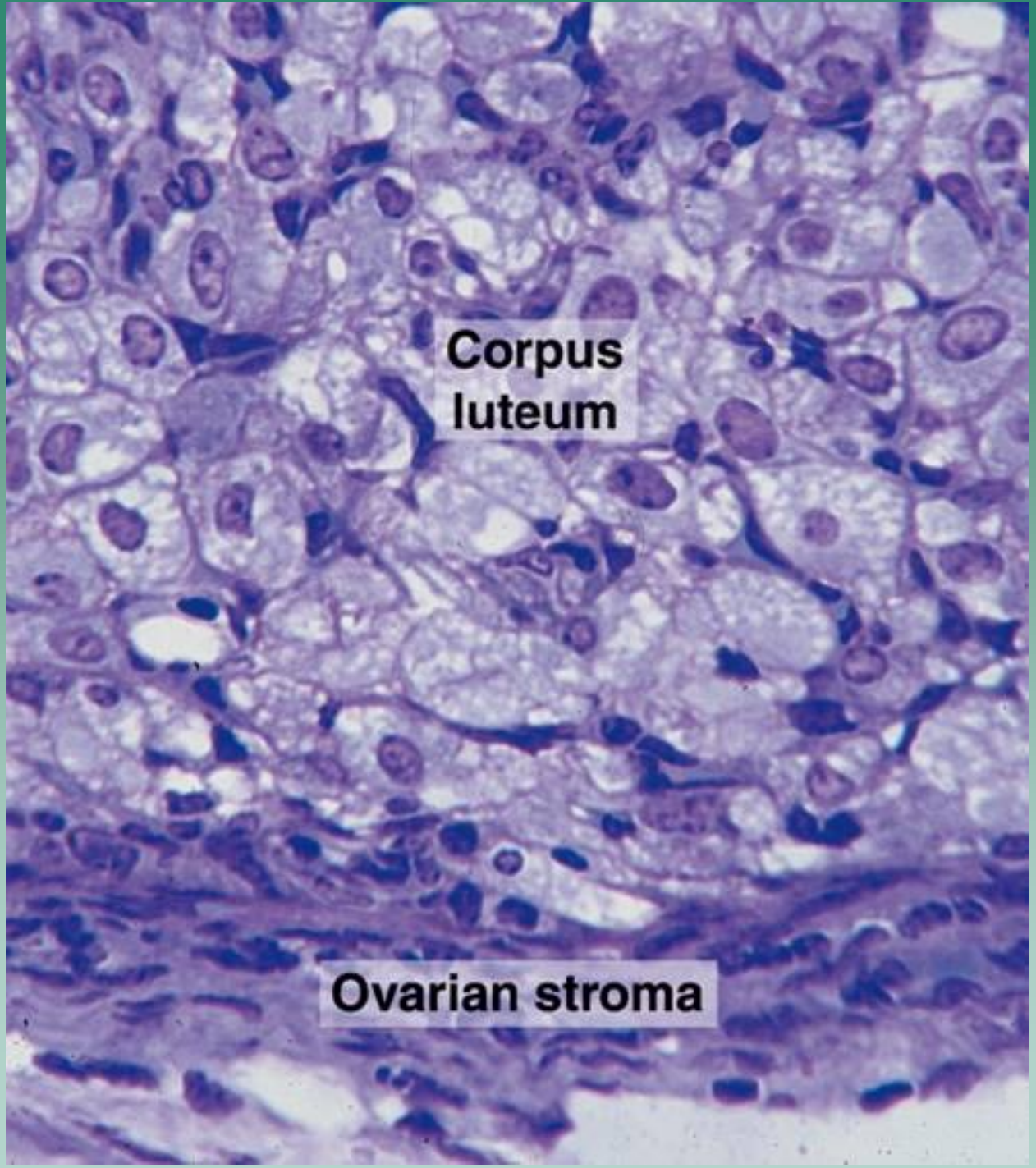


Functional cooperation between theca lutein cells and follicular lutein cells

1 Theca lutein cells, stimulated by LH, take up cholesterol or LDL, or both, from blood. Cholesterol is used for steroidogenesis. The steroid product, androstenedione, is transported to follicular lutein cells.

2 Follicular lutein cells are under control of both FSH and LH. These cells can store cholesterol taken up from blood and use it for the synthesis of progesterone.

3 In addition, follicular lutein cells utilize androstenedione –delivered by theca lutein cells– to produce estradiol.



corpus luteum graviditatis (verum)
c. l. of pregnancy

corpus luteum menstruationis (falsum)
c. l. of menstruation
|
corpus albicans |

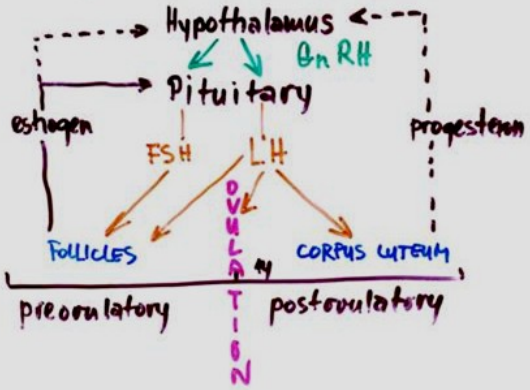
The ovarian cycle

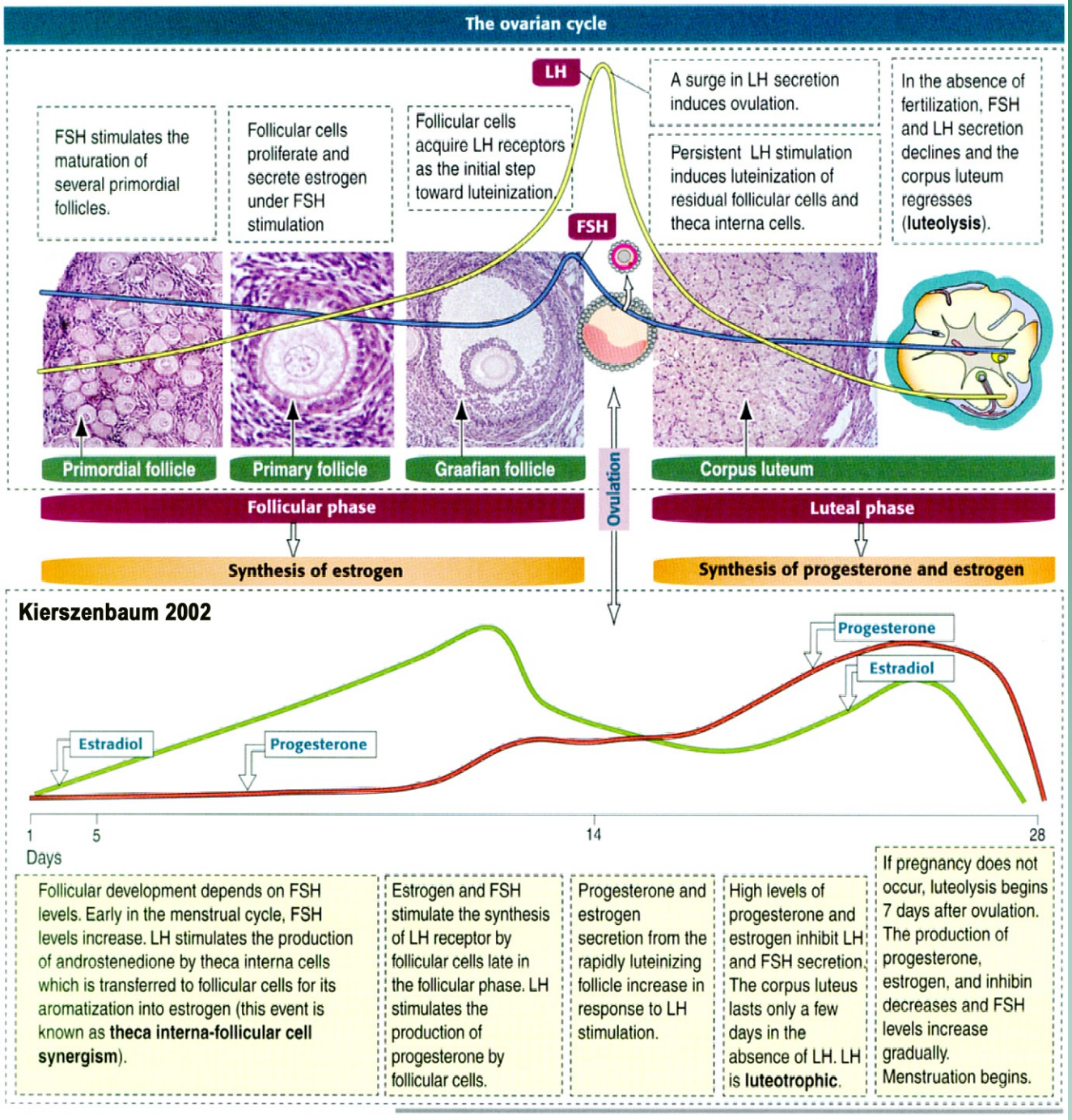
3 phases:

preovulatory – (estrogenic = follicular) – follicles gradually grow and produce estrogen FSH

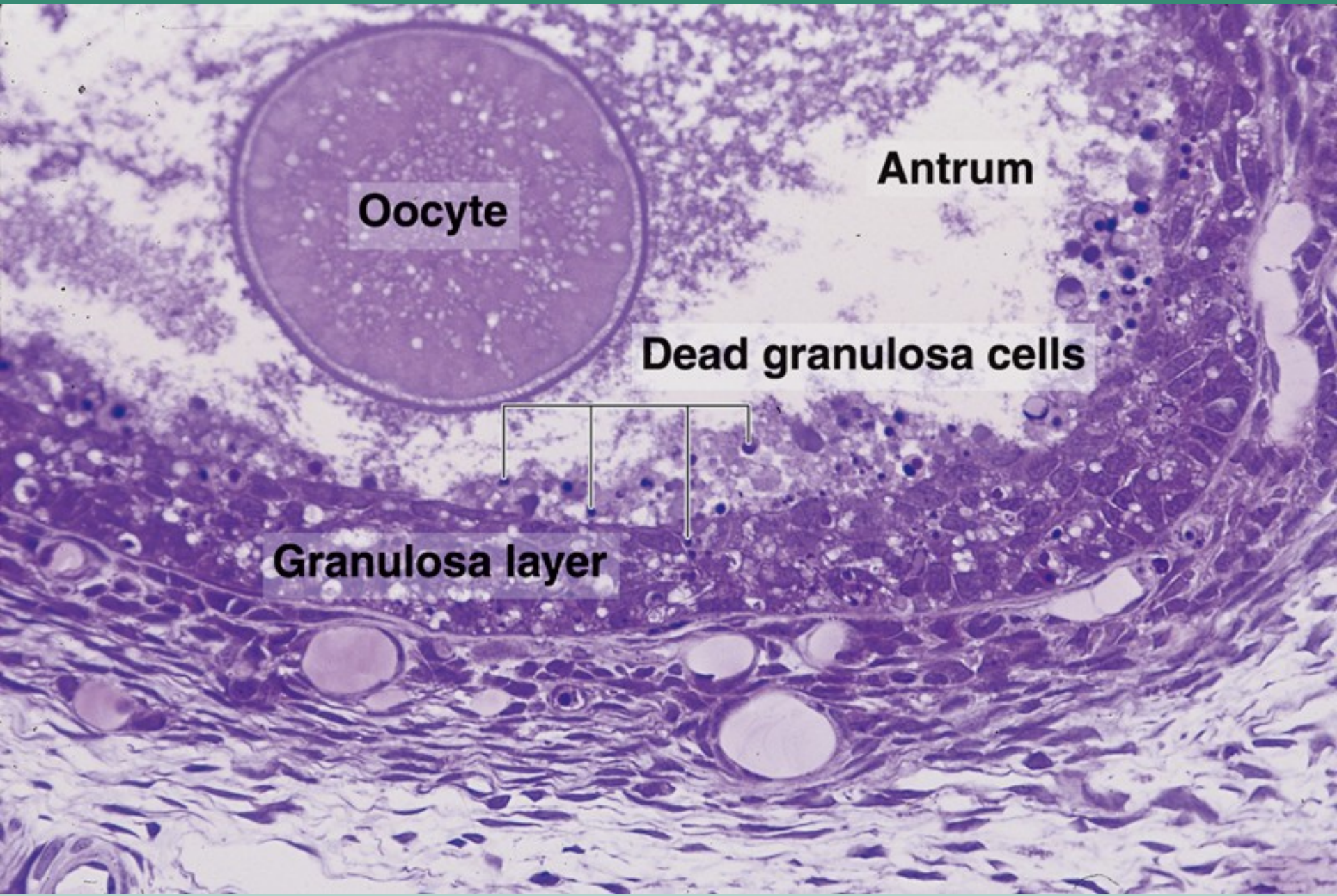
ovulation – short, rupture of the follicle and expelling of the sec. oocyte

postovulatory – (progesteronic = luteal) – corp. lut. formation, production of progesterone, LH

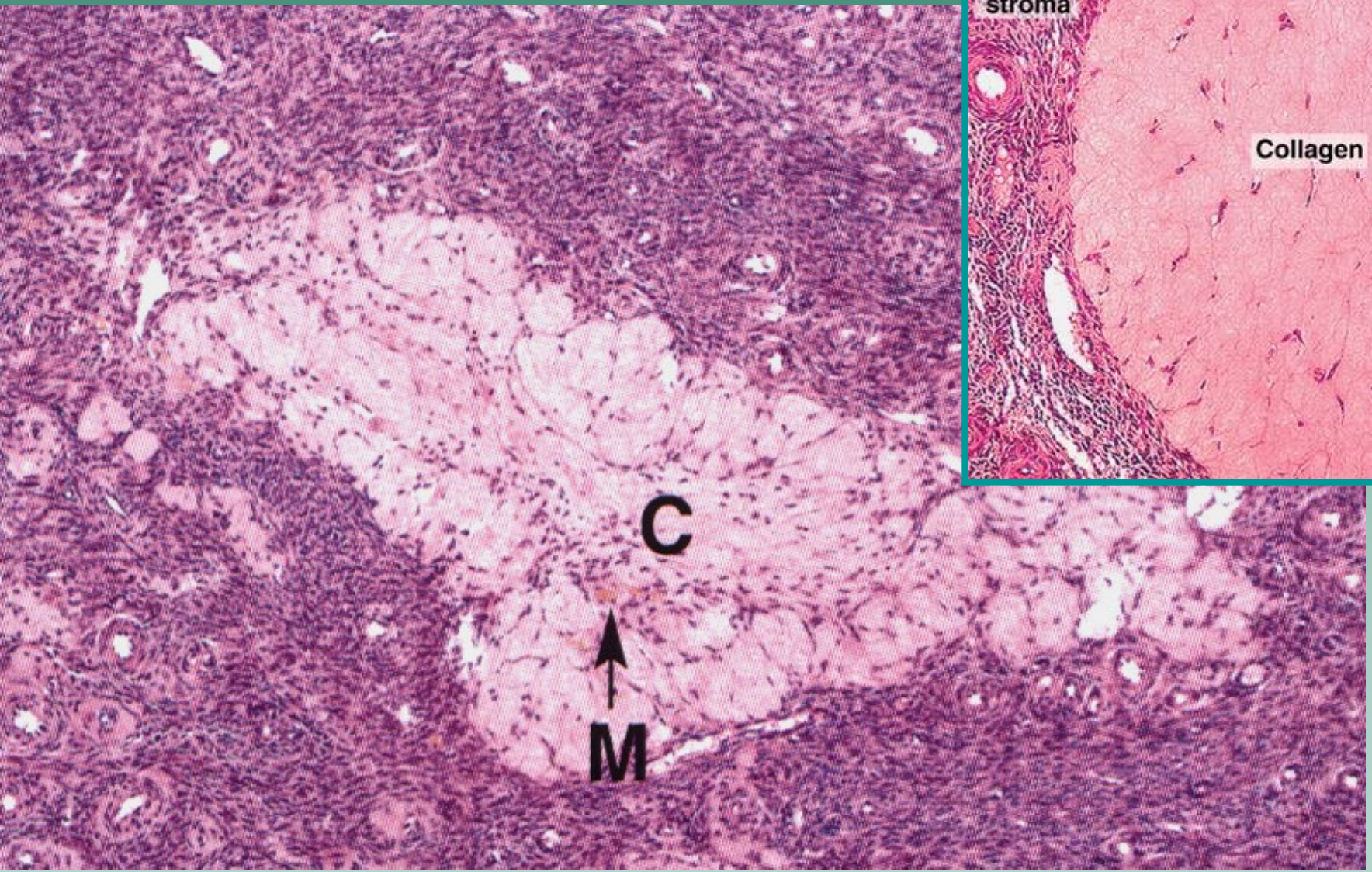




Atresia



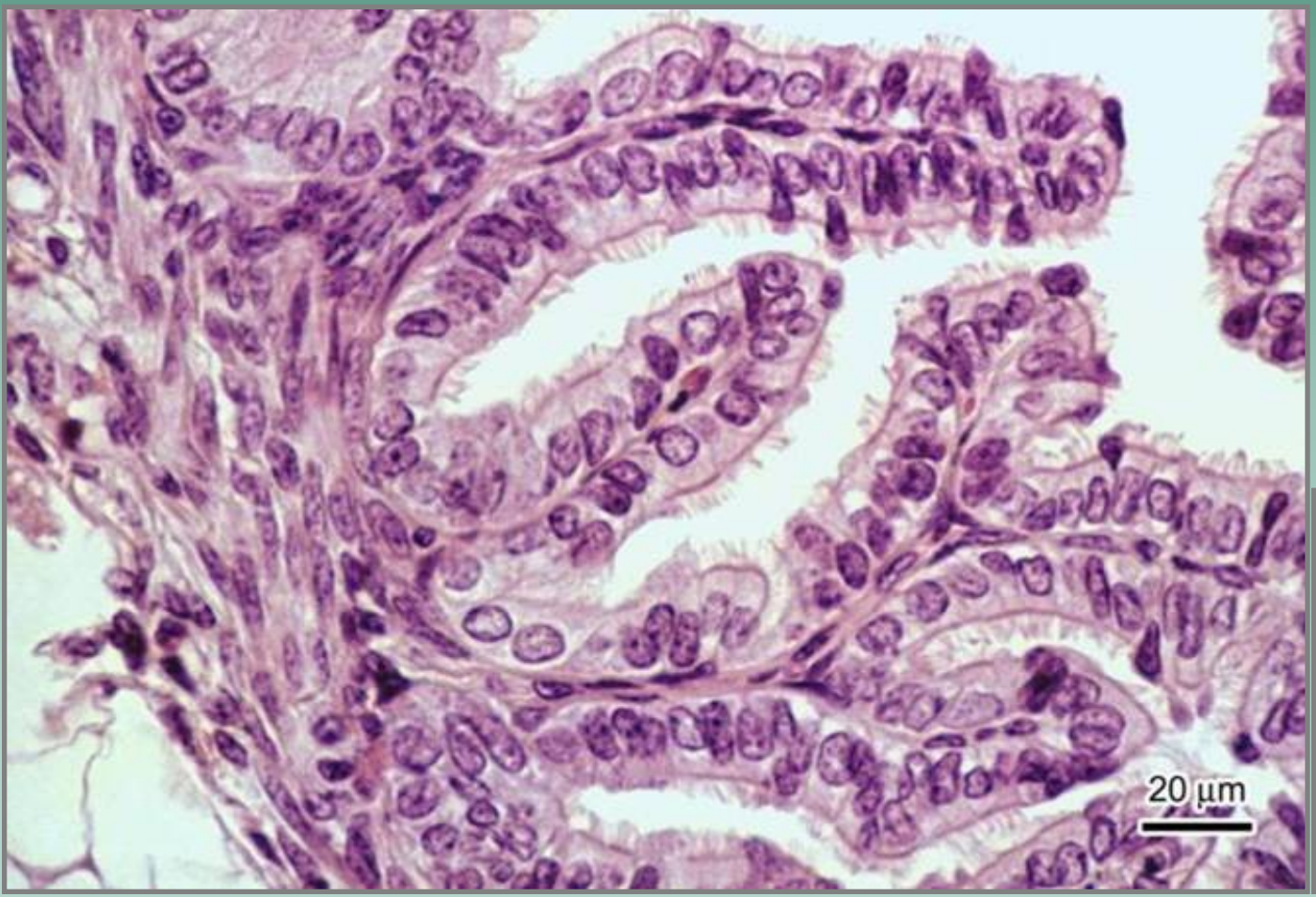
Corpus albicans

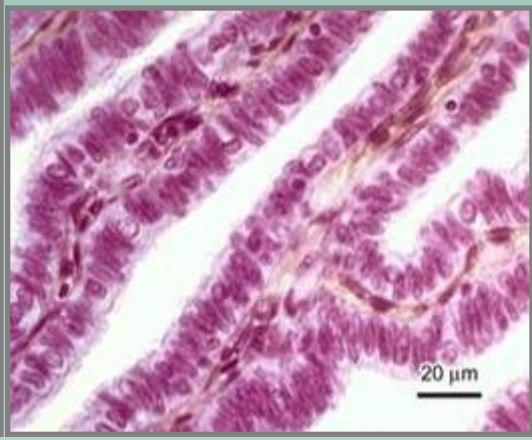


The oviduct

- is a muscular tube - about 12 cm long
- 2 extremities - one opens into the interior of the uterus, the free extremity sends off finger-like extensions - **fimbriae**

The wall consists of 3 layers: **a mucosa, a muscularis and a serosa**
Function: fertilization of the ovum (lateral third of the oviduct), its secretions contribute to the nutrition of the embryo during the cleavage of the embryo





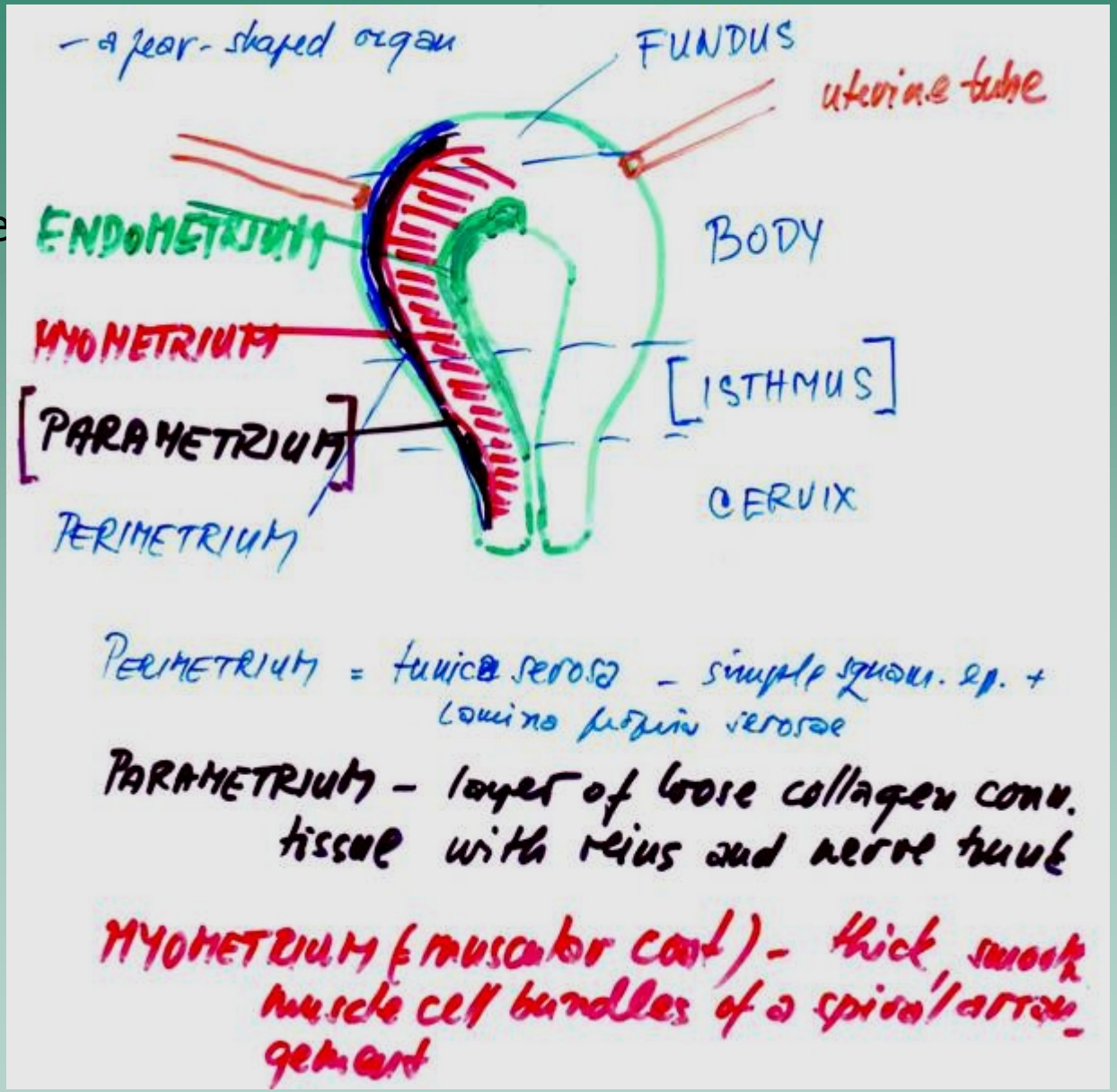

2 µm

The uterus

is a pear-shaped organ
it consists
of a **body**, a cylindrical **cervix**, and a narrowing segment - **isthmus**
a part of the body lying above points of entrance of uterine tubes is a **fundus**

The wall of the uterus:

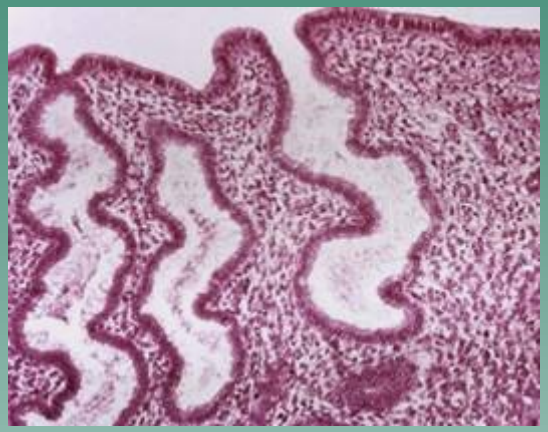
- mucosa of the uterus - **the endometrium**
- tunic of smooth muscle - **the myometrium**
- tunic of loose connective tissue - **the parametrium**
- visceral peritonium - **the perimetrium**.

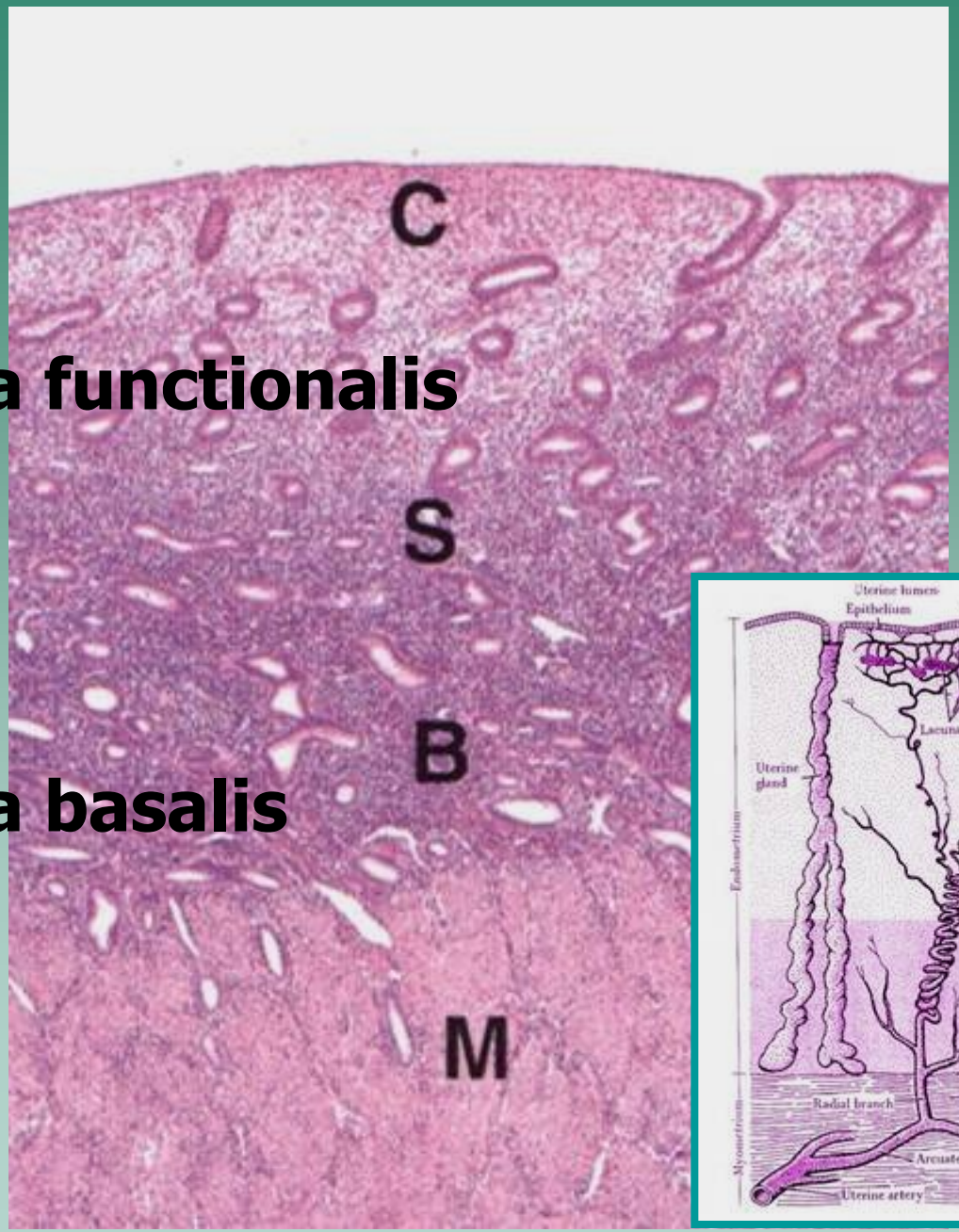


FUNDUS AND BODY

endometrium

- **epithelium**
- **lamina propria** with gll. uterinae





zona functionalis

zona basalis

Blood supply of endometrium is modified with its periodical sloughing

- straight arteries - the basalis
- coiled arteries the functionalis

Histology of the endometrium closely depends on the ovarian hormones - estrogens and progesterone
that are produced under stimulus of the anterior lobe of the pituitary

structural modifications have cyclic character and are summarizingly called as the **menstrual cycle**

duration - in average 28 days

the menstrual cycle starts between 12 to 15 years of age and continues until about age 45-50
- only during these age limits the female is fertile

menopause is a period when the menstrual cycles are ceased

menstrual cycle includes 4 phases:

- the **menstrual phase** - from the 1rst to 4th days of the cycle - menstrual bleeding
  the phase is induced by rapidly decrease of the levels of progesterone and estrogens
  the endometrium is reduced to only the basalis containing the basal portions of the uterine glands
- the **proliferative phase - (follicular phase -** because it coincides with the ddevelopment of ovarian follicles and the production of estrogen**)-** from 5th to 14th days
  is characterized by proliferation of uterine gland cells as well as connective tissues cells and deposition of the ground substance
  the endometrium is 2-3 mm thick and contains straight and unbranched uterine glands, coiled arteries grow into the regenerating stroma
  the phase is controlled with estrogens
- the **secretory phase** (**luteal phase**)- starts after ovulation and ends at day 26
  controlled with progesterone secreted by the corpus luteum
  the functionalis becomes thicker (5-6 mm at the end of the s. p.) and oedematous
  gland are coiled and branched and their cells begin to accumulate glycogen below the nuclei
  functionalis can be divided into the **pars compacta** (supercifially) and **pars spongiosa** (contains dilated lumens of uterine glands)
- the **ischemic phase** - days 27 to 28
  is characterized by a spasm of coiled blood vessels following with subsequent ischemia and necrosis of blood vessel walls and of the functionalis
  after blood constriction follows **ruptures of vessels and menstrual bleeding**

Menstrual cycle

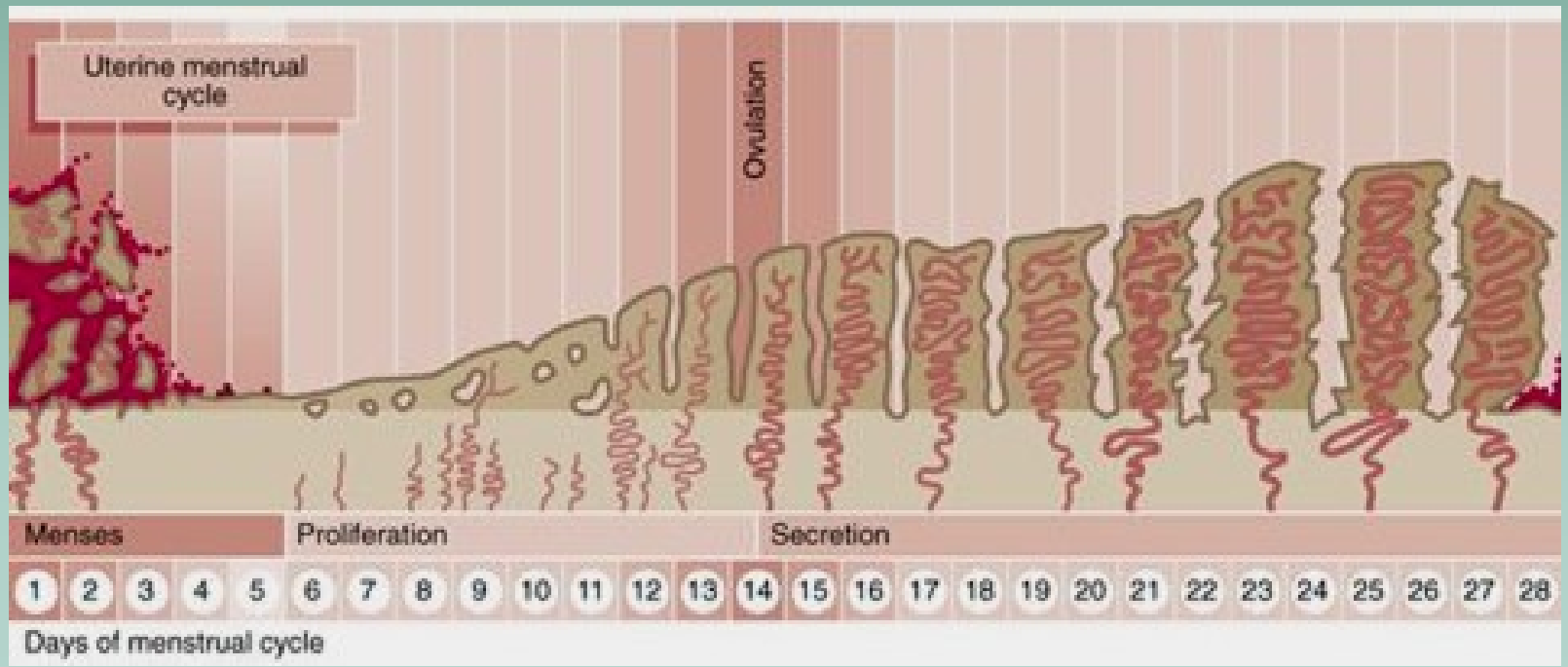
changes of uterine glands

menstrual (days 1–4) – 0,5 mm

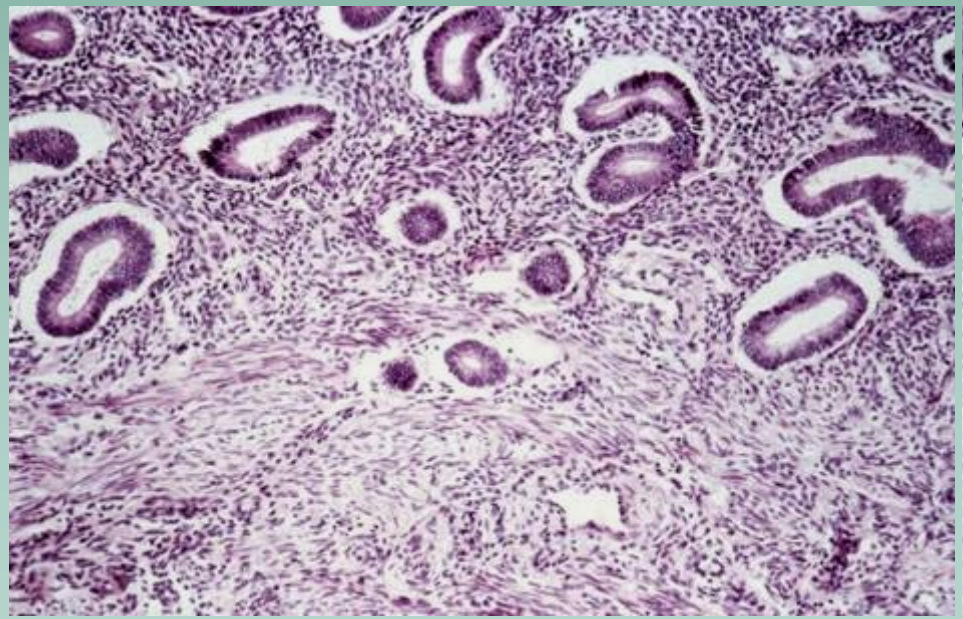
proliferative (days 5–15) – 3 - 4 mm

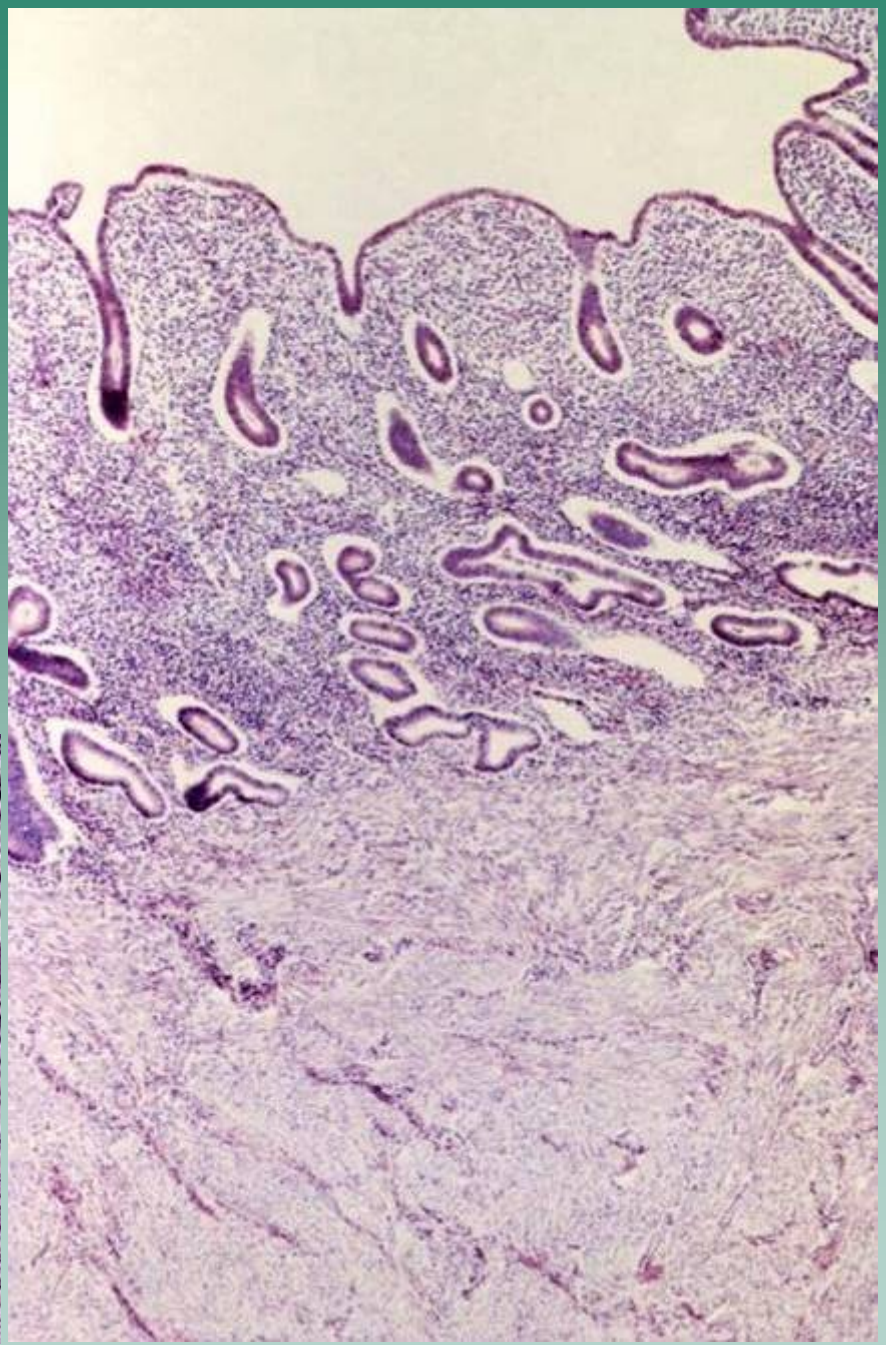
secretory (days 16– 27) – -7 mm

ischemic (day 28)

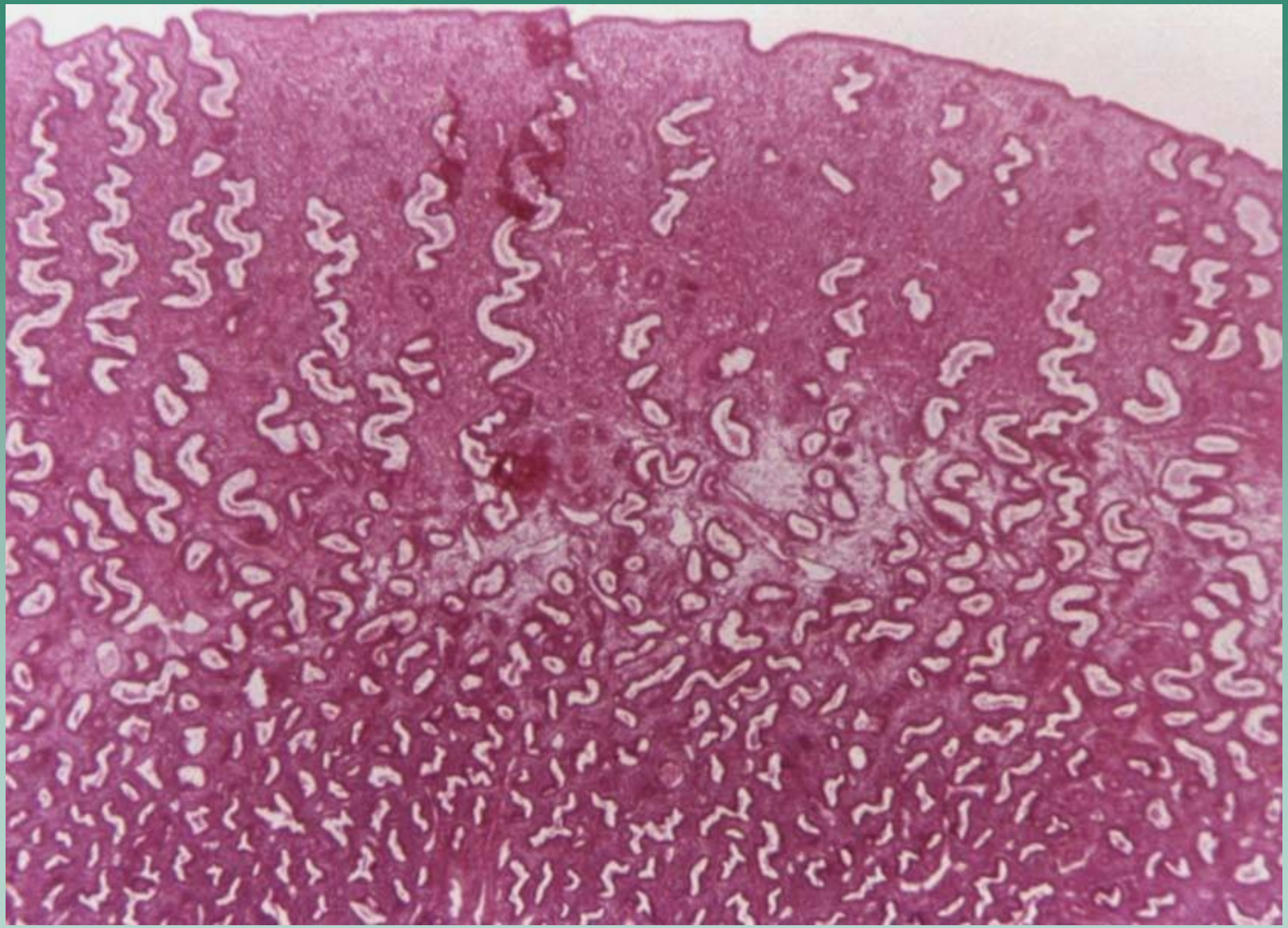


the **proliferative phase**

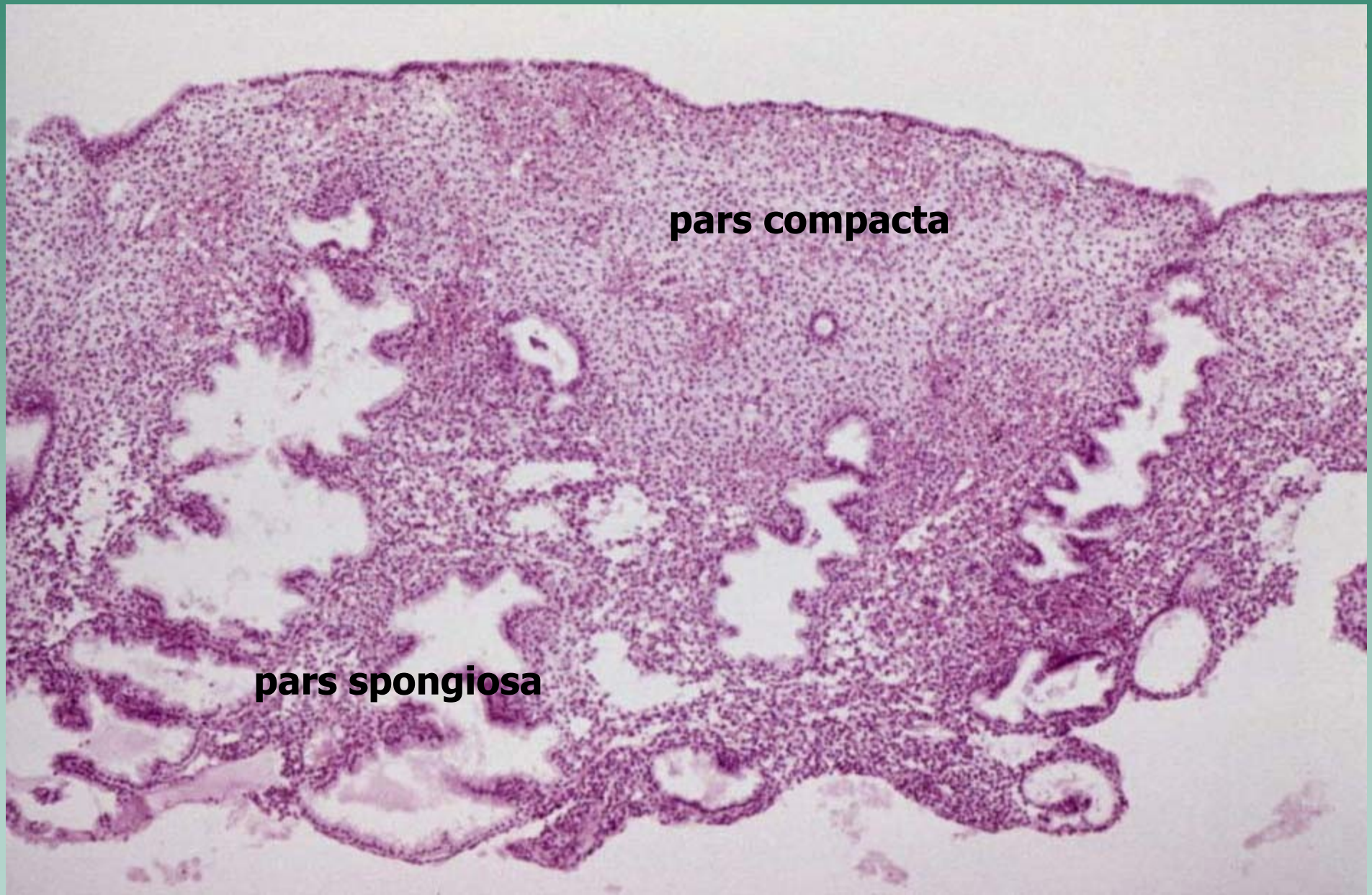




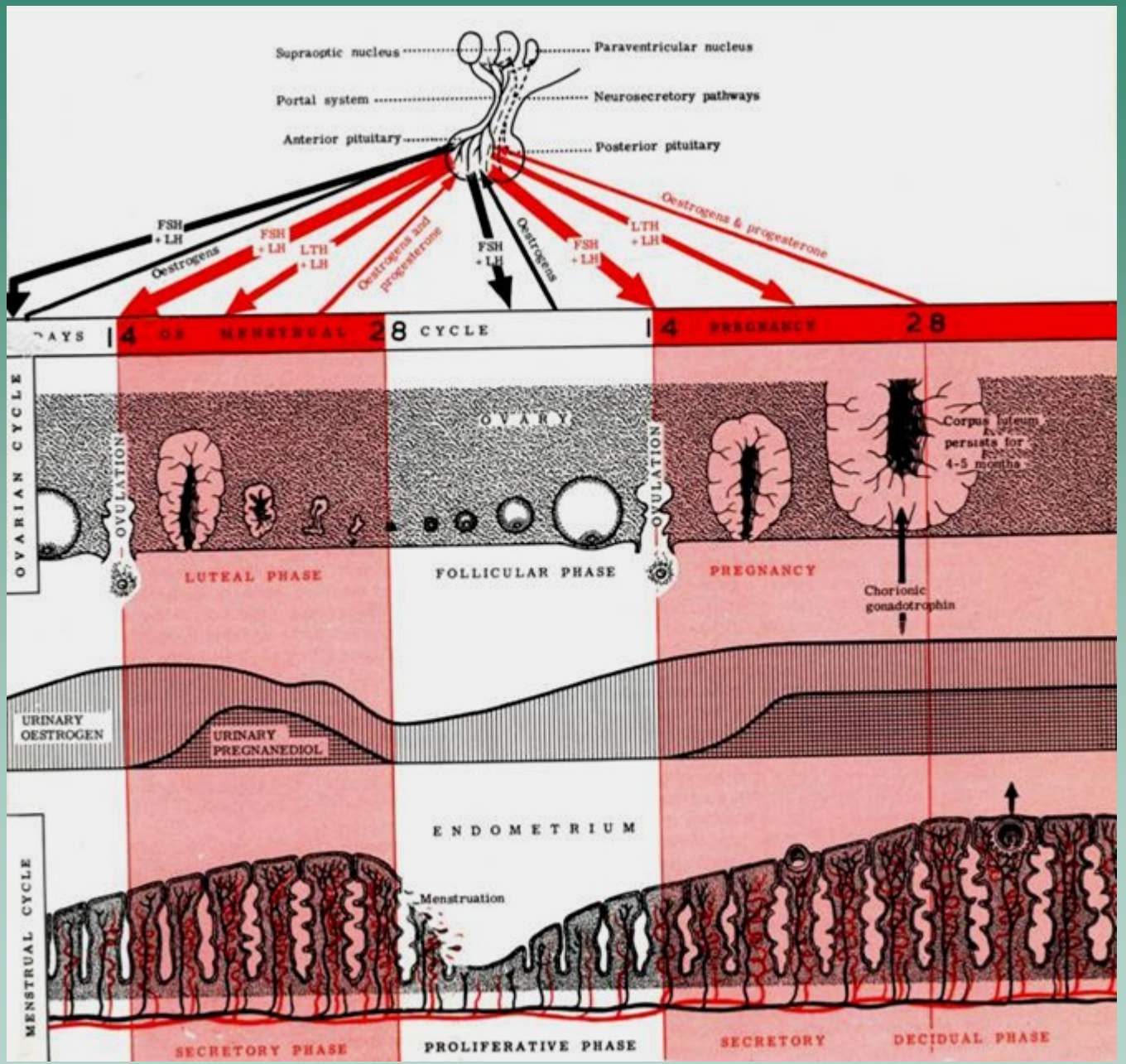
the **secretory phase**



the **secretory phase**



Relation between the menstrual and ovarian cycle



Remember:

after fertilization of the ovum and implantation of the embryo, the endometrium goes through profound changes and is called the **decidua**

cells of the stroma become enlarged and polygonal and are called decidual cells

the basal part of the decidua, **decidua basalis =**

the maternal part of the placenta

CERVIX

= inferior part of the uterus
it is divided into
an upper portion, the cervical canal
a lower vaginal portion that projects into the vagina

The cervical canal differs from the body of the uterus in

(1) its wall consists largely of dense collagenous and elastic fibers with only about 15 % of the wall being smooth muscle

(2) the mucosa contains complex mucous glands and deep branching folds - plicae palmatae

glands may become occluded and form cysts (ovula Nabothi)

the mucosa does not participate in menstruation (however, the glands undergo cyclic changes during menstrual cycle: in the proliferative phase they produce thin and watery secretion, which becomes copious at ovulation; secretion shows the consistency of egg whites and forms semisolid mucous plug that prevents the passage of sperm, microorganisms etc. from entering the uterus from the vagina)

(3) on the vaginal portion, the simple columnar epithelium is replaced with stratified squamous, nonkeratinized epithelium

VAGINA

is a fibromuscular, collapsed tube connecting the uterus to the exterior of the body wall: a mucosa, a muscularis, and an adventitia

Mucosa forms longitudinal folds - rugae. It is covered with 150 to 200 mm thick **stratified squamous, nonkeratinized epithelium**. Under the stimulus of estrogen, the vaginal epithelium synthesizes and accumulates a large quantity of glycogen, which is released into the vaginal lumen when the surface cells are exfoliated. Bacteria in the vagina (Lactobacillus acidophilus) metabolize glycogen and form lactic acid, which is responsible for the usually low pH of the vagina. **Lamina propria** is composed of loose connective tissue that is rich in elastic fibers. It also contains a few small lymph nodules and neutrophils. Lymphocytes and neutrophils invade the epithelium and pass into the lumen of the vagina during certain phases of the menstrual cycle - vaginal cytology. Lamina propria exhibits a rich vascularization that is the source of the fluid exusudate that seeps through the squamous epithelium into the lumen of the vagina during copulation.

Muscularis comprises two poorly develop smooth muscle layers: inner circular and outer longitudinal.

Adventitia surrounds the vagina and blends with adjacent organs. It is a coat of dense connective tissue, rich in thick elastic fibers. In this connective tissue are an extensive venous plexus, nerve bundles, and groups of nerve cells.

EXTERNAL GENITALIA

Labia majora - are two prominent elongated folds of skin that contain a large quantity of adipose tissue and thin layer of smooth muscle. In the external surface, coarse and curly hairs and prominent sebaceous glands are seen.

Labia minora - are two thin, hairless folds of skin with a core of spongy connective tissue permeated by elastic fibers. Sebaceous and sweet glands are present on the inner and outer surfaces of the labia minora.

Clitoris is homologous with a penis. It consists of two erectile bodies ending in a rudimentary glans clitoridis and a prepuce. The clitoris is covered with stratified squamous epithelium.

Vestibulum vaginae and hymen

Vestibular glands are 2 glandulae vestibulares majores, or glands of Bartholin + numerous glandulae vestibulares minores. Bartholin glands are homologous to the bulbourethral glands and are situated with one on each side of the vestibulum. All the glandulae vestibulares secrete mucus.

PLACENTA

a temporary organ which develops during the second month of development

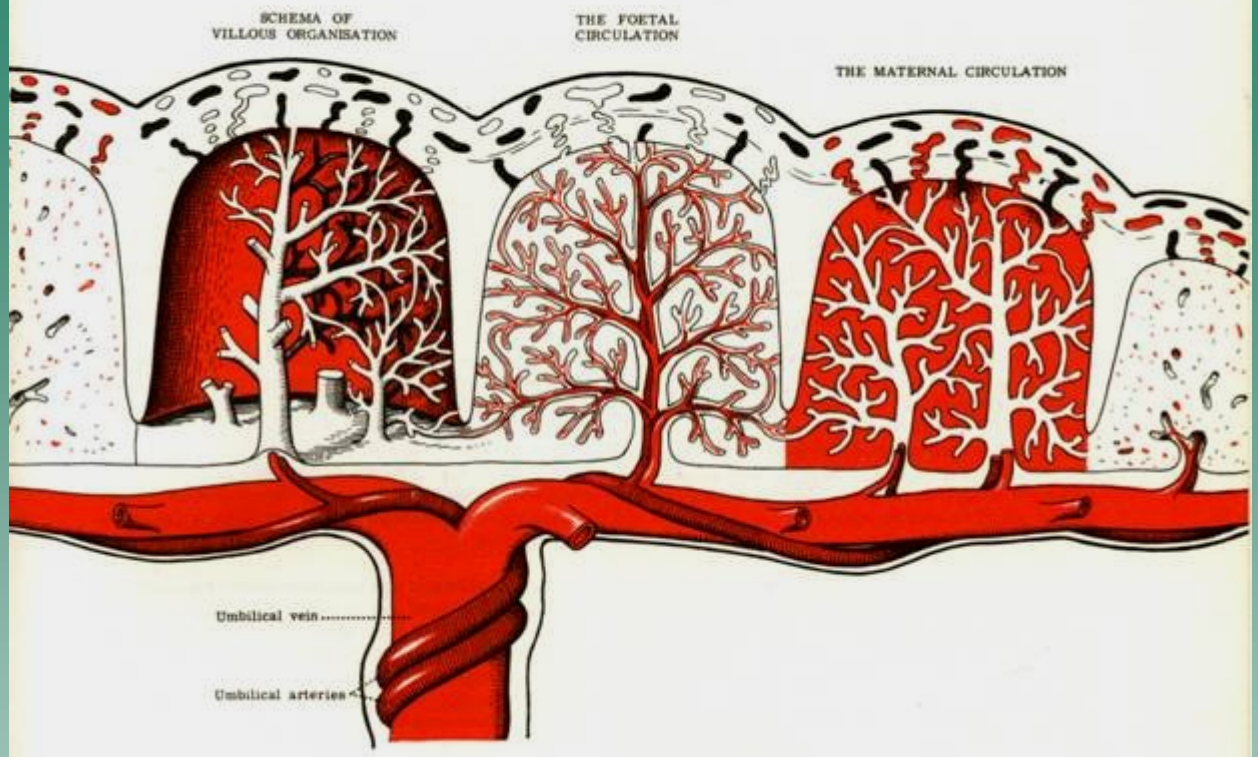
is the site of physiologic exchange between the mother and fetus

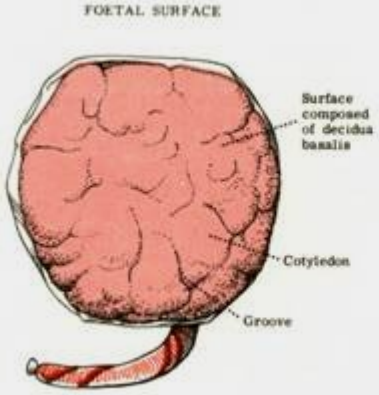
the human placenta is of discoidal shape measuring about 15 - 20 cm in diameter and 2- 3 cm in thickness and weighing 500 - 600 g at full term.

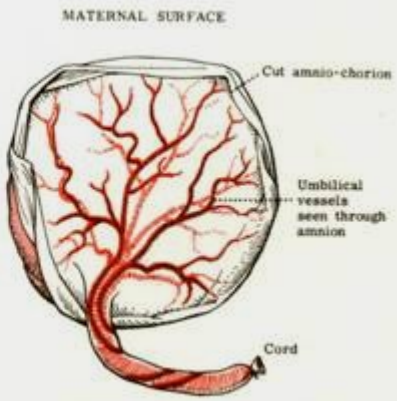
it consists of 2 parts close associated each other:

- the **fetal part** or **villous chorion** and
- the **maternal part** or **decidua basalis**

The Placenta at Term







1. **Fetal part =** the villous chorion, has a **chorionic plate** from which the **chorionic villi** project into the **intervillous spaces** through them maternal blood, bringing nutritive and other substances necessary for embryonic and fetal development, and taking away the waste products of fetal metabolism, circulates

   The chorionic villi are composed of a **connective tissue core** derived from the extraembryonic mesoderm surrounded by **the cytotrophoblast** and **the syncytiotrophoblast**. While the syncytiotrophoblast remains until the end of pregnancy, the cytotrophoblast disappears gradually during the second half. The fetal and maternal blood streams are isolated by the placental barrier which includes: the endothelium and basal lamina of the fetal capillaries, the connective tissue in the interior of the villus, the syncytiotrophoblast (during the first half pregnancy also the cytotrophoblast + its basal lamina). The chorionic villi may be either free or anchored to the decidua basalis (so-called main stem villi). One main stem villus represents a unit of the fetal part - the cotyledon

2. **Maternal part** = **decidua basalis** which usually forms a compact layer, known as the basal plate; the basal plate protrudes among individual cotyledons as placental septa.

Placental circulation:

Fetal placental circulation: Deoxygenated blood leaves the fetus and passes through the 2 umbilical arteries to the placenta. The arteries branch and ultimately give rise to the vessels of the chorionic villi. In the villi, the fetal blood receives oxygen, loses its CO_2 , and return to the fetus through the umbilical vein.

Maternal placental circulation: 80 to 100 spiral arteries that derived from the uterine artery open in the middle of the placenta; blood flows into intervillous spaces and passes over the surface of the villi where exchange of gasses and metabolic products occurs. The maternal blood leaves the intervillous spaces through endometrial veins (located near the periphery of the placenta).

Placental activities

three main activities: metabolic, transfer, and endocrine

- **Placental metabolism** - in placenta, particularly during early pregnancy, synthesizes glycogen, cholesterol, and fatty acids which all serve as a source of nutrients and energy for the embryo.

- **Placental transfer** - gases, nutrients, hormones, electrolytes, antibodies, wastes, and also several drugs are transported across the placental barrier. The transport is provided by 4 mechanisms: simple cell diffusion, facilitated diffusion, active transport, and pinocytosis.

- **Placental endocrine secretion**: the syncytiotrophoblast produces several hormones which are of 2 categories:
  - *protein hormones*: human chorionic gonadotropin (hCG), human chorionic somatomammotropin (hCS) or placental lactogen, human chorionic thyrotropin (hCT), and human chorionic corticotropin (hCACTH)
  - *steroid hormones*: progesterone + estrogens.

THE UMBILICAL CORD

is usually 1-2 cm in diameter and 30 -90 cm in length (average 55 cm)
the cord is attached near the center of the placenta

- **amnionic ectoderm** - simple squamous to cuboidal epithelium on the surface of the cord
- **Wharton's jelly** (gel-like connective tissue) - main umbilical tissue consisting of acid mucopolysaccharides, fibrocytes and thin collagen fibers arranged in a network
- **umbilical blood vessels** (vasa umbilicalia)
  - 1. umbilical arteries (arteriae umbilicales) - vessels with narrow lumina in which smooth muscle cells are arranged circularly, spirally and longitudinally; outer and inner elastic membranes are missing
  - 2. umbilical vein (vena umbilicalis) - a single vessel with a large lumen than in arteries; its wall is thin, with three distinct layers.
- **rest of the allantoic duct** (ductus allantoideus) - an all-defined patch of epithelium in the middle of a triangle demarcated by umbilical veins (sometimes appearing only as a thickening of connective fibers).