ANATOMY

☑ Sheet ○ Slide ○ Handout

Number

11

Subject

The menstrual cycle + شوية Histology

Done By

Raghad Bataineh

Corrected by

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Doctor

Dr. Faraj Bustami

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Price:

The sheet was written based on recordings of sections 1+3.

Most of the lecture was just a repetition of the information mentioned in the previous lecture.

We said that the uterus is composed of three layers:

1-endometrium 2-myometrium 3-perimetrium

1- **The endometrium:** The endometrium is formed of mucosa (there is no submucosa). The epithelial lining is simple columnar ciliated or non-ciliated (the non-ciliated contains stereocilia). Under the mucosa we have the lamina propria (the stroma of the uterus) which is full of macrophages and leukocytes to deal with invading microbes.

The epithelium bulges inside the endometrium forming simple tubular glands. The glands are arranged in two layers: stratum basale (basal layer) and stratum functionale (functional layer). The functional layer could be subdivided into compacta and spongiosa. [figure 1]

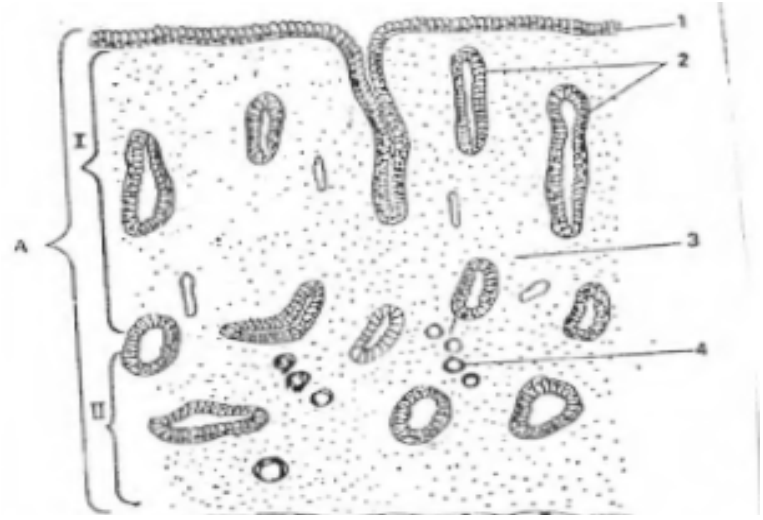


Figure 1

A: endometrium I: stratum functionale II: stratum basale

-The functional layer and the basal layer differ in their structure, function and blood supply.

-During menstruation, the functional layer is the part of the endometrium that sheds. And it's renewed after that from the basal layer.

-The shedding occurs due to degeneration of the corpus luteum after 14 days of its formation (in case there's no pregnancy). Its degeneration causes progressive decrease in estrogen and progesterone levels in the blood. The drop in their concentrations causes vasoconstriction to the spiral artery (which supplies the functional layer). The vasoconstriction causes ischemia, necrosis and shedding of the functional layer.

-The uterine artery (which is a branch from the internal ileac) enters the middle layer of the myometrium and gives rise to the so called **arcuate arteries** (circumferential course) which will give rise to **radial arteries** which give rise to two types of arteries [figure 2]:

A- **Spiral arteries** to stratum functionale: these arteries two days before menstruation are subjected to vasoconstriction due to sudden decrease in the amount of progesterone and estrogen in the blood (due to degeneration of the corpus luteum). As a result of the vasoconstriction, the superficial layer (functional layer/ stratum functionale) will suffer from ischemia, necrosis and shedding of the epithelium and the superficial parts of the endometrial glands. Ischemia and necrosis do not only affect the epithelium and the glands, they also affect the distal parts of the spiral arteries, so they rupture → there will be an extravasation of blood and it will accumulate under the epithelium. Blood accumulation causes further shedding. [**Hint**: <u>when you see a histological section of the uterus with blood accumulating under the epithelium you know that this is the menstrual phase</u>].

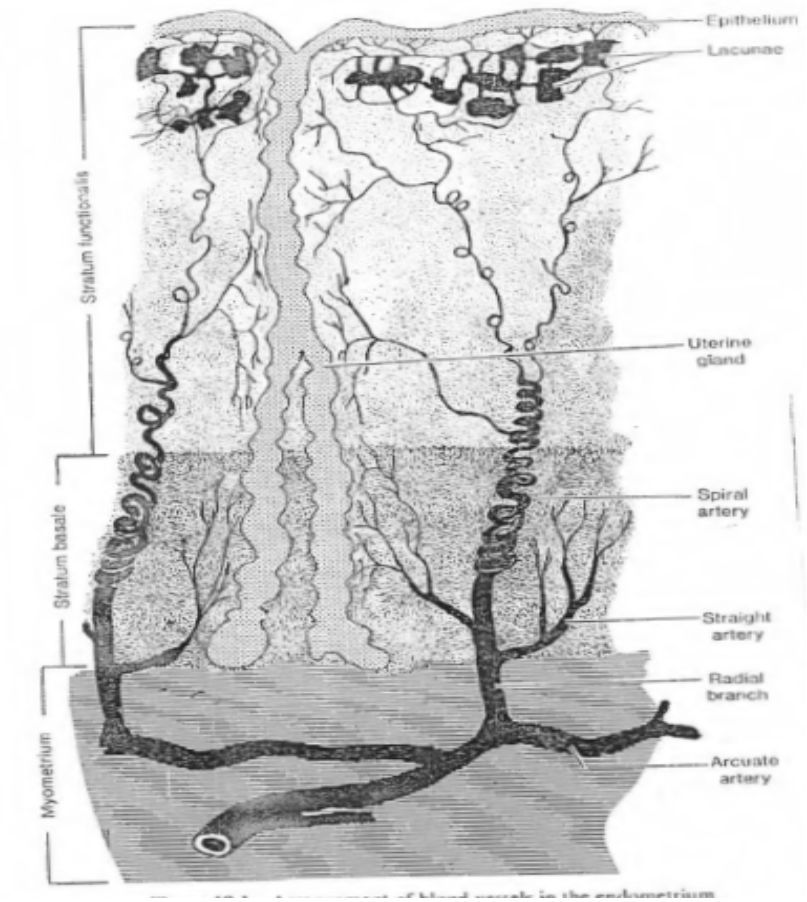


Figure 2 the arrangement of the blood vessels in the endometrium

After that the stratum functionale will regenerate from the stratum basale.

The spiral artery divides into arterioles → sinusoidal capillaries (lacunae) → venules.

B-**Straight arteries** to the stratum basale: these arteries are not affected by the levels of progesterone and estrogen and are not subjected to vasoconstriction, so the stratum basale doesn't suffer from ischemia and necrosis.

2- **The myometrium** (a very thick wall of smooth muscles- figure 3): The smooth muscles in the wall of the uterus are arranged in three layers:

-inner layer: mainly circular and longitudinal.

-middle layer: a mixture of circular, longitudinal and oblique smooth muscle cells. This layer is rich in blood vessels (this is where the uterine artery enters).

-outer layer: circular and longitudinal smooth muscles.

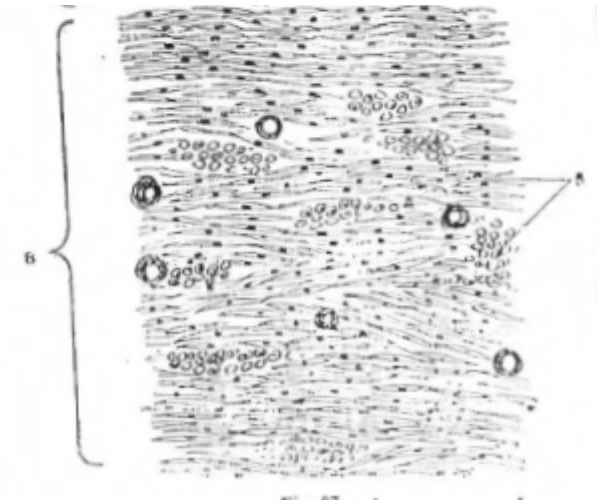


Figure 3 the myometrium

-During pregnancy the uterus enlarges and its wall becomes thinner. The length of the smooth muscles before pregnancy is 30-50 microns. During pregnancy the smooth muscles increase in length (up to 500 microns) and number (hypertrophy and hyperplasia). We know that smooth muscles after birth never undergo mitosis and are considered post-mitotic, but here we have an exception. The smooth muscles of the uterus under the effect of hormones (specially progesterone) can proliferate and increase in number. Another theory states that the increase in the number of uterine smooth muscles during pregnancy is due to their differentiation form a cell called "**undifferentiated mesenchymal cell**" in the wall of the uterus.

-The uterine smooth muscles normally cause painless intermittent contractions, but these contractions increase at the time of menstruation, so a lot of females complain from abdominal cramps due to the increase in the uterine smooth muscles activity. The contractions also increase when we place an intrauterine device, which prevents the implantation of the fetus.

On the other hand, these smooth muscles relax during pregnancy under the effect of relaxin hormone which is produced from the placenta. So during pregnancy the contractile activity of uterine smooth muscles decreases.

**Oxytocin hormone: if we inject oxytocin using a drip, it produces a powerful contraction, but it DOES NOT initiate labor. Other factors including some types of prostaglandins are responsible for the initiation of labor as their concentrations increase before delivery.

3- **The perimetrium** (a peritoneal covering).

Now we will continue talking about the different phases of the menstrual cycle. The most important thing regarding this topic is to link what happens in the endometrium, the ovaries, the hypothalamus and estrogen-progesterone levels in the blood.

The typical menstrual cycle is 28 days and since the 1st day of bleeding is considered the 1st day of the menstrual cycle then the first phase would be the menstrual phase.

***I recommend you to look at the figure 5 page 7 while studying the phases*

1- **The menstrual phase** (1-4 days)

In the endometrium: during this phase there is desquamation and shedding of epithelium and the superficial parts of the glands in the functional layer. Shedding occurs due to the sudden drop in estrogen and progesterone levels due to degeneration of the corpus luteum (the entire story was discussed before).

In the ovaries: during this phase there is recruitment of a new group of growing follicles (so the beginning of their growth is in the menstrual phase).

2- **The proliferative/follicular/pre-ovulatory phase** (day 4- day 14)

In the endometrium: during this phase, the glands in the stratum basale are responsible for regenerating the endometrium. So the main event in the proliferative phase is *regeneration and repair of the endometrium* (بدنا نرجع نبني اللي انهد). This regeneration happens under the effect of **estrogen** produced from the growing follicles. Here the glands are straight, they increase in length and number and they store little glycogen. The spiral arteries which have ruptured will also regenerate during this phase, but they will not reach the outer third of the superficial layer (functional layer).

In the ovaries: growing follicles producing estrogen.

[it's called the proliferative phase because we have proliferation of the endometrial glands. It's also called the follicular phase because we have growing follicles in the ovary producing large amounts of estrogen].

In the pituitary: in this phase (1st half of the menstrual cycle) the estrogen produced by the growing follicles exerts a negative feedback effect on the pituitary and reduces the production of LH and FSH.

3- **Ovulation**: estrogen-induced LH surge (day 14-15)

In the middle of the cycle and due to the huge amount of estrogen, it starts to induce a positive (instead of a negative) feedback effect on the hypothalamus (increases GnRH) and the pituitary to increase the levels of LH and FSH.

The LH surge: it occurs just before the midpoint of the menstrual cycle.

What causes the LH surge? The huge increase in estrogen secretion and its positive feedback effect on the pituitary which causes increased production of FSH and LH.

What are the effects of the LH surge?

- completion of the first meiotic division: LH activates "meiosis inducing substances" that stimulate the primary oocyte to complete the 1st meiotic division and form a secondary oocyte, which enters the 2nd meiotic division but remains suspended in the metaphase (doesn't complete the 2nd meiotic division unless fertilization occurs).
- Ovulation (discussed later).
- Formation of the corpus luteum from the remnants of the mature Graafian follicle.
  The corpus luteum is a temporary endocrine gland that's able to produce estrogen and progesterone. If pregnancy doesn't occur, the corpus luteum survives only for 14 days. If pregnancy occurs, the corpus luteum will survive for 3-4 months, then it will degenerate and the placenta takes its place. In the formation of the corpus luteum, the theca interna cells are converted into theca lutein cells and the granulosa cells are converted into granulosa lutein cells and both types of cells (Theca lutein cells and granulosa lutein cells) are able to produce **androgen, estrogen and progesterone**.
  **granulosa cells will have increased fat (steroids) concentration, enlargement of smooth endoplasmic reticulum and become endocrine producing cell.

MUST-KNOW:

- The ovum which is released from the ovary each month is a secondary oocyte suspended in the metaphase of the 2nd meiotic division (it's NOT mature).
- The menstrual discharge contains: arterial and venous blood, degenerated epithelial and stromal cells, glandular secretions.

4- **The secretory phase /luteal phase/post-ovulatory phase** (day 15- day 28)

In the endometrium: there is further growth and regeneration of the endometrium under the effect of progesterone –mainly- which is coming from the corpus luteum. There is also further increase in glands' length and number and they store more and **more glycogen**. There is a huge amount of secretions (hence the name) starting from the basal part of the gland until reaching the apex. This huge amount of secretions causes the glands to become highly **tortuous**. The endometrium in this phase is highly edematous and highly vascular in **preparation to receive a fertilized ovum (zygote)**. And the spiral arteries continue to regenerate during this phase until they **reach the outer third of the superficial layer**.

In the ovaries: there is the corpus luteum which produces progesterone –mainly- and estrogen.

In the pituitary: in this phase (2nd half of the menstrual cycle), progesterone is the one exerting the negative feedback effect on the pituitary and lowering the levels of FSH and LH.

[Figure 4 is extremely important: If you look at a histological section in the uterus and you recognize tortuous glands then it's the secretory phase and in the ovaries there is the corpus luteum.

If the glands are straight then it's the proliferative phase and in the ovaries we have growing follicles

If the superficial parts of the glands are shed, it's the menstrual phase and we have recruitment of new follicles in the ovary].

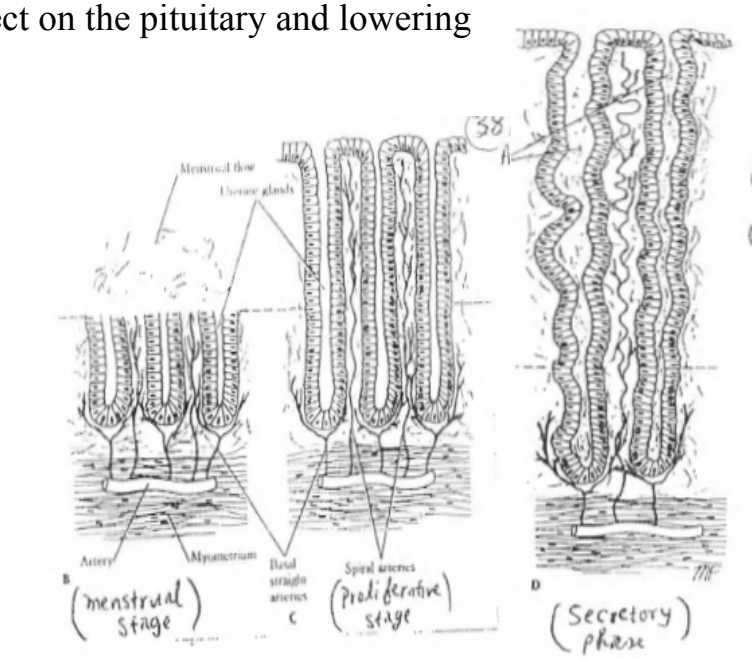


Figure 4 the differences in glands appearance between the menstrual cycle phases

Figure 5 illustrates the events occurring during the different phases of the menstrual cycle. Please make sure you're able to link all the changes in the endometrium, the ovaries, the pituitary with estrogen and progesterone levels.

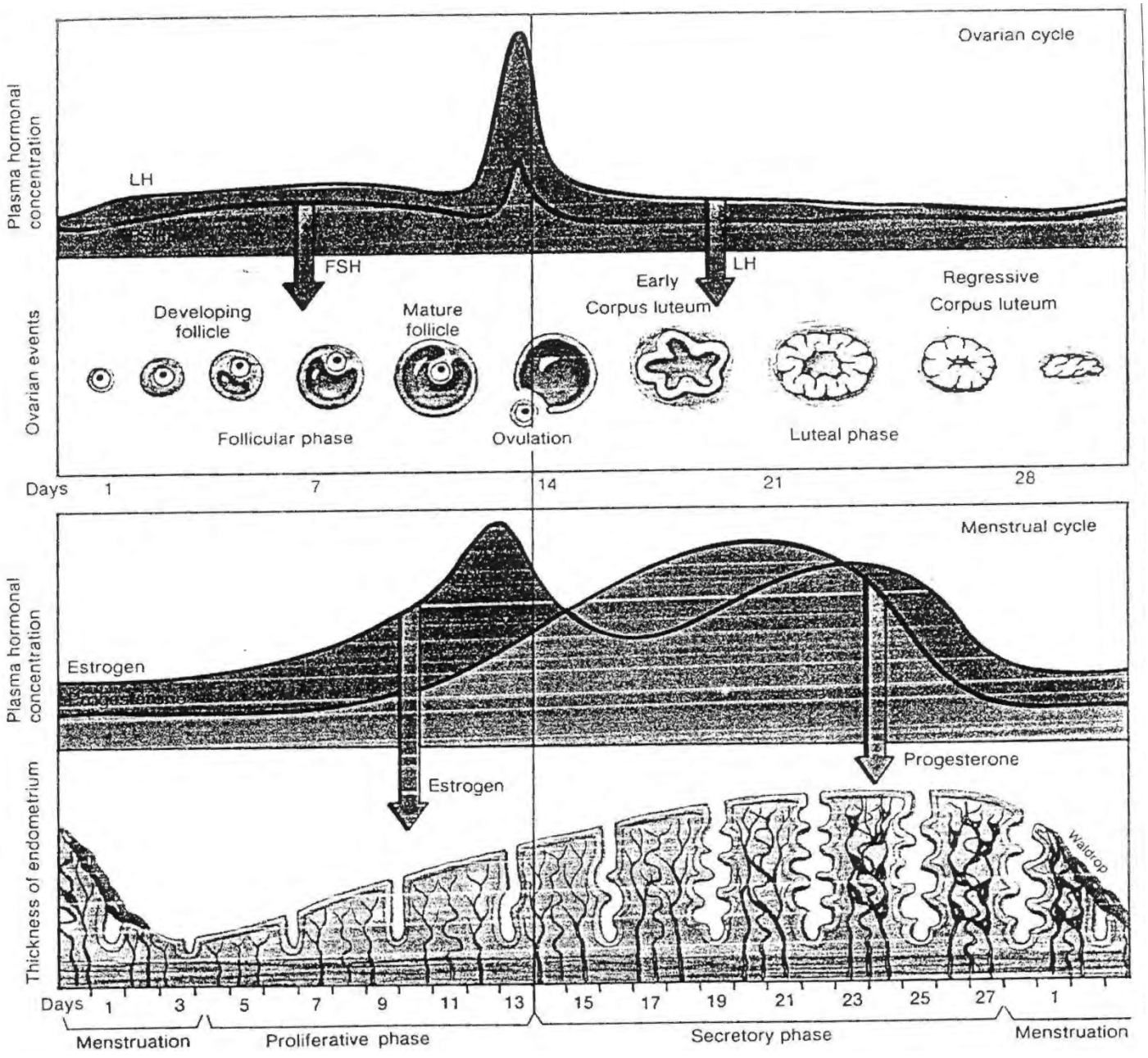


Figure 5

Figure 6 shows the feedback effects of estrogen and progesterone on the pituitary during different phases.

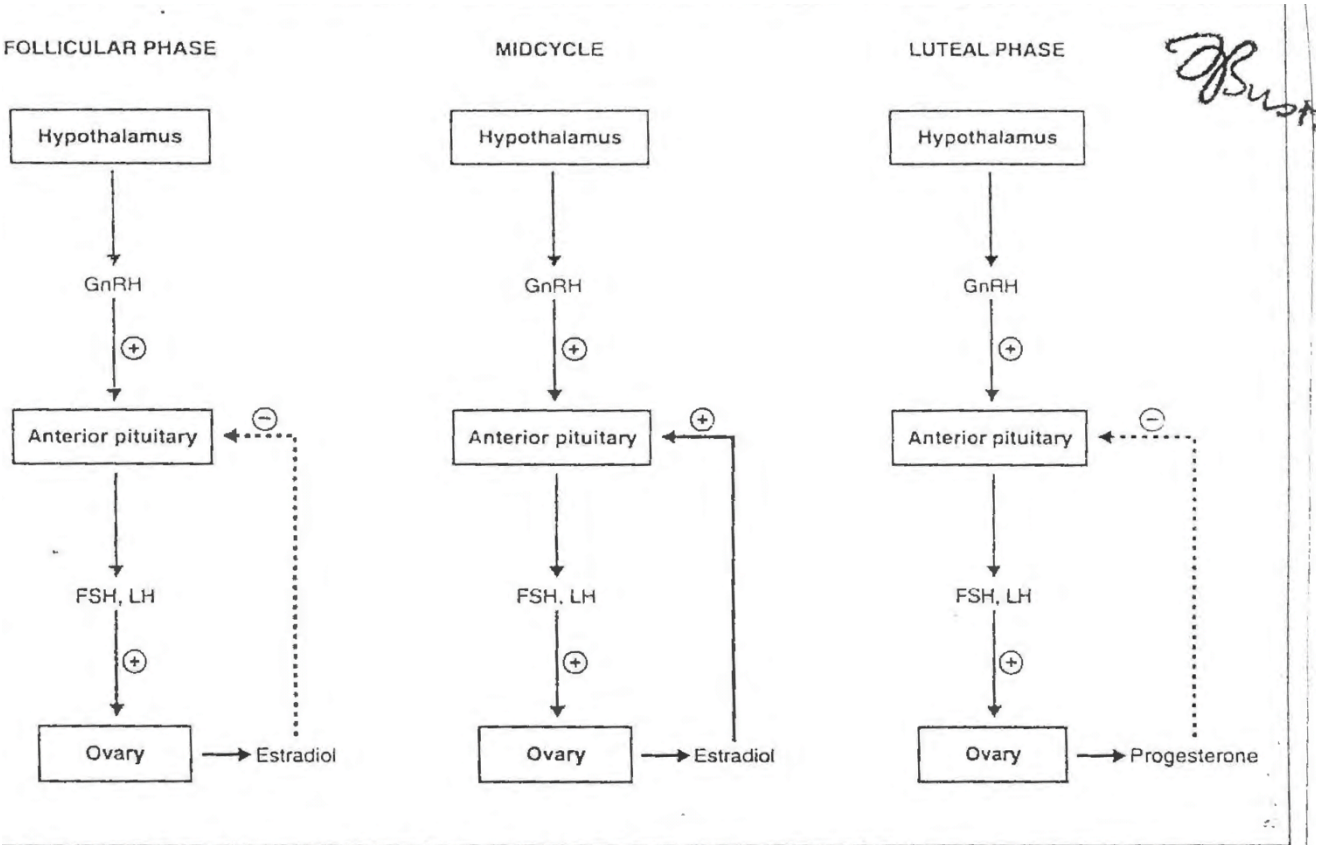


Figure 6

In order to keep the corpus luteum functioning we need LH, but because progesterone produced by the corpus luteum reduces the levels of LH, the corpus luteum is unable to survive for more than 14 days.

In case fertilization and pregnancy occur, the corpus luteum will survive for 3-4 months under the effect of LH in the beginning, then under the effect of chorionic gonadotropin hormone (aka human chorionic gonadotropin,HCG) coming from the placenta.

If the corpus luteum was removed from an ovary of a pregnant lady in the first 3 months → abortion. This indicates the significance of the corpus luteum and its secretory products (specially progesterone) in the first 3 months of pregnancy.

Progesterone injections are used to prevent abortion.

After that the placenta takes the role of the corpus luteum, and if the corpus luteum was removed the pregnancy isn't affected.

The important role of progesterone in the first months of pregnancy is that it reduces the uterine contractions (progesterone is a uterine relaxant) which allows for the zygote to get implanted in the uterus and prevents abortion.

We mentioned in the previous lecture the different stages of follicular development: [figure 7]

1- **the primordial follicle** = immature ovum (primary spermatocyte suspended in prophase of the 1st meiotic division) surrounded by a single layer of simple squamous epithelium.

2- **the primary unilaminar**= immature ovum surrounded by a single layer of cuboidal epithelium.

3- **the primary multilaminar follicle** = immature ovum surrounded by multiple layers of cuboidal epithelium.

4- **the secondary follicle**: appearance of fluid containing cavities.

5- **the mature Graafian follicle**: the small cavities become a single cavity and the ovum becomes eccentric.

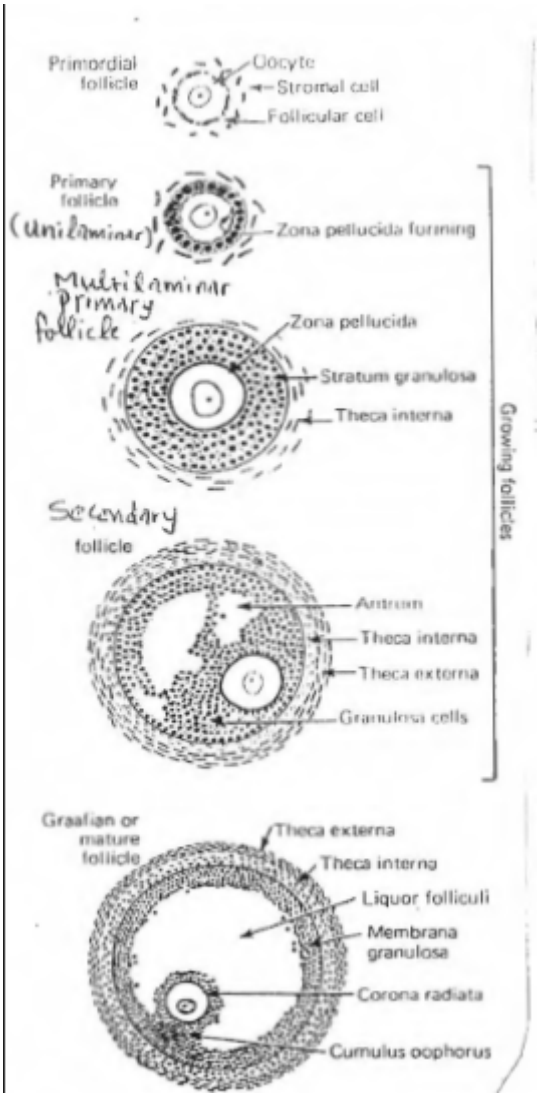


Figure 7

The first stages in the follicular growth (from primordial follicle→ primary unilaminar follicle → primary multilaminar follicle) do not require FSH, they're FSH independent.

However, the growth of the primary multilaminar follicle into a secondary follicle and then into a mature Graafian follicle **requires FSH**, they are FSH-dependent. FSH is required for estrogen production and without FSH the follicle never makes it to the stage of the mature Graafian follicle.

[Lack of FSH → the follicle can grow up to the primary multilaminar stage, but can't grow any further to become a secondary follicle and then a mature Graafian follicle].

→At the time of birth, the ovary of female newborn contains primary oocytes suspended in prophase of the first meiotic division **ONLY** (no primordial germ cells or oogonia).

Q: What prevents the primary oocytes from completing the 1st meiotic division?

A: The follicular cells surrounding the primary oocytes secrete the so called "**oocytes maturation inhibiting factor**" that prevents the completion of the 1st meiotic division and the differentiation of the primary oocyte into a secondary oocyte.

Q: Since the first stages of the follicular development are FSH independent, then what stimulates the follicles to grow?

A: The oocyte produces **activin** which stimulates the growth of the follicles and the proliferation of the follicular cells in the first stages.

Q: How does FSH act on the follicles?

A: The follicular/granulosa cells are the only cells in the ovary which have FSH receptors. FSH has to bind to its receptors in order to exert its effect on the growing follicles.

Q: During the 1st half of the menstrual cycle, the FSH concentration in the blood is low due to the negative feedback effect exerted by estrogen. Yet, it's still able to stimulate the follicle to grow from primary multilaminar to secondary despite its low concentration! How is this achieved?

A: the estrogen produced from the growing follicles upregulates the FSH receptors on the follicular cells and increases the cells' response to FSH despite its low concentration.

→The androgen is produced from the theca interna cells under the effect of LH (so **the theca interna cells have LH receptors**). And the follicular cells are characterized by the presence of the aromatase enzyme which converts the androgen into estrogen (under the effect of FSH→so **the follicular cells have receptors for FSH**).

After ovulation, the remnants of the follicle should form the corpus luteum. This process is mediated by LH. So the follicular cells should also have LH receptors in order to be able to form the granulosa lutein cells. [LH converts the follicular cells from estrogen-producing cells, into estrogen and progesterone producing cells] .

Q: What stimulates the formation of LH receptors on follicular cells?

A: FSH and estrogen. Estrogen is present around the follicular cells and FSH is present in the blood, and **both** hormones stimulate the formation of LH receptors on granulosa cells.

- ➔ So the follicular cells have receptors for FSH to stimulate their growth. And they acquire receptors for LH to be able to get converted into the corpus luteum.

→Although we say that ovulation is caused by estrogen-induced **LH** surge [because just before ovulation, estrogen causes positive feedback effect on LH and FSH release] but the exact effect of LH on ovulation is unknown. In fact, **FSH** is the hormone responsible for **the growth of the follicle and the thinning of its wall** which causes rupture of the follicle and release of the oocyte.

It's also said that the **theca externa** produces proteolytic enzymes that help in the lysis of the follicular wall and its rupture.

→"The follicle sets the time for its own ovulation": this means that the follicle determines the time of its ovulation because ovulation is triggered by the LH surge and the LH surge is triggered by the levels of estrogen in the blood and estrogen is produced by the follicles. The bigger the follicle, the more the estrogen in the blood. So ovulation doesn't occur unless the follicle is big enough to produce enough estrogen to induce the LH surge.

When the follicles are small→ production of little amount of estrogen → no ovulation.

When the follicles are big → production of more estrogen → ovulation.

→The follicular cells of the secondary follicle produce activin, inhibin, folliostatin. And the corpus luteum also produces inhibin. Each of these factors works by a special mechanism **to regulate the release of FSH** (by a negative feedback effect on the pituitary). So the regulation of FSH release in females isn't achieved by inhibin alone. [Flashback from sheet 6: in males, inhibin is produced by Sertoli cells to inhibit the release of FSH]

→After ovulation, we enter the luteal phase (so called because of the presence of the corpus luteum in the ovary during this phase).

During the second half of the menstrual cycle, what prevents the growth of a new set of follicles and the occurrence of another ovulation?

Inhibin that's produced from the corpus luteum. Inhibin prevents the secretion of FSH (by a negative feedback mechanism). The reduction of FSH means there's no growth of the follicles and no production of estrogen, so there will be no ovulation.

In the menstrual phase there will be a drop in inhibin levels, no more inhibition of FSH release, a new set of follicles will start to grow.

The histology of the cervix [figure 8]: Mucous membrane (endocervix) → The wall → Adventitia.

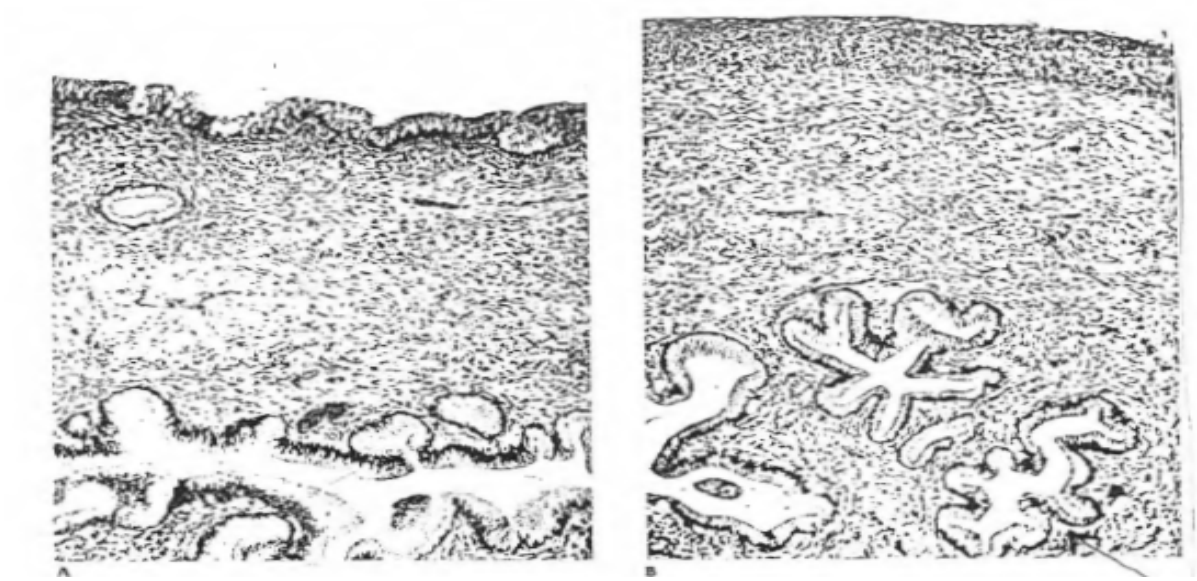


Figure 8

The cervix has a supravaginal part and a vaginal part, and the vaginal part opens into the vagina through the external os.

The vaginal part of the cervix (aka portio vaginalis) is covered from outside by non-keratinized stratified squamous epithelium and from the inside (the cervical canal) by simple columnar epithelium.

The region where the epithelium transforms from stratified squamous into simple columnar is called '**the transitional zone'**. The transitional zone lies just inside the external os. It's thought that the carcinoma of the cervix starts in the transitional zone. [figure 9]

The wall of the cervix, unexpectedly, contains **minimal smooth muscles**. It mainly contains collagen and elastin and is still able to dilate progressively in the first stages of labor.

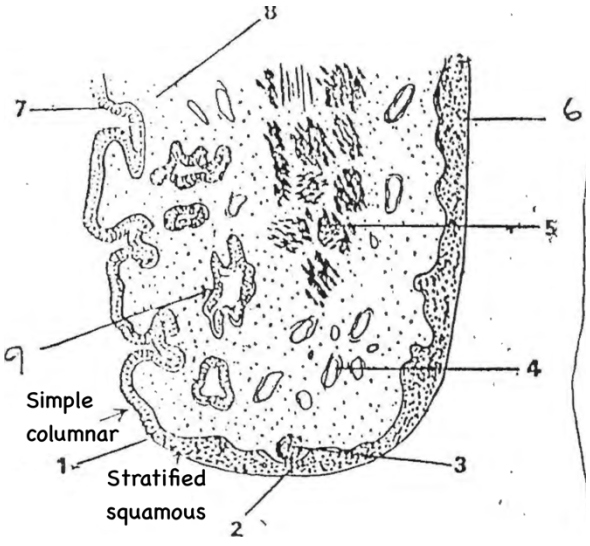


Figure 9

1: the external os, inside it there is the transitional zone

2-stratified squamous epithelium non keratinized

7- simple columnar epithelium

The upper third of the cervix (the lower uterine segment) differs from the rest of the cervix in that it contains more smooth muscles compared to the lower two thirds.

The wall of the cervix contains glands that secrete mucous secretions and send it to the vagina. The source of any secretion in the vagina is the cervix, which means there's no glands in the wall of the vagina. [Bartholin's glands open into the entrance of the vagina, but in the inside of the vagina the secretions come from the mucous glands in the wall of the cervix]. In case there's a lot of secretions in the vagina, this doesn't indicate vaginitis, because the source of the secretions is the cervix.

If the ducts of the cervical mucous glands close, the glands will enlarge forming a follicle or a cyst called "**Nabothian follicle**" or "**Nabothian cyst**". This is not a tumor, it's simply a mucous gland with an obliterated duct. [Figure 10]

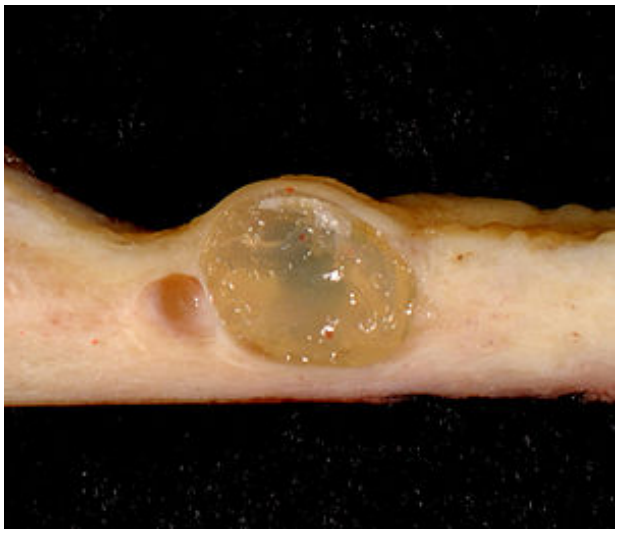


Figure 10 Nabothian follicle

Histology of the uterine tube [figure 11]: Mucosa → Muscularis → Serosa (the uterine tube is completely covered with peritoneum).

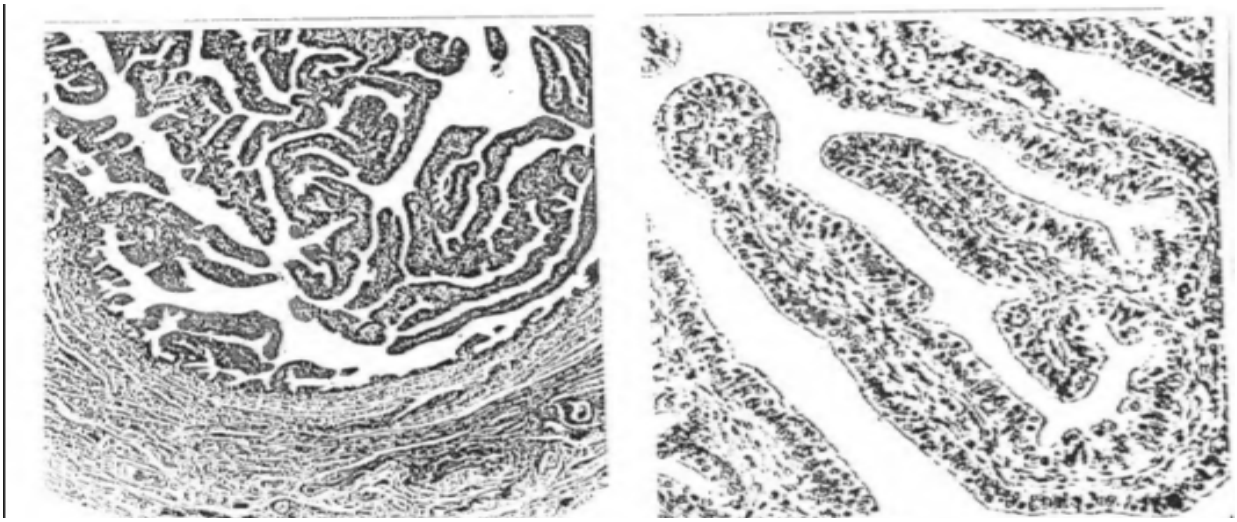


Figure 11

The mucosa is highly folded (longitudinal folds). A primary fold divides into two secondary folds which could further divide into tertiary folds and so on. Since we have so many folds, the lumen is very narrow (a mild inflammation could close the uterine tube and cause infertility).

The mucous membrane of the uterine tube contains three types of cells [figure12]:

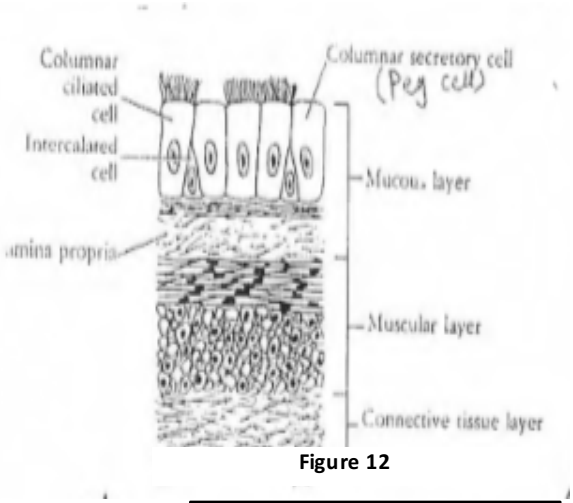


Figure 12

1- **Columnar secretory –non ciliated-** (Peg cells which produce secretions)

These cells are secretory, so in the ampulla for example where fertilization occurs, the zygote is nourished by the secretions of the mucous membrane of the ampulla. So in case of ectopic pregnancy, the fetus stays in the ampulla and fails to get implanted in the uterus, the fetus will live for a few weeks due to the secretions of the mucous membrane, then the uterine tube will rupture, causes bleeding and the pregnancy is terminated. The surgeon removes the ruptured uterine tube and the female lives with a single uterine tube.

Ectopic pregnancy might occur in the ovaries

2-**The ciliated columnar cells:** These are concentrated in the fimbria (the projections from the infundibulum, which is the most lateral part of the uterine tube). One of these fimbria is long and reaches the ovary and we call it "ovarian fimbria".

The mucous membrane of these fimbria is largely ciliated columnar, and the movement of the cilia facilitates the movement of the ovum from the ovary to the uterine tube, and the movement of the zygote from the ampulla of the uterine tube to the lumen of the uterus.

Clinical correlate: in chronic salpingitis (chronic inflammation of the uterine tube), there is loss of cilia and the female becomes infertile.

3- **The intercalated undifferentiated cells**.

The lining epithelium of the uterine tube has a common feature with the lining epithelium of the uterus, they both undergo cyclic changes. The changes in the uterine tubes mainly are in the number of cilia and in the secretions.

-**Regarding the cilia :** In the proliferative phase, the cilia increase in height and number, because they facilitate the movement of the ovum from the ovary to the uterine tube before ovulation. In the secretory phase, the cilia decrease in height and number.

-**Regarding the secretions:** In the proliferative phase there's an increase in the **synthesis** of uterine tube secretions, and in the secretory phase there's an increase in the **release** of these secretions; because they're needed to nourish the zygote in case fertilization occurred.

The muscular coat: 2 layers of smooth muscles, inner circular and outer longitudinal, these are responsible for peristalsis. The exact significance of peristalsis is unknown and it's not proved yet whether it facilitates the movement of the ovum and the zygote.

Serosa: peritoneum covering the uterine tubes.

The following was only mentioned in section 3:

Histology of the vagina [figure 13]:

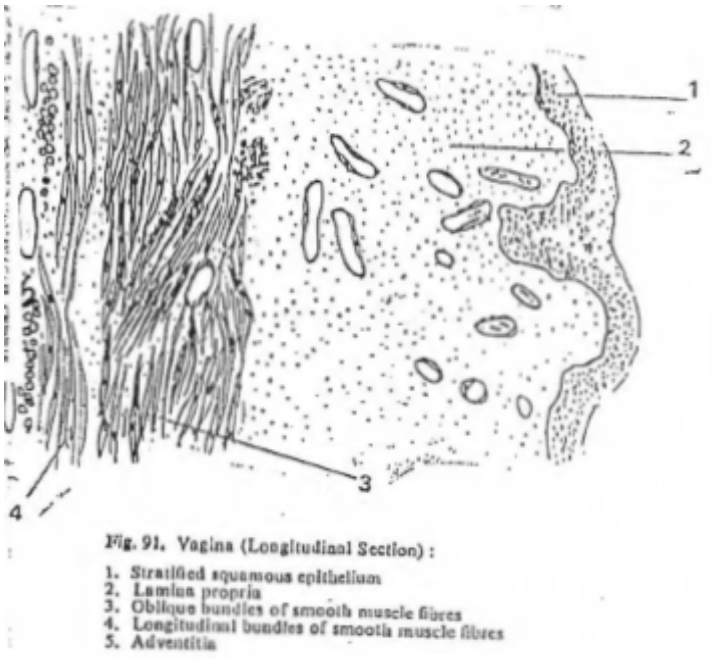
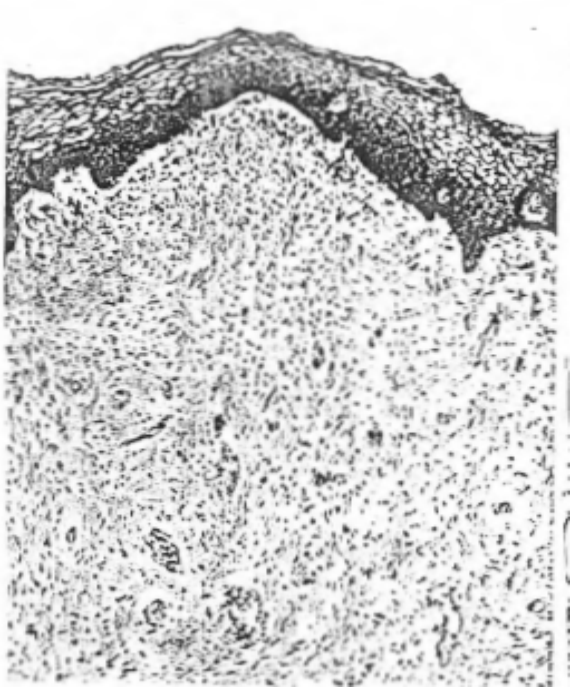


Fig. 91. Vagina (Longitudinal Section) :
1. Stratified squamous epithelium
2. Lamina propria
3. Oblique bundles of smooth muscle fibres
4. Longitudinal bundles of smooth muscle fibres
5. Adventitia



The first thing to remember about the histology of the vagina is that it has no glands and no submucosa.

Mucous membrane → folds (rugae) and stratified squamous epithelium non-keratinized. The epithelium here is subjected to desquamation (continuous loss and regeneration of cells).

Lamina propria → devoid of any glands and no submucosa.

Muscularis → two layers of smooth muscles, inner circular and outer longitudinal.

The epithelial cells in the vagina are filled with glycogen, when they desquamate they fall into the lumen of the vagina, glycogen will undergo fermentation and gets converted into lactic acid under the effect of a special type of bacteria called **"Döderlein's bacilli".**

The fermentation of glycogen in the vagina is what makes the vaginal cavity acidic. And this acidity prevents the growth of pathogenic bacteria.

[Remember that the seminal fluid produced from the seminal vesicles, the prostate and the bulbourethral glands is alkaline to neutralize the acidity in the vagina.

If it wasn't alkaline, the sperm couldn't survive in the acidity of the vaginal cavity]. So the acidity in the vagina protects the female from the pathogenic bacteria, yet it's harmful to the sperm and has to be neutralized by the alkaline secretions of the male accessory glands.

Again, in the vaginal vestibule, the two greater vestibular glands (Bartholin's glands) empty their secretions, but the secretions inside the cavity of the vagina come from the cervix.

"رفعتُ لله قنديلي فأوقدهُ، فهل تظنُّ يداً في الأرض تطفئني؟!"

D: بالتوفيق جميعاَ فيما تبقى من المشوار