UGS

Physiology

Doctor 2021

Sheet (5)

Name: Dania Abu Samha

Corrector: Juman Al-Heyari

Doctor: Alaa Bawaneh

Reproductive Physiology

-Slides will be in blue, doctor's note in black.

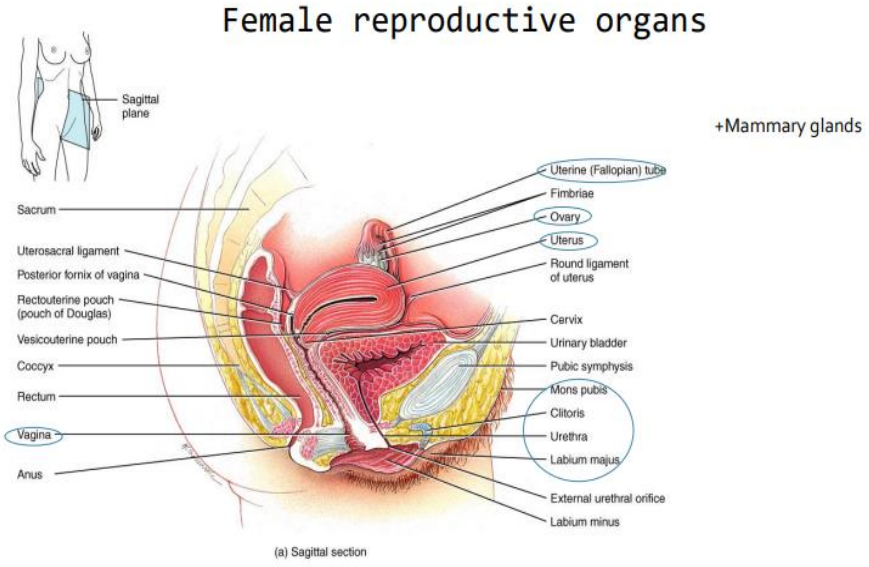
➢ Female Physiology Before Pregnancy and Female Hormones Female reproductive function

Female Reproductive Functions:

1. Preparation of the female body for conception and pregnancy
2. The period of pregnancy itself.

As we all know, the aim of productive systems in both female and male is to produce offsprings, the male is responsible for the production of male hormone (testosterone) and male gamete (sperm). While female is responsible for the production of (estrogen & progesterone), the female gamete (ovum) and the conception of the baby.

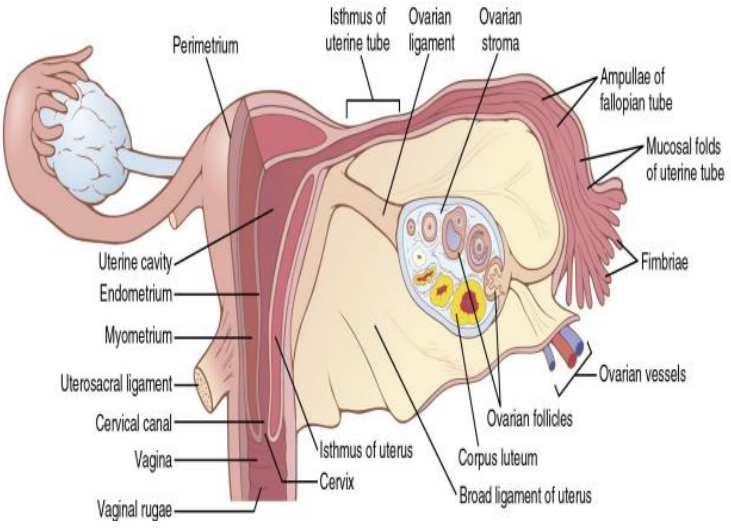
This is a sagittal view from the lateral side of the female body, we have the uterus lying above the urinary bladder, the fallopian tubes & ovaries in the pelvis. The uterus continues as cervix and then vagina.



All these parts along with mammary glands and breast form the female reproductive system.

The figure shows anterior view of the system, the ovaries are responsible of ovum production, and this ovum will be expelled out from the ovary by an ovulation process, and then it will be caught by fimbriae (finger like structure at the end of fallopian tube). If there are sperms in the fallopian tubes, fertilization will take place and the zygote will move to the uterus, it implements there, and pregnancy takes place.

Relationship of the uterine tubes to the ovaries, uterus, and associated structures



If there are no sperms, then the ovum will degenerate, and this will end up with female menstrual cycle.

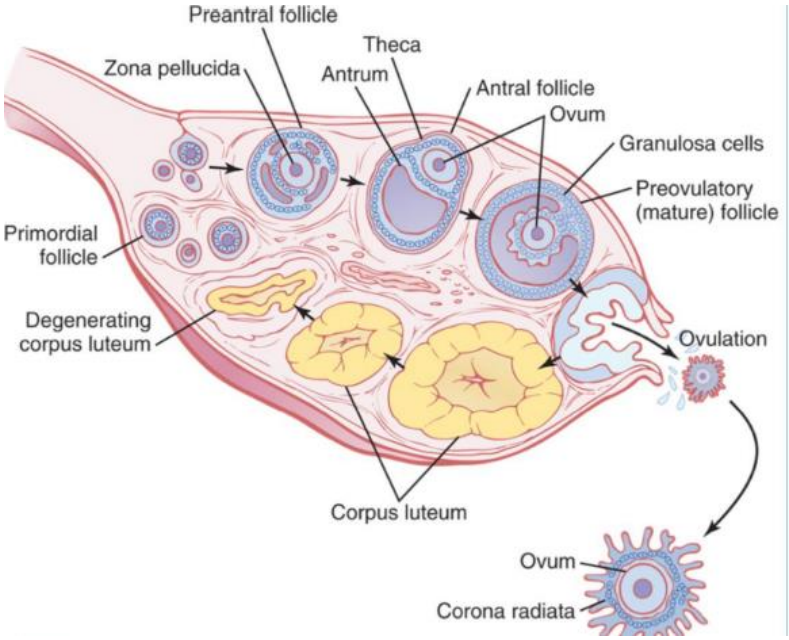
So, the female reproductive system passes through phases during 28 days on average.

Note from slides:

Reproduction begins with the development of ova in the ovaries. In the middle of each monthly sexual cycle, a single ovum is expelled from an ovarian follicle into the abdominal cavity near the open fimbriated ends of the two fallopian tubes. This ovum then passes through one of the fallopian tubes into the uterus; if it has been fertilized by a sperm, it implants in the uterus, where it develops into a fetus, a placenta, and fetal membranes—and eventually into a baby.

➢ Oogenesis

The first part of cycle is preparation of follicles, ovaries have follicles which have an egg inside them. This follicle will go through maturation and then the egg will be expelled out from the ovaries.



The remnant of the follicle will be filled with fat and become yellow; it's called corpus luteum. The function of corpus luteum is estrogen and progesterone production which will maintain pregnancy in the first trimester (1st three months) until formation of placenta which will take its role.

- **Follow the figures below through reading the upcoming explanation:**

Oogenesis is the process of ovum production; oogenesis in females starts before birth. In ovaries there are <u>primordial germ cells</u>, they will undergo repeated cell divisions then they will migrate to ovarian cortex. (all of this happens in the 5th month of gestation). In the ovarian cortex, those primordial germ cells are called <u>primordial ovum or oogonium</u>.

Group of stromal cells in ovarian cortex called <u>granulosa cells</u> will gather around primordial ovum forming one layer of cuboidal granulosa cells and we call the result <u>primordial follicle</u>.

يعني في خلايا بتتجمع حوالين البويضة وبتعمل طبقة واحدة والنتيجة النهائية للبويضة مع هدول الخلايا بنسميها Primordial follicle.

- **Note: granulosa cells are spindles in shape, but when they become cuboidal when they surround the primordial ovum.**

The primordial follicle will contain the primary oocyte inside it, the primary oocyte will be surrounded by more than one layer of garnulosa cells, those granulosa cells around primary oocyte are called <u>primary follicles</u>.

The function of granulosa cells is nourishing and supporting the ovum. In addition, they produce <u>oocyte inhibiting maturation factor</u> which will prevent further divisions of ovum, لأنه نحنا لسا بعدنا في الشهر الخامس من الحمل وما بدنا البويضة تكمل انقسام فهاد بمنعها لحد ما يحين وقت الإباضة مستقبلاً عند البلوغ.

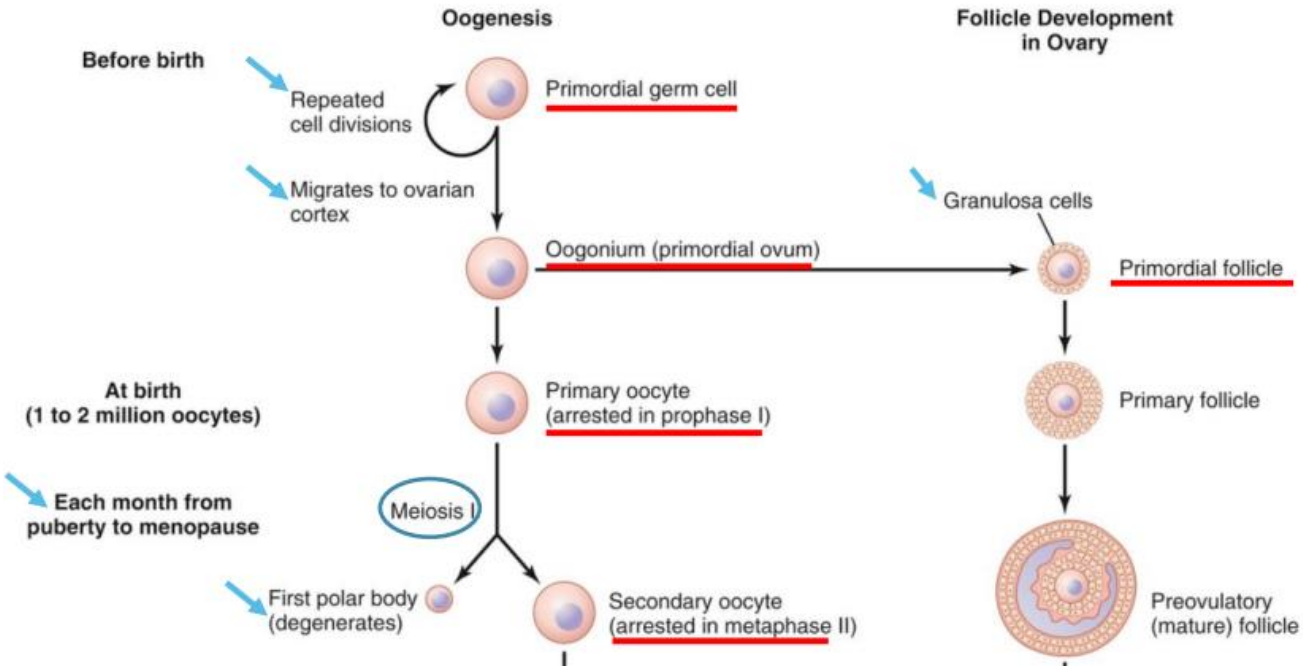
So, the female will born with 1-2 million of primary oocyte inside primary follicles in both ovaries. Those primary oocytes will be arrested in prophase 1, no further divisions until puberty.

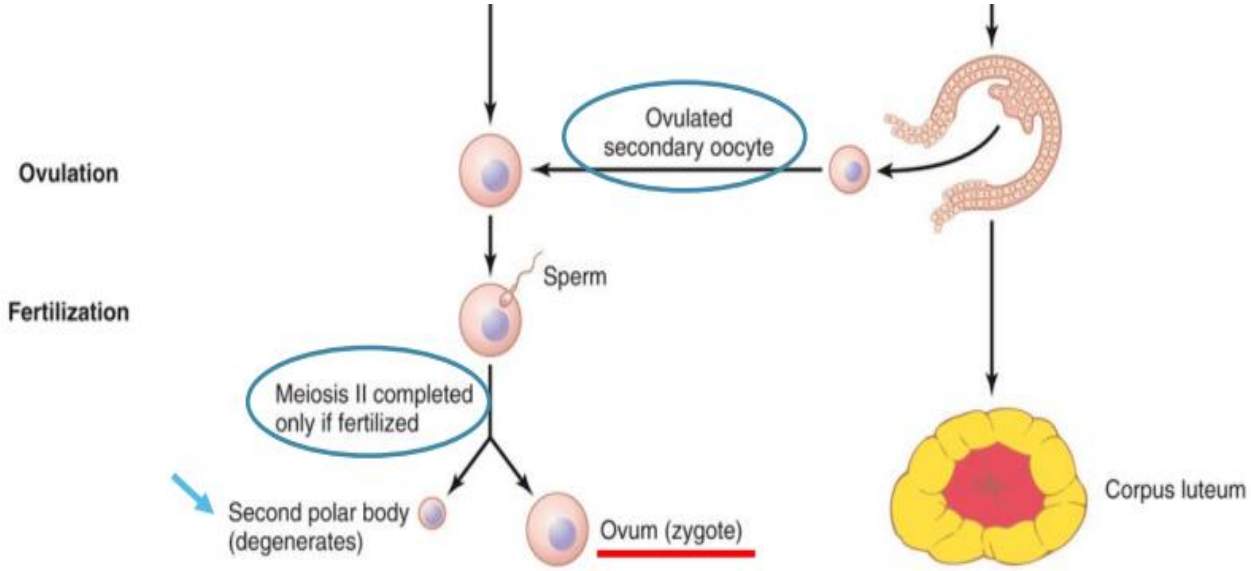
At puberty, under control of hormones from hypothalamus and anterior pituitary gland the primary oocyte will go under further divisions (meiosis 1) that will produce secondary oocyte and 1st polar body (it will degenerate).

The secondary oocyte is found in preovulatory (mature follicle) which provides it with nourishment and vascular connection. All divisions of the ovum happen inside the follicle, now this follicle is matured, and the secondary oocyte is ready to be expelled out form the follicle (ovulation).

The rest of the follicle remains in the ovary (corpus luteum) and the ovum goes to fallopian tubes, if there are any sperms it will be fertilized, and 2nd meiosis takes place. 2nd meiosis produces the second polar body (it will degenerate) and the zygote.

This process happens from puberty until menopause, at menopause no further ovulation since ovaries are not able to produce hormones for follicles maturation or there are no more follicles in ovaries.





Don't panic, they are repeated notes.

- **Notes form slides:**

**During early embryonic development, primordial germ cells migrate to the outer surface of the ovary, which is covered by a germinal epithelium.

**During this migration, the germ cells divide repeatedly.

**Once these primordial germ cells reach the germinal epithelium, they migrate into the substance of the ovarian cortex and become oogonia or primordial ova.

**Each primordial ovum then collects around it a layer of spindle cells from the ovarian stroma (the supporting tissue of the ovary) and causes them to take on epithelioid characteristics; these epithelioid-like cells are then called granulosa cells. The ovum surrounded by a single layer of granulosa cells is called a primordial follicle. At this stage, the ovum is still immature and is called a primary oocyte.

**The first meiotic division of the oocyte is completed after puberty. Each oocyte divides into two cells, a large ovum (secondary oocyte) and a small first polar body. Each of these cells contains 23 duplicated chromosomes.

**The ovum undergoes a second meiotic division, and after the sister chromatids separate, there is a pause in meiosis. If the ovum is fertilized, the final step in meiosis occurs and the sister chromatids in the ovum go to separate cells.

- **Further notes:**

- **The oogonia in the embryonic ovary complete mitotic replication, and the first stage of meiosis starts by the fifth month of fetal development.**
- **The germ cell mitosis then ceases, and no additional oocytes are formed.**
- **At birth the ovary contains about 1 to 2 million primary oocytes.**
- **At puberty, only about 300,000 oocytes remain in the ovaries, and only a small percentage of these oocytes become mature.**
- **During all the reproductive years of adult life, between about 13 and 46 years of age on average, only 400 to 500 of the primordial follicles develop enough to expel their ova, one each month; the remainder degenerate (i.e., become atreticاضمحلال).**

From 300,000 why do we end with 400 to 500? Because in each month from puberty until menopause under control of hormones 6 to 12 follicles will compensate in maturation and at the end one of them will be fully matured and go to fallopian tube, and the rest will go under degeneration.

- **At the end of reproductive capability (at menopause), only a few primordial follicles remain in the ovaries, and even these follicles degenerate soon thereafter.**

Female hormonal system

➢ Gonadotropic Hormones and Their Effects on the Ovaries

- **The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH.**
- **In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood, when almost no pituitary gonadotropic hormones are secreted.**
- **At age 9 to 12 years, the pituitary begins to secrete progressively more FSH and LH, which leads to onset of normal monthly sexual cycles beginning between the ages of 11 and 15 years.**
- **This period of change is called puberty, and the time of the first menstrual cycle is called menarche.**

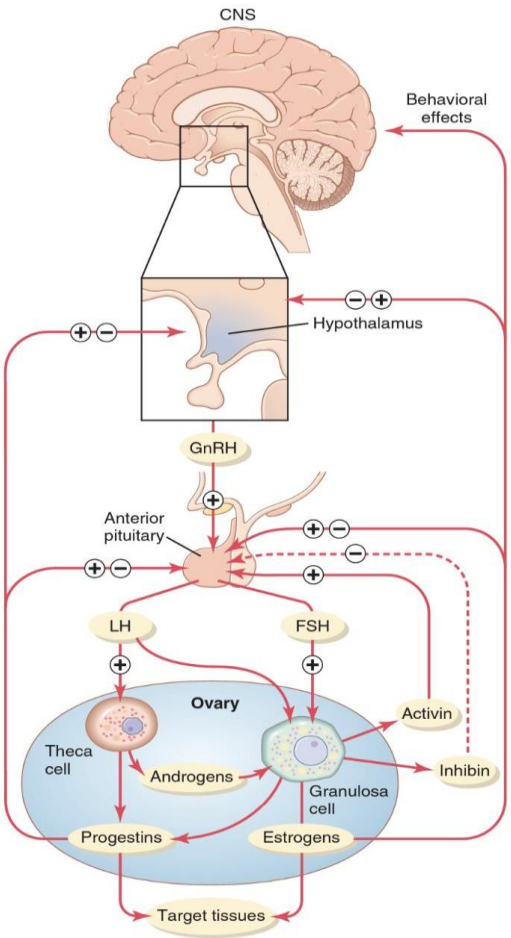
All the previous processes happen under control of hormones, so the productive system is part of endocrine system. When the female is in puberty age, hypothalamus will produce hormone called gonadotropin releasing hormone (GnRH) which will stimulate anterior pituitary to produce FSH & LH.

How hypothalamus knows that the female is in puberty age? In the period form age 9 to 13 the female pass through several changes like environmental changes, bone growth, temperatures changes in the body, neural changes (CNS) and another changes. All these factors stimulate the hypothalamus to start GnRH production.

FSH & LH will go to ovaries in females. Remember we said at puberty in the ovaries we have primary primordial follicles, and now under control of FSH they will start maturation. FSH will stimulate between 6-12 follicles to start maturation process.

Maturation starts in granulosa cells, the granulosa cells will multiply around the ovum, and they will produce estrogen, inhibin & activin.

When granulosa cells are multiplied and estrogen is produced, it means that the follicle is now matured (2nd follicle) and now it's ready to rupture and expel the ovum.



Whatever is the level of FSH, it will not help the mature follicle to rupture, its function is just maturation (increase granulosa cells around ovum and estrogen release).

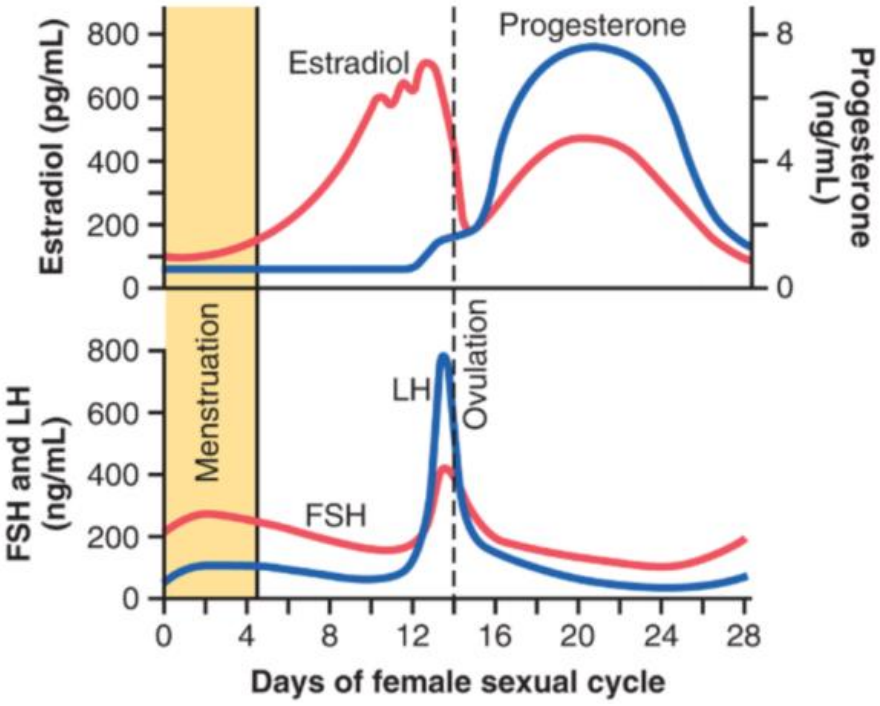
Estrogen and FSH will help in LH releasing form anterior pituitary. LH hormone is responsible for ovulation, LH increases as a *surge.*

(يعني بالبداية مستواه كثير بكون متدني، ولما تصير البويضة جاهزه انها تطلع من البويصلة برتفع مرة وحدة 8 أضعاف كميته)

And this is called LH surge.

After 24-48 hrs. of LH surge, ovulation happens. Another function of LH is affecting theca cells (outer layer of cells around granulosa cells), they help in production of sex hormones like androgens and some of the progestins.

- **Now, follow this figure while reading the upcoming explanation:**



On average, female sexual cycle (menstrual cycle) happens for 28 days, it could be as short as 20 days or as long as 45 days. The 1st part of cycle is under control of hormones coming from the higher levels (anterior pituitary which is under control of hypothalamus). Anterior pituitary produces FSH & LH. At the beginning FSH is produced at high levels to allow follicles maturation. LH is produced but in lower levels than FSH until follicles maturation.

When follicles are matured and ready for ovulation, LH will be produced in high levels approximately 8 times of its previous level (LH surge), FSH also increases but not as much as LH.

LH surge will end up causing ovulation (the dotted line in the figure means ovulation). Whatever the length of period, ovulation takes place on day 14, LH takes place before day 14 (in 24-48 hrs.).

During maturation of follicles, estrogen is produced by granulosa cells, estrogen rises slowly until before ovulation where is reduces and then it rises again.

Estrogen is responsible for endometrium maturation, it increases endometrial proliferation, thickness, and vasculature. In addition, estrogen increases follicles' responsiveness towards FSH, and towards LH before ovulation.

So, estrogen has two functions; it increases FSH & LH receptors on follicles increasing their responsiveness, and it's responsible for endometrial maturation.

After ovulation estrogen and progesterone levels increase while FSH & LH levels decrease because of negative feedback by estrogen and progesterone to prevent further follicles maturation.

Corpus luteum is responsible for progesterone & estrogen production. Progesterone levels are so much higher than estrogen, it increases thickness and vasculature of endometrium. In addition, it increases glands in endometrium to increase secretions. And all of that is to make uterus ready for pregnancy in case of fertilization.

If no fertilization happened, progesterone and estrogen abruptly decrease which leads to endometrium sluffing and menstruation happens. FSH & LH will rise up again, and a new cycle starts.

- **Notes form slides:**

  **** These various hormones are secreted at drastically differing rates during different parts of the female monthly sexual cycle.**

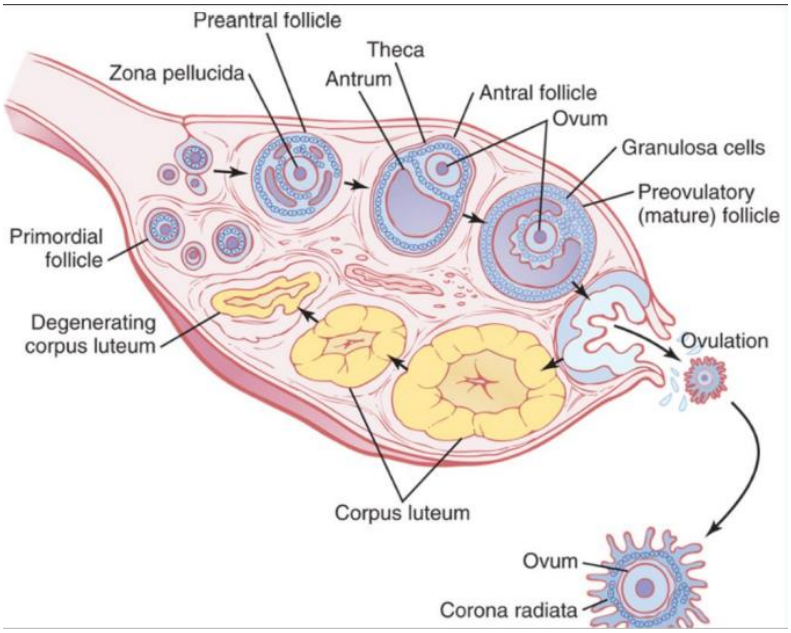
  **** The amount of GnRH released from the hypothalamus increases and decreases much less drastically during the monthly sexual cycle. It is secreted in short pulses averaging once every 90 minutes.**

  **** During the first few days of each monthly female sexual cycle, the concentrations of FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days.**

  **** FSH, cause accelerated growth of 6 to 12 primary follicles each month.**

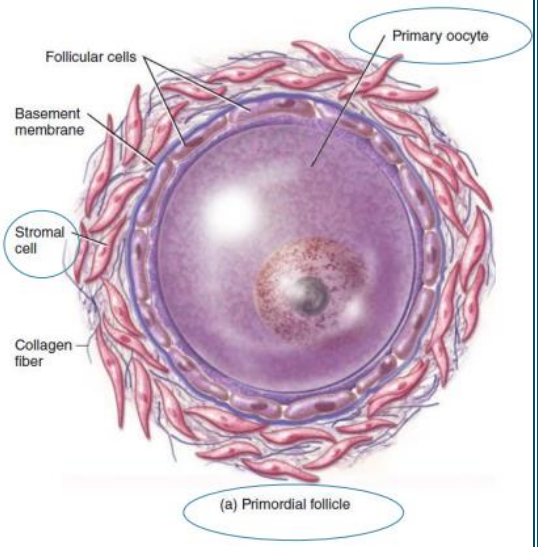
➢ Follicular development

Under the effect of hormones, follicles go through stages we mentioned before, now we will talk in the details about each stage.



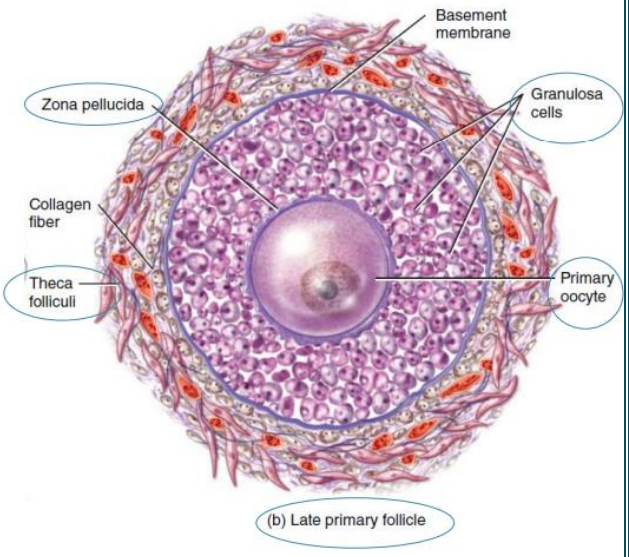
Primordial follicle:

- **When a female child is born, each ovum (primary oocyte) is surrounded by a single layer of granulosa cells; the ovum, with this granulosa cell sheath, is called a primordial follicle.**
- **Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an <u>oocyte maturation-inhibiting factor</u> that keeps the ovum suspended in its primordial state in the prophase stage of meiotic division.**



Primary follicle:

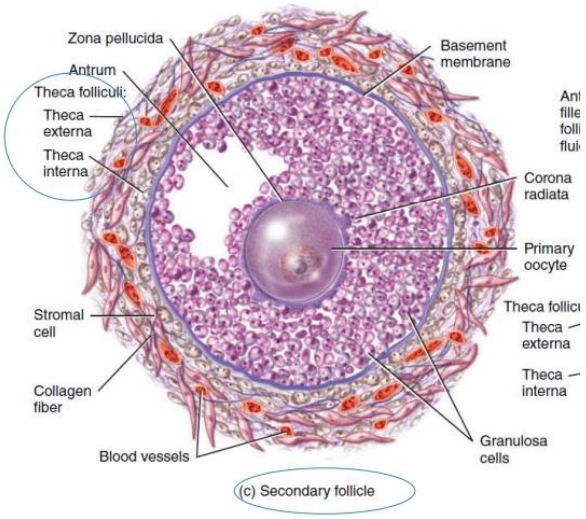
- Then, after puberty, when FSH and LH are secreted in significant quantities, the ovaries (together with some of the follicles within them) begin to grow.
- Consists of a primary oocyte that is surrounded by several layers of cuboidal and low columnar granulosa cells.
- zona pellucida, a clear glycoprotein layer **(it protects the ova).**
- Stromal cells surrounding the basement membrane begin to form **(theca cells).**



The main changes that happened here are under FSH effect, the granulosa cells become more cuboidal in shape and their number becomes more than primordial follicle. With more FSH, primary follicle becomes secondary follicle.

Secondary follicle:

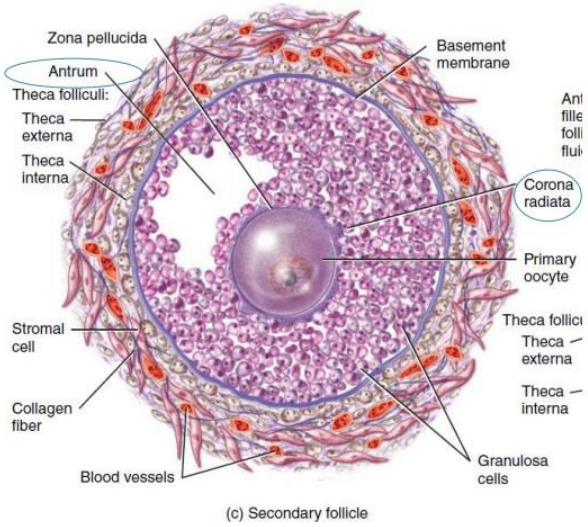
- The theca differentiates into two layers:
  1) Theca interna, epithelioid characteristics, secrete additional steroid sex hormones **(androgens & some progesten).**
  2) The theca externa develops into a highly vascular connective tissue capsule **which provide protection.**



In this stage, we have antrum which is space filled by high concentration of estrogen produced by granulosa cells. And outside we have theca cells which means that LH production started. Theca cells have two divisions: theca interna & theca externa. Theca cells are spindle in shape.

Secondary follicle/Antral stage:

- **The granulosa cells begin to secrete follicular fluid, which builds up in a cavity called the antrum. (high concentration of estrogen)**
- **The innermost layer of granulosa cells becomes firmly attached to the zona pellucida and is now called the corona radiata (it has spikes).**



(c) Secondary follicle

As sensitivity to FSH increases, antrum increases, and the follicle becomes hollow form inside (the ova is surrounded with space filled by high concentration of estrogen).
Look at the innermost layer of granulosa cells how it's firmly attached to zona pellucida.
All of those are signs that means that the ova is now ready to be expelled out of the follicle and get ovulated. At this point LH surge happens and ovulation happens. Now the secondary follicle is transferred to *vesicular follicle*.

Ovulation doesn't happen at one time, the follicle is swelled due to estrogen, and then estrogen get out of the follicle gradually which stimulates more LH to come and rupture the follicle.

Vesicular follicle:

- **The early growth of the primary follicle up to the antral stage is stimulated mainly by FSH alone.**
- **Greatly accelerated growth then occurs, leading to still larger follicles called vesicular follicles and this due to:**

1. **Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors, which causes a positive feedback effect because it makes the granulosa cells even more sensitive to FSH.**
2. **The pituitary FSH and the estrogens combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even more rapid increase in follicular secretion.**
3. **The increasing estrogens from the follicle plus the increasing LH (LH surge) from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion.**

Only One Follicle Fully Matures Each Month, and the Remainder Undergo Atresia:

- **FSH stimulates 6-12 follicles to mature, but one of them (the strongest one) will make it until the end and ovulate and expel the ovum and the rest will go under atresia.**
- **Large amounts of estrogen from the growing follicle (strongest) will have negative feedback on hypothalamus, no more GnRH, no FSH, which prevent maturation of the less well-developed follicles.**

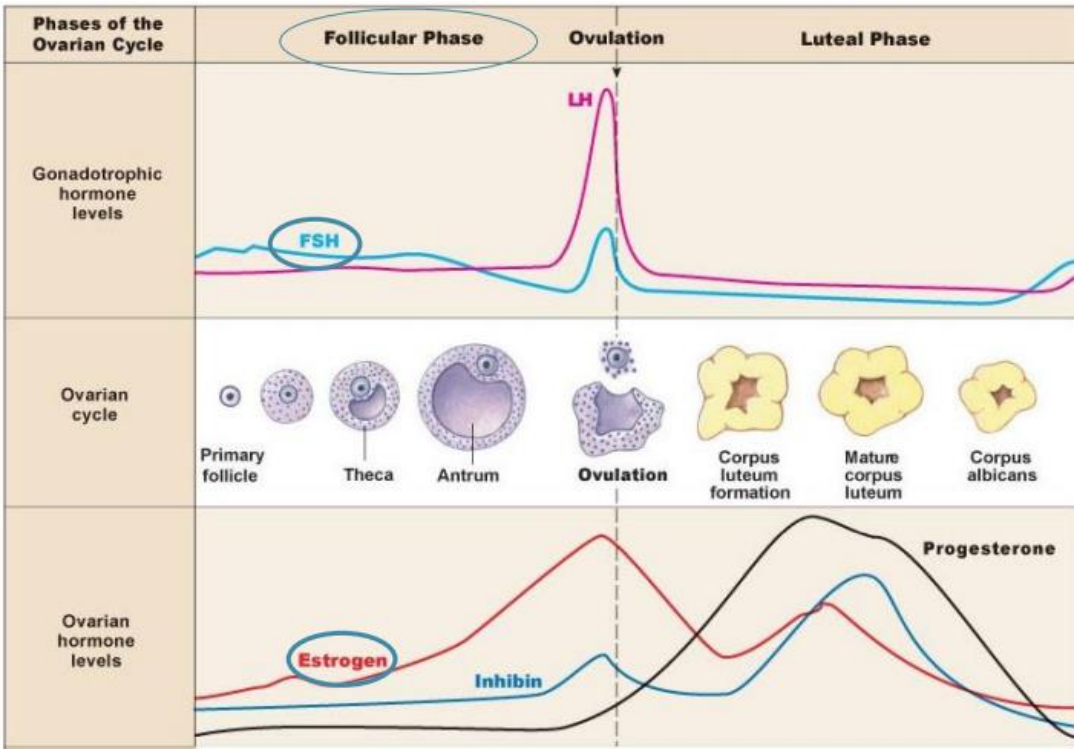
يعني البويضة الأقوى رح تفرز كميات عالية جداً من الإستروجين فبتمنع إفراز ال FSH فالبويضات الأضعف ما رح يكملوا النمو وبتحللوا

- **Before ovulation occurs, one of the follicles begins to outgrow all the others; the remaining 5 to 11 developing follicles involute *(a process called atresia).***
- **The large amounts of estrogen from the most rapidly growing follicle → the hypothalamus to depress further enhancement of FSH secretion →in this way blocking further growth of the less well-developed follicles.**
- **→The largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute.**
- **This process of atresia is important because it normally allows only one of the follicles to grow large enough each month to ovulate.**

- **Note form slides:**

*** About every 28 days, gonadotropic hormones from the anterior pituitary gland cause 8 to 12 new follicles to begin to grow in the ovaries.**

***One of these follicles finally becomes "mature" and ovulates on the 14th day of the cycle.**



This figure summarizes everything, the cycle of female is divided into many parts. Our boarder line is ovulation, before ovulation is follicular phase which depends on FSH for follicular maturation. When antrum is formed, it means estrogen increases until before ovulation where we have LH surge and ovulation happens. After ovulation ova goes to fallopian tube, the rest of follicle becomes corpus luteum which gives us estrogen & progesterone, and they both make negative feedback on FSH & LH to prevent further follicles from maturation.