



The Urogenital System

Subsystem: Physiology

Lecture Title: Female Reproductive System: Ovarian Cycle

Lecture Date: 6/5/2020

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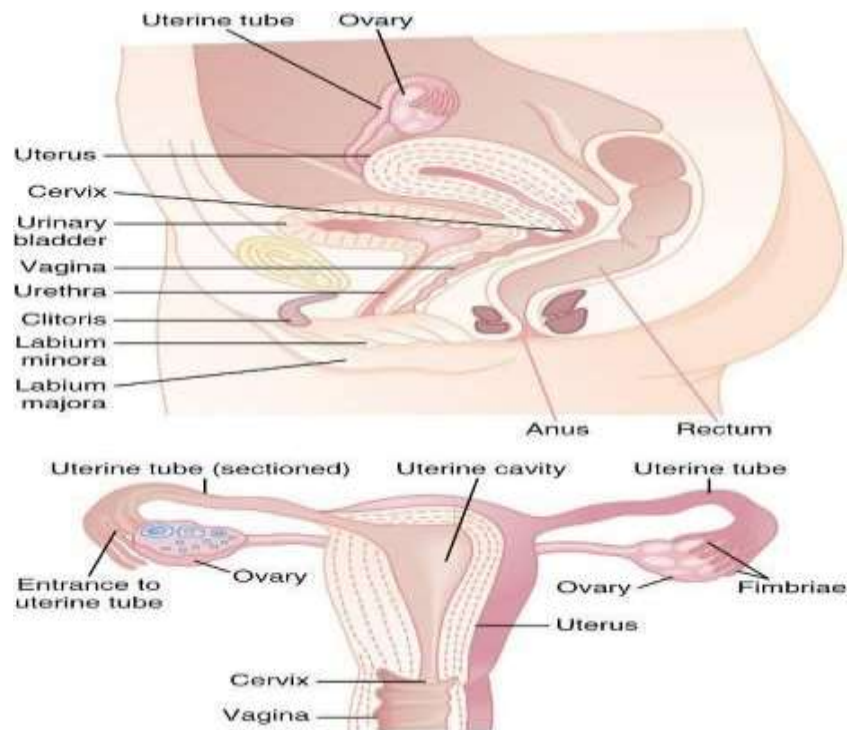
Editor:

Note: I rearranged the slides and added some extra info form the book for better understanding.

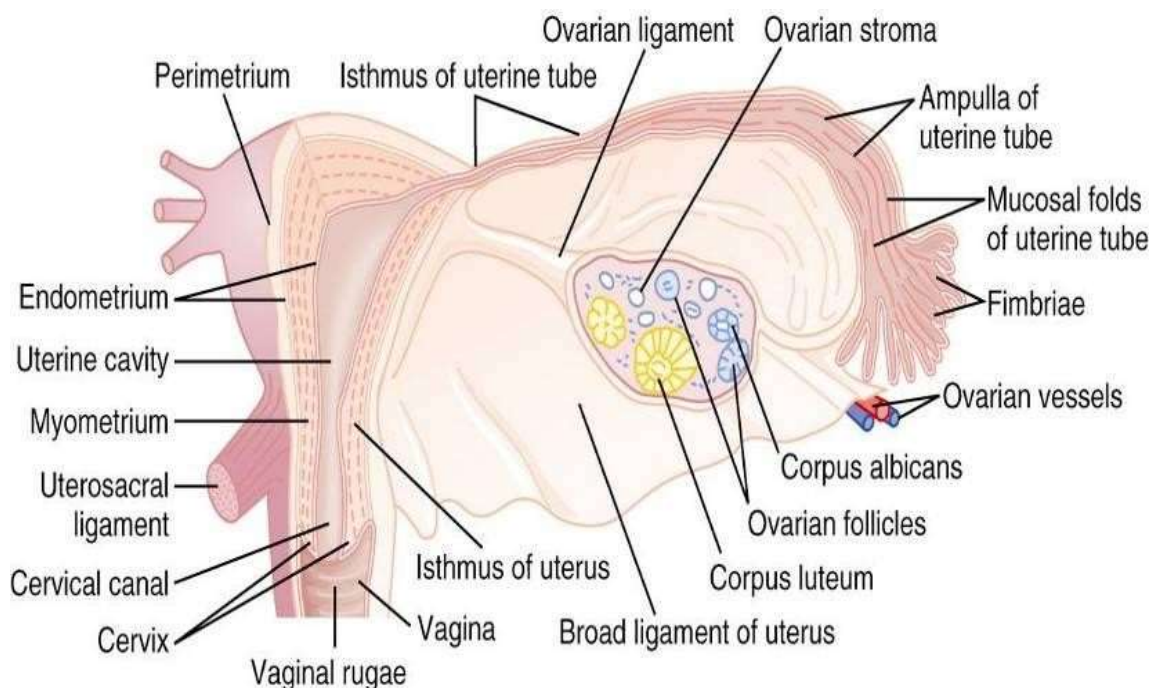
Sheet correction link: <http://bit.ly/gusphysio>

Female Reproductive System

The principal organs of human female reproductive tract include: Ovaries, fallopian tubes, uterus, and vagina.



Internal structures of the uterus, ovary, and fallopian tube:



OÖGENESIS

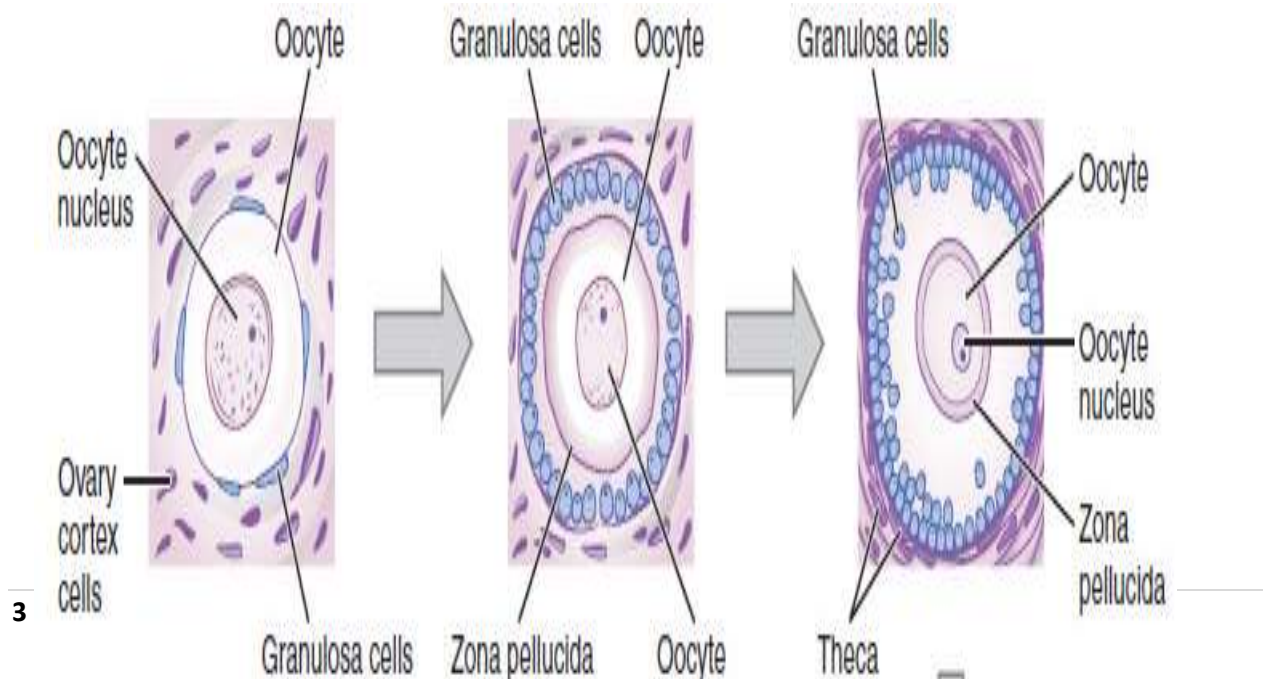
Oögenesis: a series of steps that forms a mature egg (Ovum) from a developing egg (Oocyte).

Fundamental reproductive unit = single ovarian follicle, composed of one germ cell (oocyte), surrounded by endocrine cells.

The process starts with primordial germ cells (oogonium) in the fetal ovaries that divide mitotically to give rise to 6-7 million **Oögonia**. Then during the last part (5th month) of fetal life, mitotic proliferation ceases and prophase of 1st meiosis starts but does not complete – forming **primary oocytes** (they contain diploid number of chromosomes 46 but do not separate). The primary oocytes stay in this meiotic arrest for years until puberty to prepare for ovulation. Before birth each primary oocyte is surrounded by single layer of granulosa cells, together called **primordial follicle**. Oocytes that are not incorporated into follicles are self-destructed by apoptosis (cell suicide).

At birth only about 2 million primary follicles remain each contain single primary oocyte capable of producing a single ovum. **No new oocytes or follicles appear after birth.**

The number of primary oocytes decreases throughout childhood from 1-2 million to 400,000 just before puberty.



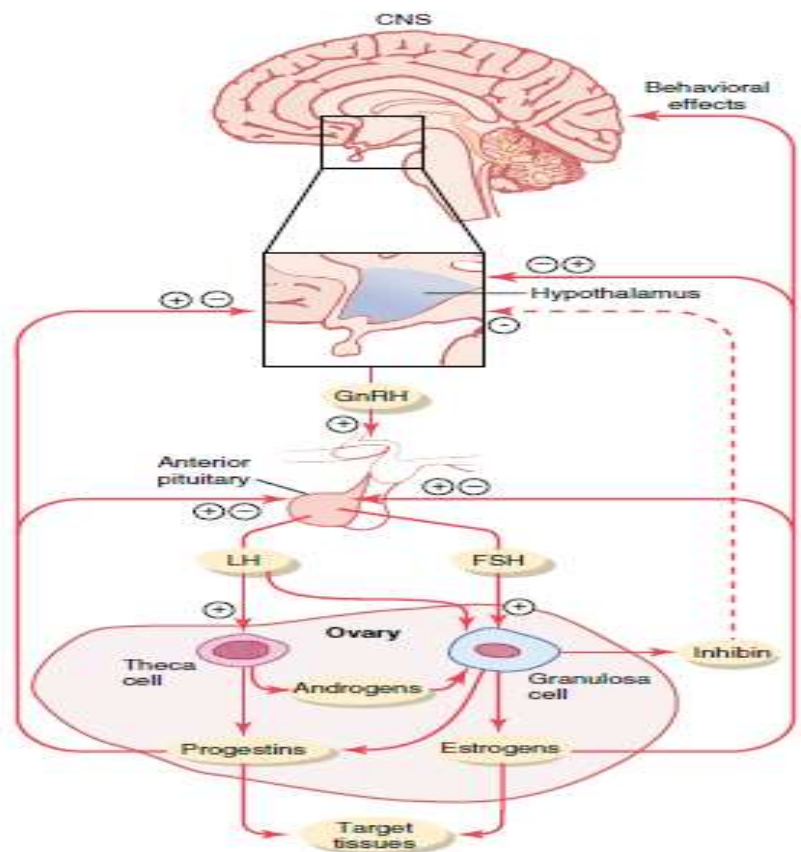
Even before puberty primary follicles started to develop and they either:

- A- Will reach maturity and ovulate OR
- B- Will degenerate by atresia

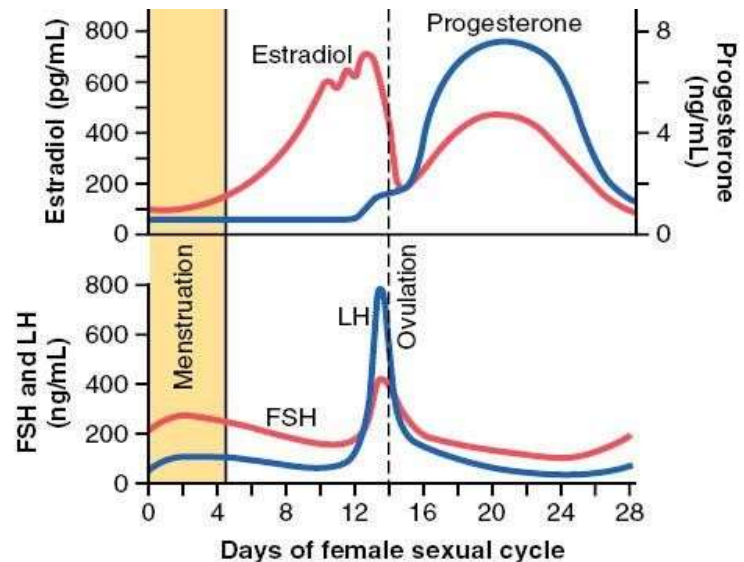
Most of the follicles undergo atresia and until puberty only 300,000-400,000 remains and only 400 will mature and release ova in the whole life of the female subject.

Female hormonal system

1. Hypothalamic releasing hormone, **gonadotropin releasing hormone GnRH**
2. Anterior pituitary sex hormones
,FSH and LH
3. Ovarian hormones , **estrogen and progesterone** secreted in response to pituitary hormones
 - Granulosa cells also secrete **inhibin** which has a negative feedback effect on anterior pituitary
 - Both estrogen and progesterone have negative and positive feedback effects on the hypothalamus and anterior pituitary depending on the stage of ovarian cycle
 - These hormones are secreted at different rates during different parts of the female monthly sexual cycle:
 1. Before ovulation (follicular phase): FSH is more than LH, and estradiol (estrogen) is more than progesterone.
 2. During ovulation: significant increase of LH, which is necessary for ovulation. Estradiol concentration is still high.



- After ovulation (Luteal phase): LH is back to being less than FSH and progesterone concentration increases.

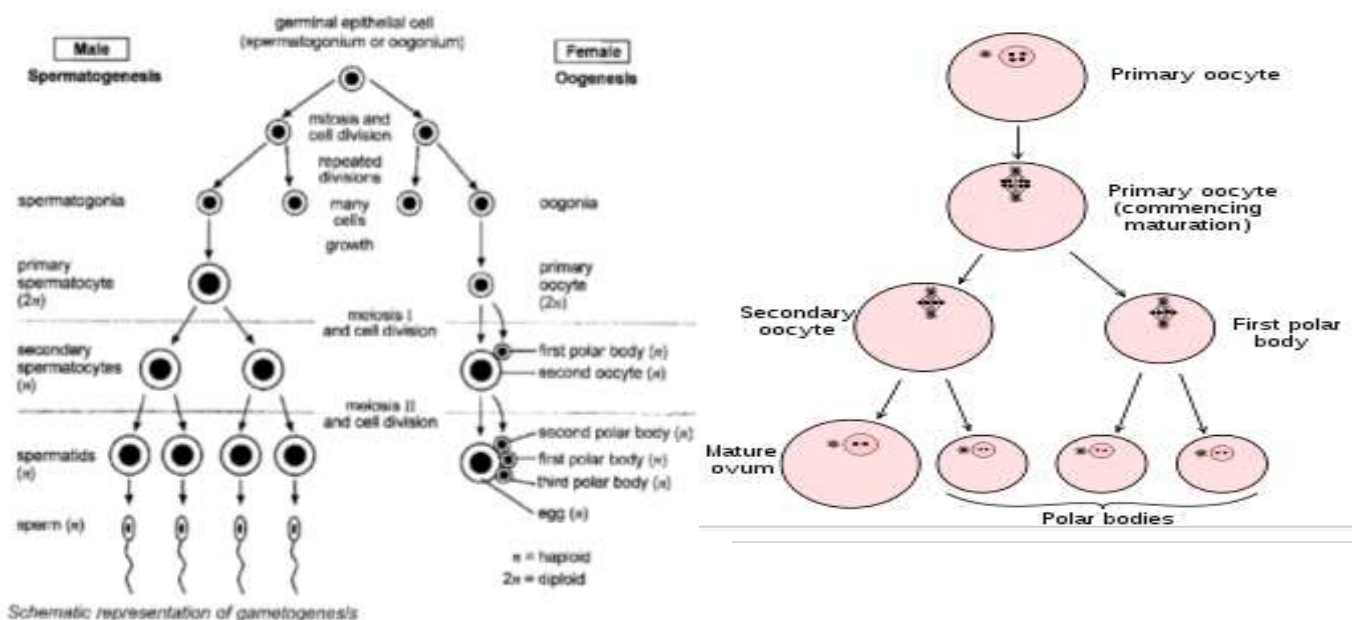


Differences between spermatogenesis and oogenesis

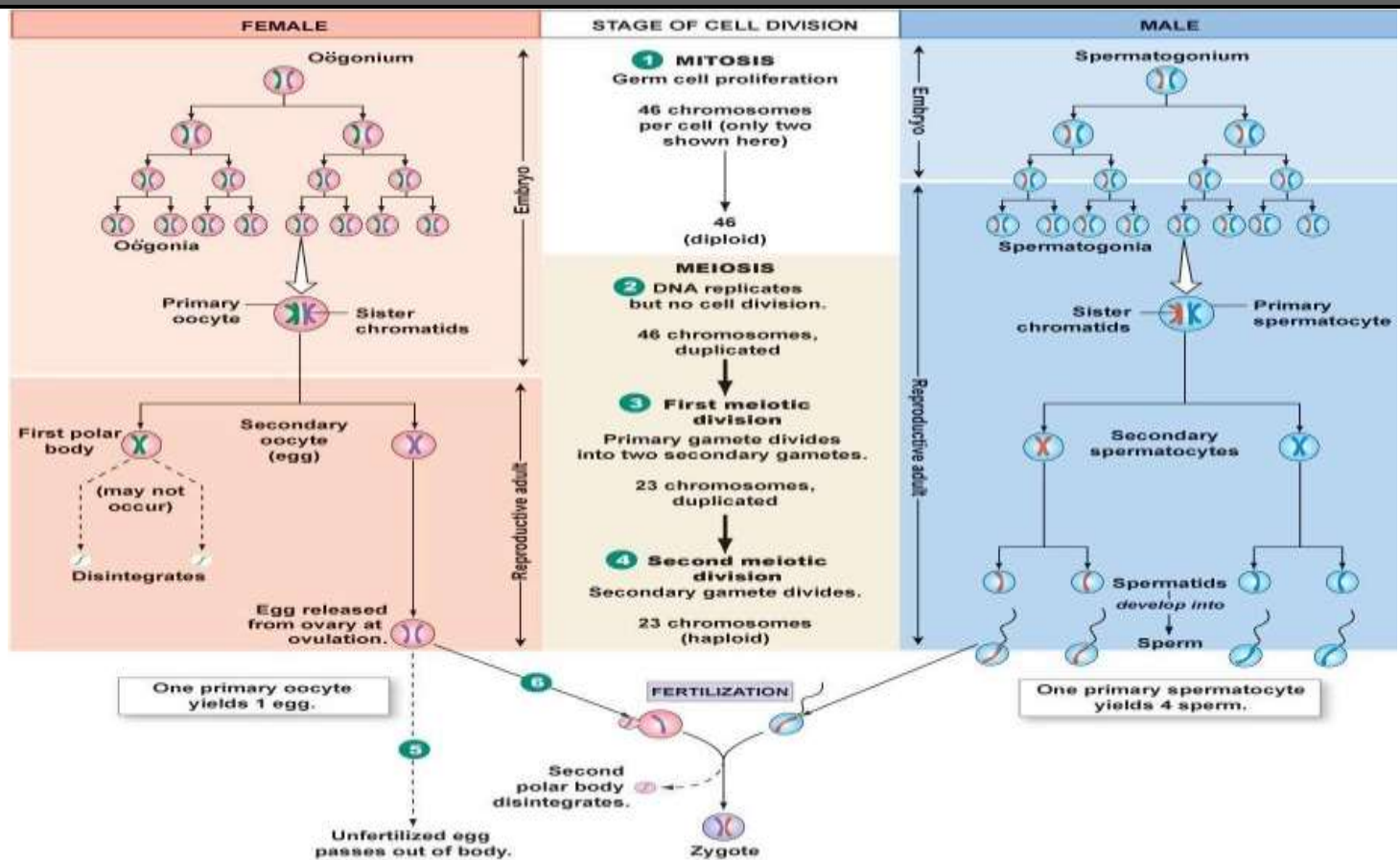
- In females, mitotic proliferation of oogonia occurs prior to birth. In males, spermatogonia proliferate only after puberty.
- In females, meiotic divisions of oocyte produce only one mature ovum and 3 polar bodies that degenerate. In males, meiotic divisions of primary spermatocyte produces 4 mature spermatozoa
- In females, second meiotic division is completed only upon fertilization. In males, the products of meiosis (spermatids) undergo substantial differentiation in the maturing process.

Gametogenesis and Hormone Control

Gametogenesis showing Spermatogenesis and Oogenesis



Schematic representation of gametogenesis



Female Sexual Cycle

Or the **menstrual cycle**: is monthly rhythmical changes in the rates of secretion of the female hormones and corresponding physical changes in the ovaries and other sexual organs. It's controlled by gonadotropins and gonadal hormones. The duration of it averages 28 days.

- There are two significant results of this cycle according to which it can be divided into two cycles:

Ovarian cycle:

1. Follicular phase: avg 15 days (range: 9-23 days)
2. Ovulatory phase: 1-3 days -- culminates with ovulation
3. Luteal phase: 13 days -- less variable than follicular

Endometrial cycle: (will be discussed in the next lecture)

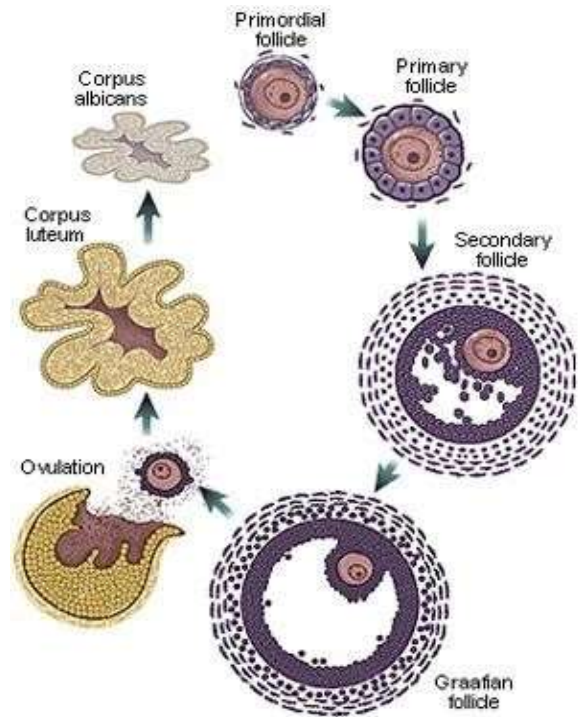
1. Menstruation : Duration 3-5 days
2. proliferative : Duration 9-11 days
3. secretory phases : Duration about 12-14 days

Ovarian Cycle

Ovarian cycle is a series of **monthly repetitive physiological and developmental changes in the ovaries**, which **prepare the ovaries for ovulation** and subsequent development of a **Corpus luteum** (CL) whose hormones will assist in regulating the uterine cycle and, if the implantation of a developing embryo occurs, assist in regulating the pregnancy.

It is regulated by FSH and LH from the anterior pituitary.

- The changes that occur in the ovary during each cycle can be divided into three phases:
 1. Follicular phase (day 1-13)
 2. Ovulatory Phase (day 13-15)
 3. Luteal Phase (day 15-28)
- These phases run in parallel with the phases of the uterine cycle and together comprise the menstrual cycle



1. Follicular Phase:

- Starts from the first day of menstruation until ovulation.
- Main Goal: to develop a viable follicle capable of undergoing ovulation.

In female child each ovum is surrounded by single granulosa cells sheath called primordial follicle. Granulosa cells provide nourishment to the ovum and secrete **oocyte maturation inhibition** factor that keeps the ovum suspended in its primordial state.

After puberty, when **LH and FSH** begin to increase, the ovaries together with some of the follicles begin to grow.

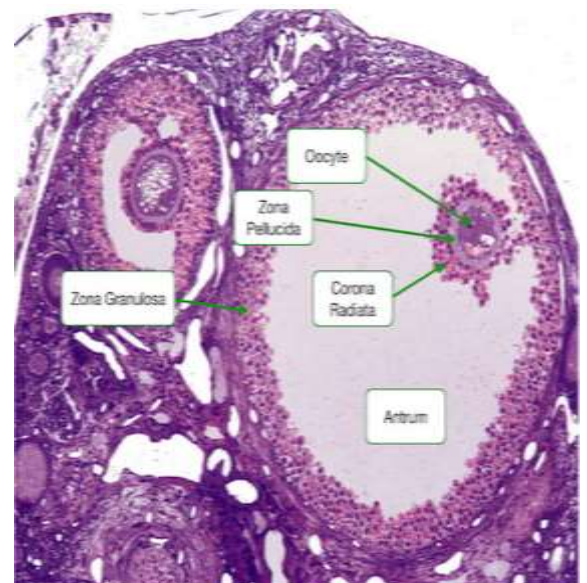
- i. The initial effect is rapid proliferation of granulosa cells (GC) giving rise to many more layers of these cells. The follicles now are known as **Primary Follicles**. There are 300,000-400,000 primary follicles in the ovaries. Each month, LH and FSH (especially FSH) cause accelerated growth of 6-12 primary follicles.

In addition, some spindle cells derived from ovary interstitium collect in several layers outside granulosa giving rise to mass of cells outside granulosa cells called **Theca Cells**. These cells are divided into 2 layers:

- 1- Theca interna: secrete estrogen and progesterone
 - 2- Theca externa: form capsule of the developing follicle
- ii. After the proliferation, the mass of GC secretes a follicular fluid that contains high concentration of estrogen. The accumulation of this fluid causes an **Antrum** to appear within the mass of GC.
 - **Note: until now, the growth is stimulated only by FSH**

- iii. Greatly accelerated growth occurs leading to larger follicle called **Vesicular Follicle**. This growth is caused by estrogen that makes GC more sensitive to FSH, and then both FSH and estrogen combine to promote LH receptors on the original GC, allowing LH stimulation to occur creating an even more rapid proliferation working with both FSH and estrogen.

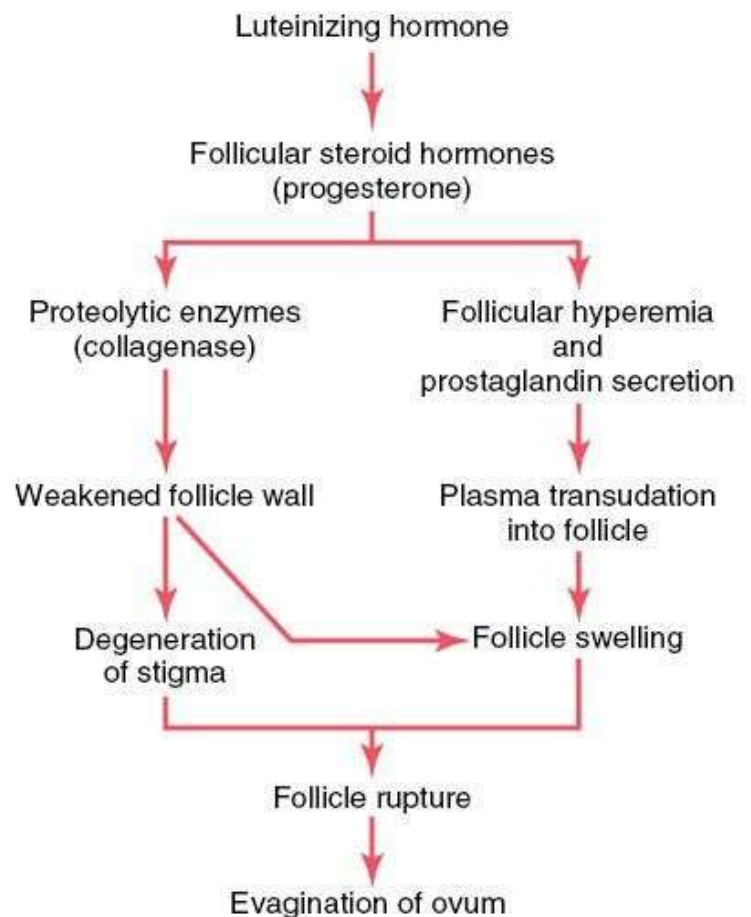
- iv. On the 6th day one follicle becomes **Dominant Follicle** while others regress, forming atretic follicles. High levels of estrogen acts on hypothalamus to decrease FSH by anterior Pituitary. Only one Graafian F (mature Follicle with 1-1.5 cm diameter) is formed each month.



Vesicular Follicle:
a follicle containing a cavity;
a mature ovarian
(graafian) follicle.

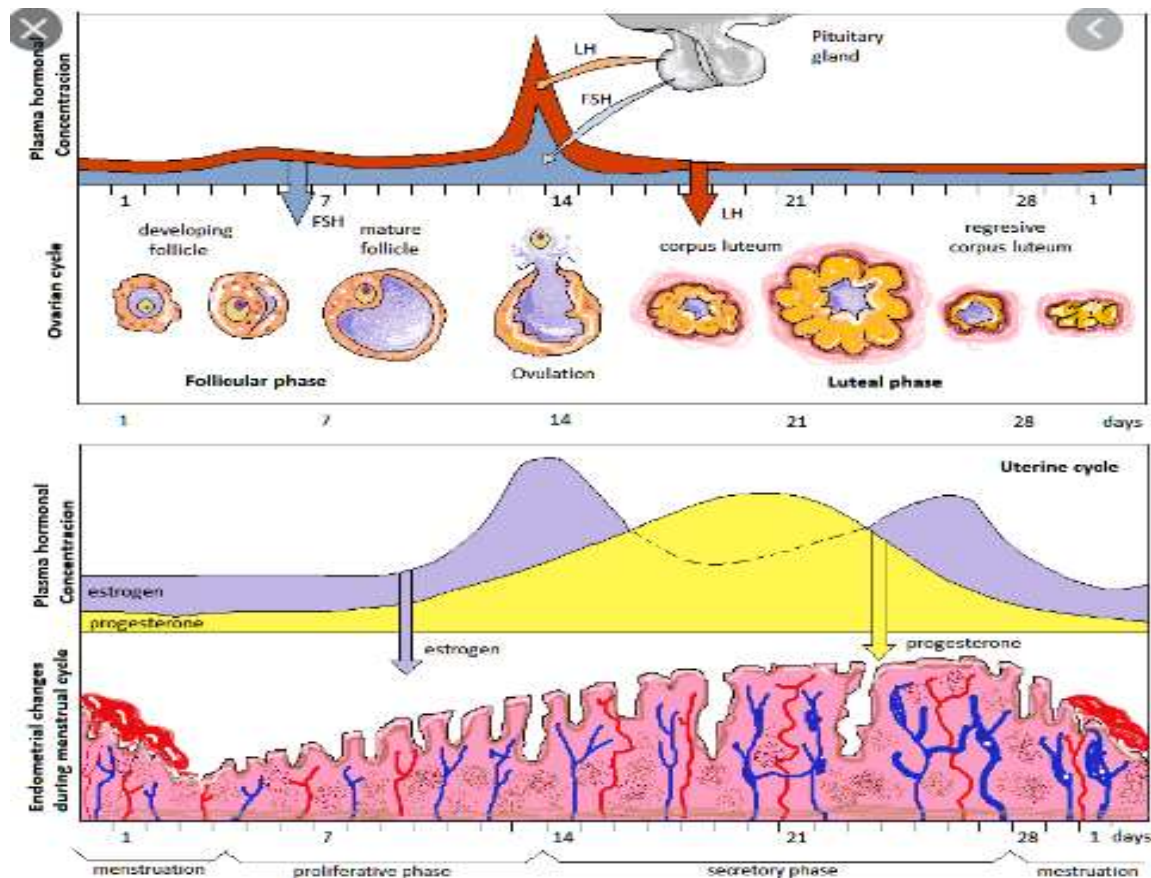
2. Ovulation:

- The follicle ruptures→ releasing the secondary oocyte and corona radiata into the peritoneal cavity to be taken up by the oviduct.
- The zona granulosa and thecal cells remain in the ovary.
- Discharge of the ovum occur (with part of the cumulus) of the mature Graafian follicle from the surface of ovary at the middle of the cycle (14 ± 2 days before the subsequent menstruation).
- Approximately 400 oocytes are ovulated over the course of a lifetime.
- Day of ovulation= length of menstrual cycle – 14 d.
- As said before, LH is necessary for ovulation. Without it, even with large quantities of FSH, the follicle will not progress to the stage of ovulation.
- This figure gives a scheme for the initiation of ovulation: LH causes rapid secretion of follicular steroid hormone that contains progesterone. within few hours two events occur, both of which are necessary for ovulation: **(1)** The theca externa releases proteolytic enzymes that cause dissolution of the follicular wall resulting in swelling of the follicle and degeneration of the stigma. **(2)** Rapid growth of new BVs and secretion of prostaglandins into follicular tissue cause plasma transduction into the follicle and swelling. Combination of both these events eventually leads to rupture of follicle and evagination of ovum.



3. Luteal Phase (Corpus Luteum)

- Morphological changes occur in the remaining part of the follicle within the next 2-3 days converting it to CL.
- After expulsion of the ovum from the follicle the remaining granulosa and theca interna cells change into granulosa lutein cells and theca lutein cells + some capillaries + some connective tissue, respectively. Cells become cuboidal with central nucleus. 80% granulosa cells, 20% thecal cells. This process is called **Lutinization** and is caused mainly by LH.
- Predominant hormone: progesterone
- Provides necessary hormones for implantation of blastocyst and maintenance of zygote until placenta can take over
- Granulosa cells secrete mainly progesterone and estrogen (more progesterone than estrogen)
- Theca cells form androgen, androstenedione and testosterone and these are converted by enzyme aromatase in the granulosa cells into estrogens, the female hormones.
- Local hormone in the follicular fluid called luteinization-inhibiting factor hold luteinization until after ovulation
- **In the absence of fertilization**, 12-14 days → apoptosis → **Corpus albicans** (avascular scar).
- Involution stimulating hormones:
 1. Estrogen and progesterone inhibit the secretion of anterior Pituitary FSH & LH cause degeneration of CL.
 2. Lutein cells secrete small amount of inhibin hormone which inhibit FSH secretion cause degeneration of CL
- **If pregnancy occurs:** the chorionic gonadotrophin have LH like action → causes further growth of CL (and its hormonal production) **CL of pregnancy** → (support the early embryo until placenta takes over the function of estrogen & progesterone production).



❖ Hypothalamus Pituitary Ovary axis

1. Positive feedback

Sex hormones (E)↑ → GnRH or LH/FSH↑

E peak ($\geq 200\text{pg/ml}$) → LH/FSH peak → This is during ovulation only but it has negative effect during remainder of the cycle.

2. Negative feedback

Sex hormones (E)↑ → GnRH or LH/FSH↓

Follicular phase: E↑ → FSH↓

Luteal phase: E↑P↑ → LH/FSH↓ (formation)

E↓P↓ → LH/FSH↑ (regression)

❖ Indicators of Ovulation:

- Mid-abdominal pain (irritation of the peritoneum).
- ↑elasticity of cervical mucus

- iii. Cervical mucus dries in Arborizing form (To have or produce branching formations) .
- iv. ↓Cornified cells in the vaginal mucosa
- v. ↑Basal body temperature (0.5°C)
- vi. ↑Urinary E, and pregnanediol or plasma progesterone level during luteal phase(day 21)
- vii. Absolute proof of ovulation is pregnancy

Summary of Ovarian Cycle

1. Every 28days GnH cause growth of 8-12new follicles
2. .Only one of them grow and become mature and ovulates
3. During growth of follicles estrogen mainly secreted
4. After ovulation secretory cell of ovulated follicle develop into Corpus Luteum and secrete large amount of progesterone and estrogen
5. After 2 weeks CL degenrates and estrogen and progesterone decrease and menstruation begins.
6. A new ovarian cycle then follow

