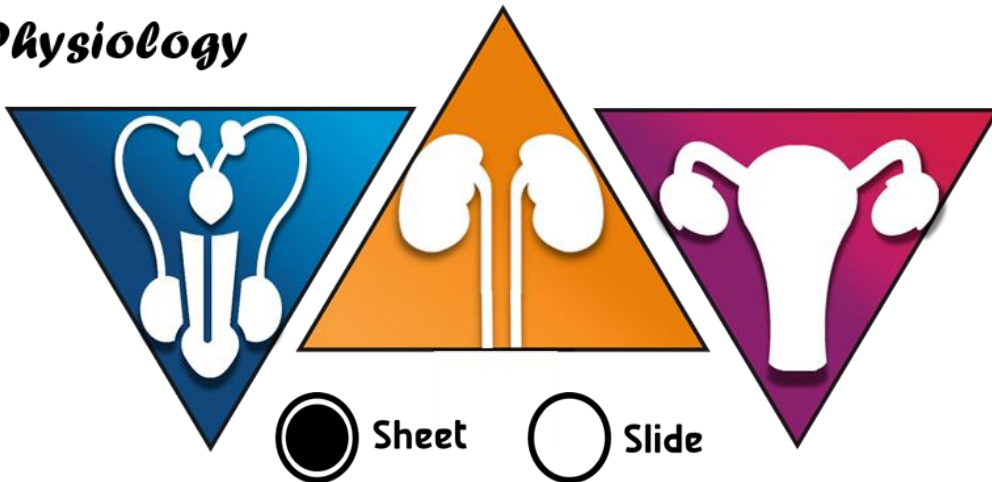




Urogenital system

Physiology



Number: - 3

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Female reproductive system

- Similar to the males (Leydig cell and Sertoli cells in the testes) two types of cells exist in the ovaries that regulate the endocrine function in females: -

1. Theca cells

- They are affected by LH and they produce progesterone and 2 androgens (testosterone and androstenedione)
- These androgens pass to granulosa cells
- note that androstenedione is a precursor of testosterone

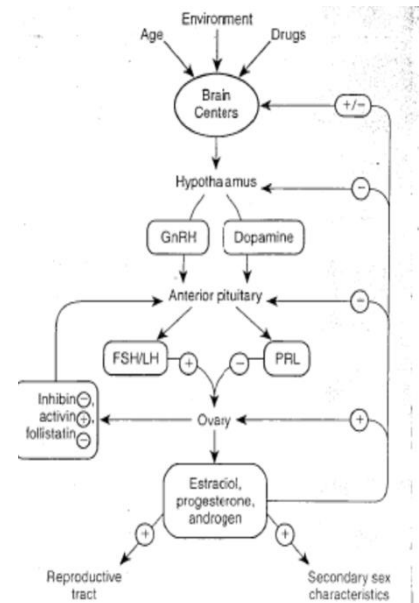
2. Granulosa cells

- Produce estrogens (estrone and estradiol), estradiol passes to the circulation. They also produce many glycoprotein hormones (similar to Sertoli cells).
- Affected by LH and FSH.
- LH causes the production of progesterone, progesterone produced here passes to theca interna cells.
- FSH causes the production of enzymes (aromatases); the products of theca interna (testosterone and androstenedione) pass to granulosa cells, and in granulosa cells testosterone is converted by aromatases to estradiol.
- androstenedione converted by aromatases first to estrone and then to estradiol.
- Estrone is the end product of both estrone and estradiol.
- **These two cells function as a one unit and can't function separately.**

Puberty

- Brain centers are affected by many factors like hormones, age, stress, environment, drugs, diseases
- Hypothalamus gets affected by these stimuli as well and produces GnRH and Dopamine
- GnRH affects the anterior pituitary which produces FSH, LH, and prolactin.
- FSH and LH stimulate the ovaries to produce estrogen, progesterone, and androgens (testosterone and androstenedione)
- Prolactin inhibits the ovarian cycle in 50% of women.

Note: Ovarian hormones affect female secondary sex characteristics and secondary sex organs.



Regulation

- On the level of the ovaries, anterior pituitary, hypothalamus, and brain centers. This regulation is either stimulatory or inhibitory

Reproductive cycles

- Primary sex organs (ovaries) functions: -
 1. Ova production
 2. The production of hormones (estrogens, progesterone and androgens)
- The gonadotropins (LH, FSH) from the anterior pituitary regulate the follicular steroidogenesis, androgens, and estradiol secretion.
- LH regulates the secretion of progesterone especially during the luteal period.
- Inhibins suppress the secretion of FSH and activins stimulate the secretion of FSH.
 - Both Inhibins and activins are produced by granulosa cells, corpus luteum, pituitary, brain, bone marrow, kidney, and adrenal glands and placenta.
 - Inhibins are a group of hormones that differ in the number of amino acids.
- Follistatins inhibit the secretion of FSH.

- There are 2 cycles in the menstrual cycle 1. Ovarian cycle and 2. Uterine cycle.
 - The ovarian cycle dominates the uterine, so if we stop the ovarian cycle, we stop the uterine cycle.
 - They both start at puberty and stop at menopause.
 - Each one is 28 days long on average and could be more, or less than 28 days, but it's constant in a specific woman. The two cycles occur at the same time.
 - These cycles don't stop unless there is pregnancy or disease.

Ova production

- At the 30th week of gestation, 7 million ova are present in the two ovaries, that means that there is production of ova during fetal life, there is also activation of follicles, but they don't continue to maturation or the production of an egg (ovum).
- 2 million ova are present at birth, the other 5 million degenerate.
- 300,000-400,000 ova reach puberty
- During reproductive years (13-50) about 450 of these follicles develop to expel an ovum. One ovum each month is expelled, and ovaries alternate. But sometimes 2 ova are expelled each from an ovary or both from the same ovary, and 1 ovum can make 2 babies (monozygotic twins)
- Note that nowadays puberty starts at an age earlier than 13 and menopause won't start until 55 years of age
- At menopause only few follicles remain which later disappear.
- Note also that bad lifestyle habits may cause menopause to happen at an age younger than 50
- Throughout the reproductive life 90% to 95% of all follicles are primordial follicles
Note primordial stage is the first stage and it is inactive.
- In fetal life and childhood some primordial follicles develop all the way to become primary follicles however all these follicles degenerate (become atretic) and don't end in the production of ova, and their duration is about 3-4 months.

Ovarian cycle.

- The ovarian cycle is the changes that occur in the ovaries
- Three phases occur
 1. Follicular phase (0-14 days)

2. Ovulation phase
3. Luteal phase (14-28)

Follicular phase and ovulation:

- In which follicles develop until the maturation of 1 follicle and the ovulation occurs at day 14 and after that the ovulated body is called corpus luteum and the luteal phase begins.
- Starts before the end of the previous cycle by 2-3 days by the activation of primordial follicles (low hormone period)
- The follicles are in their primordial phase (nongrowing cells) and they are activated **genetically** (no need for hormones, as it's a low hormone period), the number of activated primordial follicles depend on the individual let's say 6 follicles get activated.
- Activated primordial follicles become primary follicles and only one of these primary follicles become dominant
Note dominant follicles are the biggest in size, the most sensitized to FSH, have the best blood supply, and are positioned in the periphery.
- Dominant primary follicle produces estrogen which inhibits the release of FSH, the non-dominant follicles can't be sustained on this low level of FSH, so they degenerate. Dominant follicle is highly sensitized to FSH so it can be sustained on this low FSH level.
Another reason for the degeneration of the other follicles is because they don't produce sufficient amounts of the estrogens, instead, they concentrate the androgens inside them in the form of dihydrotestosterone which can't be used to synthesize estrogens and increases atretic conditions
- The dominant primary follicle will develop to secondary follicle then to graafian body which at day 14 ovulates (according to the doc secondary follicle is the one that ovulates)
- The ovulated body is called corpus luteum and marks the beginning of luteal phase
- **Ovulation:**
- The number of ovulating ova is species dependent and is influenced by genetic, nutritional and environmental factors
In humans usually one ovum, could be more sometimes.

- 4 ovarian proteins are essential for ovulation
 - 1-Progesterone receptors
 - 2-Cyclooxygenase enzyme which converts arachidonic acid to prostaglandins
 - 3-Cyclin D2
 - 4-The transcription factor **CBPBP**

The mechanism by which these proteins interact with each other to regulate follicular rupture is not known ; however, these proteins are required for ovulation to occur and if any one of them isn't present then ovulation won't occur
- The earliest responses of the ovary to the midcycle LH surge (will be explained later) are the release of vasodilatory substances such as histamine, bradykinin and prostaglandins which mediate increased ovarian and follicular blood flow. The highly vascularized dominant follicle becomes hyperemic and edematous and swells.
- In response to the LH surge plasminogen activator is produced by theca and granulosa cells of the dominant follicle and converts plasminogen to plasmin. Plasmin is a proteolytic enzyme that acts directly on the follicular wall and stimulates the production of collagenase, an enzyme that digests the connective tissue matrix.
- It's believed that prostaglandins cause the release of lysosomal enzymes that digest the follicular wall.
- The follicle must be exposed to the **appropriate sequence** of hormones:
 1. FSH
 2. Estradiol
 3. LH
- Not every cycle ends in ovulation and these cycles are called **anovulatory cycles**. Examples include cycles that happen at the beginning of puberty and at the beginning of menopause or while using contraceptives. Such cycles are shorter than normal because of the deficiency or absence of progesterone.

Luteal phase

- Corpus luteum will prepare the endometrium for pregnancy
- Corpus luteum produces a lot of progesterone and little estrogen

Note: No pregnancy without progesterone and no female characteristics without estrogen.

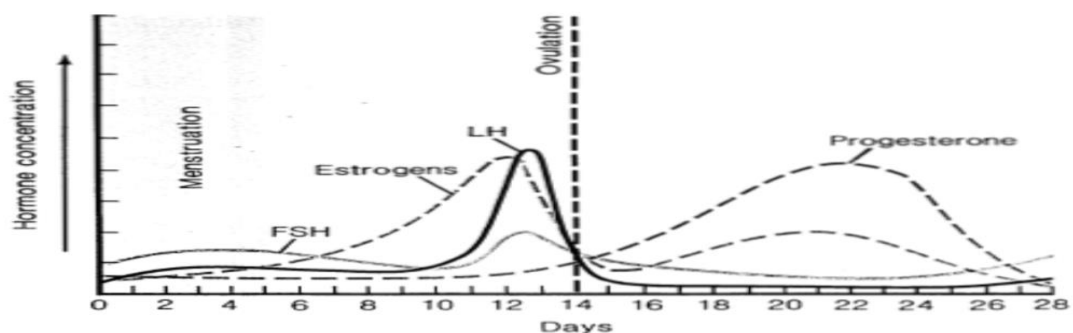
Progesterone is the pregnancy hormone while estrogen is the female hormone

- Within 2 weeks if there is no pregnancy corpus luteum will shrink and become corpus albicans which disappears in 2 months.

Note: Primordial follicles may remain in a nongrowing phase for years so if the women is healthy and not exposed to drugs then no problem she can have children at age of 50-55 and even 60.

If the women is not healthy exposed to drugs then she risks having abnormal children if she was to have children at age 60.

Level of ovarian hormones during the ovarian cycles



- Menstrual phase: As can be seen in the beginning of the cycle all hormones levels are low (no hormones), the highest is FSH needed by the follicles and it is low before this cycle. the follicles are activated before the menstrual cycle (lowest FSH level) not shown in the graph
- After the first week estrogen levels begin to rise, and between days 10 and 12 estrogen level reaches the peak above normal level and positively stimulates LH and FSH but LH more. This is the only conditions in which estrogen stimulate the release of LH and FSH. Usually estrogen inhibits LH and FSH.
- Usually when the estrogen level is between 70-200 pg/ml, estrogens inhibit LH, FSH, but when they become too high then they stimulate LH, FSH release. So, there is a level in which estrogens inhibit FSH, LH and **when this level is exceeded (> 200 pg/ml) then they are stimulated.**
- LH causes ovulation so if we inhibit LH then there will be no ovulation, also if we inhibit estrogen → no LH → no ovulation.
- **So ovulation is caused by estrogen induced LH surge.**

- Progesterone levels increase a little bit, but it has a permissive action

Note: Permissive presence of one hormone is required in order for another hormone to exert its full effects on a target cell.

Summary

- Follicular phase: multiple follicles develop → dominant follicle selected → dominant follicle matures → ovulation → corpus leutum after 28 days becomes → corpus albican → albican degenerates if there is no pregnancy it disappears and if there is pregnancy it continues to grow producing progesterone and estrogen.