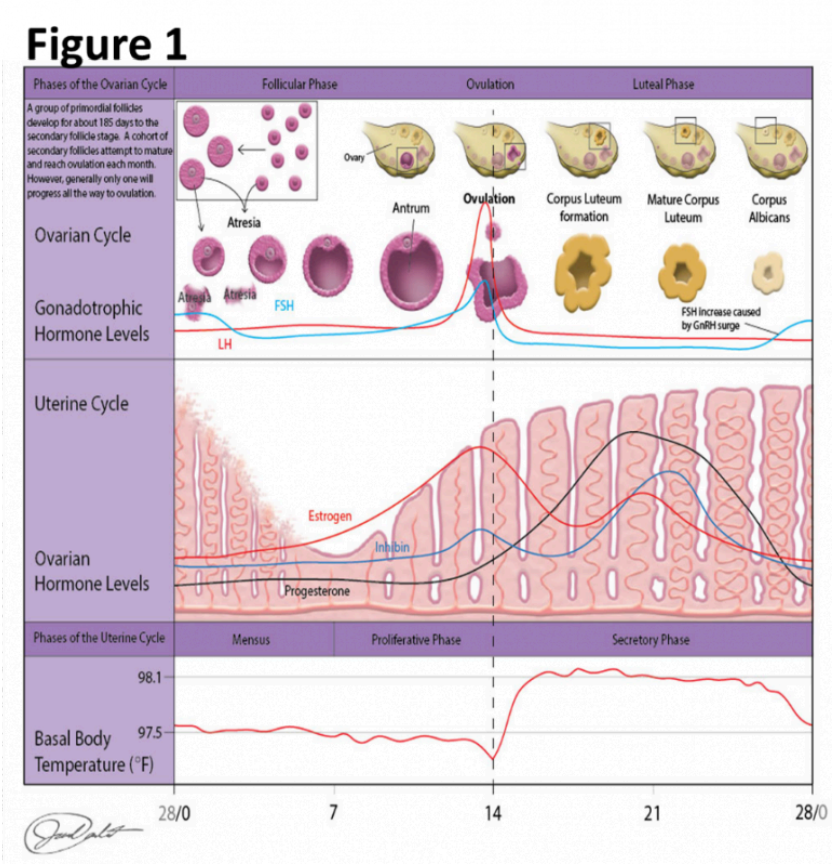
11.2.3

Review of the Physiology of the Menstrual Cycle

Review the image below and refresh your memory of the uterine and ovarian cycles:

- The ovarian cycle is divided by **ovulation** into two phases: the **follicular phase** and the **luteal phase**.
- **Estrogen** is highest in the follicular phase of the ovarian cycle while **Progesterone** is highest in the luteal phase.
- The uterine cycle has a **proliferative phase** and **secretory phase** that are followed by **menses** if pregnancy does not occur.
- The hypothalamus releases **GnRH** that stimulates the release of **luteinizing hormone (LH)** and **follicle stimulating hormone (FSH)** from the anterior pituitary gland. GnRH (and LH and FSH) are elevated at the beginning and throughout the follicular phase. Following ovulation, increased progesterone inhibits GnRH release and thus reduces LH and FSH levels during the luteal phase.
- Estrogen and progesterone provide negative feedback to the hypothalamus and pituitary that decreases the production of GnRH, FSH and LH.
- Near the end of the follicular phase, rapidly rising estrogen has the paradoxical effect to cause positive feedback on the hypothalamus and pituitary instead of negative feedback. This positive feedback triggers the **"LH surge"** that leads to ovulation.
- The **corpus luteum** produces a lot of progesterone during the luteal phase.
- The lack of LH during the latter luteal phase causes the corpus luteum to regress and become the **corpus albicans**. The corpus albicans does not produce much progesterone and estrogen which triggers the beginning of menses.
- A pregnancy would result in a zygote implanting in the uterus towards the latter part of the luteal phase. An implanted zygote produces **Human chorionic gonadotropin (hCG)** which is an LH agonist that keeps the corpus luteum functional.



Images by JC BYU-I F16

Estrogen and Progesterone Production

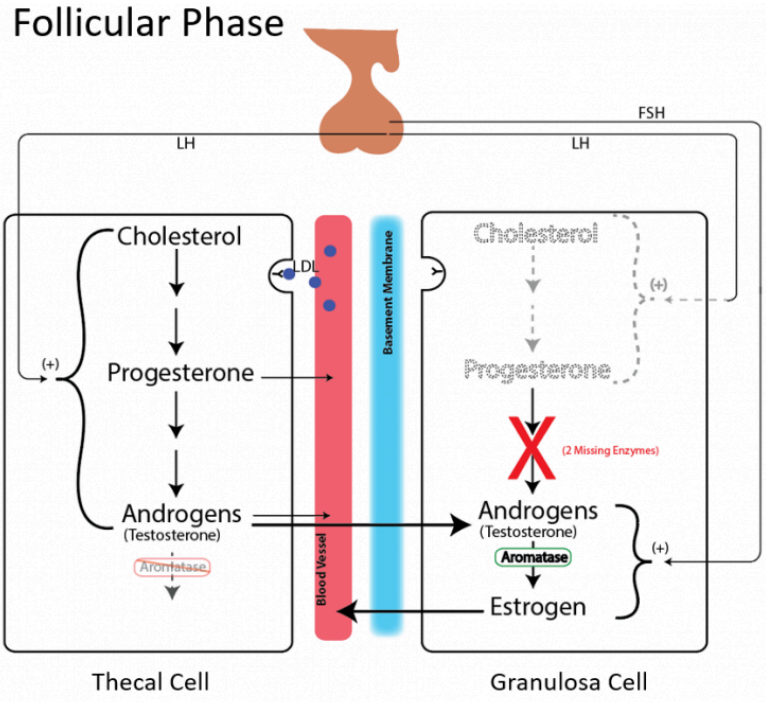
Watch the video [Estrogen & Progesterone Production by Theca & Granulosa Cells]

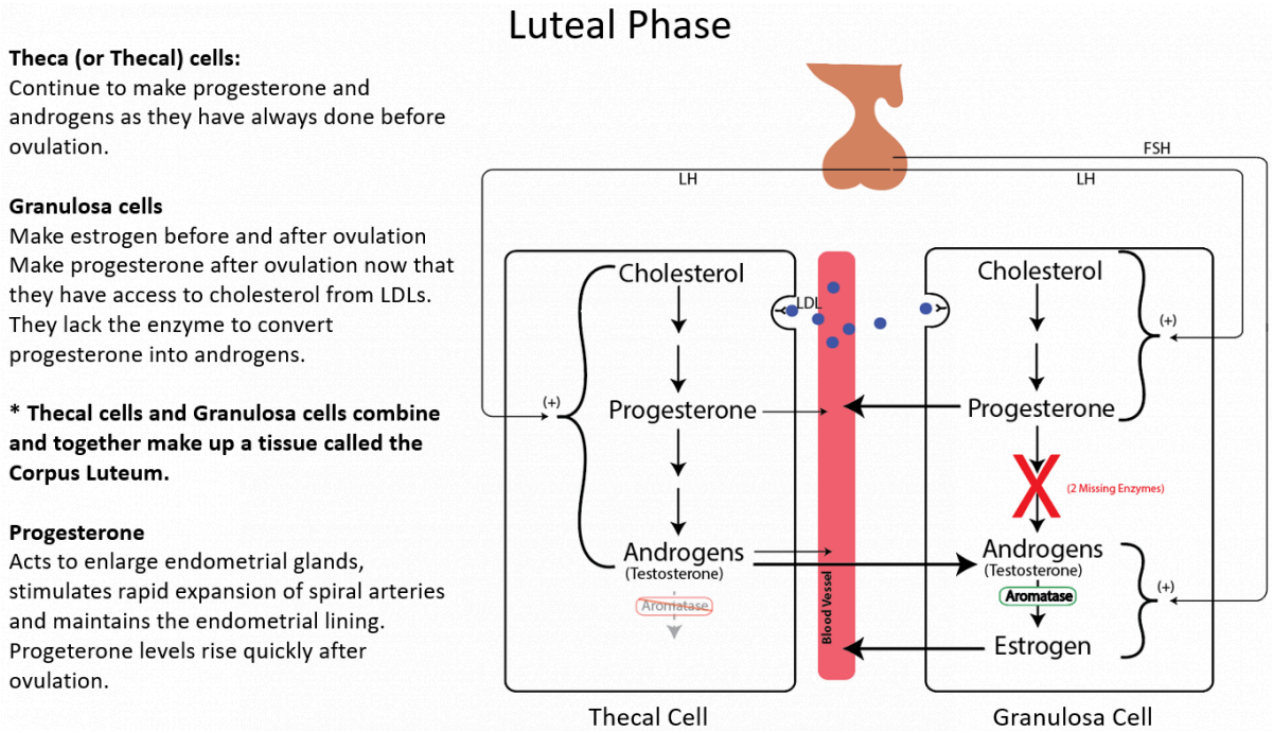
Theca (or Thecal) cells:
Make androgens (testosterone) under the stimulation of LH.

Granulosa cells
Make estrogen before and after ovulation
Make progesterone after ovulation

Estrogen
Increases LH receptors (granulosa and thecal Cells).
Estrogen produced by late secondary follicles has a positive feedback on hypothalamus instead of a negative feedback leading to the LH surge.
Causes proliferation of endometrial tissue.
Increases progesterone receptors on endometrial cells.

Summary
Thecal and granulosa cells work together to increase estrogen which brings about the LH surge which brings about ovulation.





Images by JS BYU-I F16

The video and images above help us understand the production of steroid hormones (estrogen and progesterone) via the theca and the granulosa cells found in the ovaries. The top picture shows hormone production before ovulation and the bottom picture shows hormone production after ovulation. Notice that the theca and granulosa cells cooperate to make estrogen and progesterone. Also note that LH is a strong stimulator of theca cells while FSH is a strong stimulator of granulosa cells.

Theca cells: "Theca" is a Latin word for "casing" or "sheath." The theca cells of the ovarian follicle are stromal cells (connective tissue cells) that encase the granulosa cells surrounding the ovum. The theca cells and the granulosa cells are separated by a basement membrane before ovulation. The theca layer is vascularized and thus plays a key role in the diffusion of nutrients to the deeper layers of the follicle. At the secondary follicle stage, theca cells express LH receptors. The binding of LH to these receptors stimulates the cells to increase their absorption of LDLs from the blood. Granulosa cells during the follicular phase lack this vascularization and are limited LDL availability. Remember, LDLs deliver cholesterol which is used to synthesize steroid hormones through multi-step processes. The image above does not list all of the intermediaries or the specific enzymes involved in steroidogenesis; however, the key point is that progesterone is an important intermediate in the biosynthesis of androgens (e.g. testosterone) in theca cells. These cells do not express the enzyme aromatase, which is required to convert androgens into estrogens, so the androgens from the theca cells diffuse to the granulosa cells which then make estrogen via aromatase activity. This explains why estrogen levels are higher than progesterone levels during the follicular phase.

Granulosa cells: At the secondary follicle stage, granulosa cells differ from thecal cells in that they express FSH receptors in addition to LH receptors. Granulosa cells have the ability to respond to LH stimulation to absorb LDL particles like theca cells, but LDL particles from the blood do not cross the basement membrane easily. As a result, the activation of LH receptors and the resulting initiation of steroidogenesis with cholesterol is not significantly observed until after the basement membrane ruptures due to ovulation. Notice in the image above representing the follicular phase that the biochemical pathways to make progesterone from cholesterol are grayed out in granulosa cells. After ovulation, blood vessels gain access to granulosa cells which enable the delivery of LDL-contained cholesterol for steroidogenesis. Although steroidogenesis is initiated in granulosa cells after ovulation, it is only possible to produce progesterone since they lack the enzymes to convert progesterone into the androgen precursors needed for estrogen synthesis. This results in elevated progesterone levels during the luteal phase because progesterone is coming from

BOTH theca and granulosa cells. Theca cells continue to produce androgens that can be converted by granulosa cells into estrogen, but these levels are reduced compared to progesterone during the luteal phase.