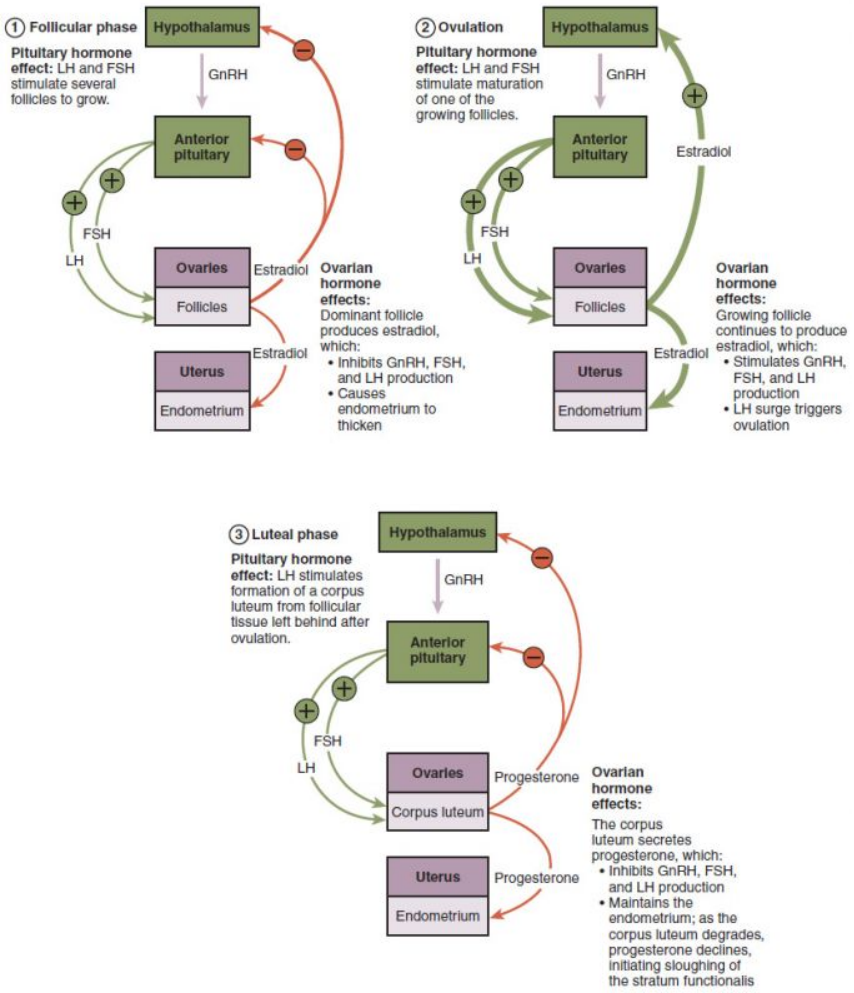
5.7.8

The Ovarian Cycle

As explained in previous sections of this unit, once spermatogenesis begins at puberty in males it is relatively constant throughout the remainder of life. Granted there is a gradual decline after about age 50 but the process continues virtually until the death of the man. In women, on the other hand, the process is much different and beginning at puberty follows a cyclic pattern with increasing and decreasing hormone levels as well as changes in the ovaries and uterus, repeating itself about every 28 days. This series of events is referred to as the **menstrual cycle.** Since this cycle involves changes in both the ovaries and the uterus it can be divided into two cycles, the ovarian cycle and the uterine cycle. We will explore the cycles separately but keep in mind they happen simultaneously and are intimately connected. For both of the cycles, we start counting the days on the first day of menstrual flow or menses. The culminating event in the cycles is release of the ovum (ovulation), which typically occurs on day 14 in a typical 28-day cycle. Note that not all cycles are exactly 28 days and there can be differences between women, and even differences from one cycle to the next in the same women. Normally the most consistent portion of the cycle is the second half, the time from ovulation to the onset of the next menses. This portion is expected to last 14 days. In women whose cycles are not the typical 28 days, ovulation usually occurs 14 days prior to the onset of the next menses. Please refer to the image above as we discuss the Ovarian and Uterine cycles below.

Ovarian Cycle

The ovarian cycle describes the hormonal changes that occur during the menstrual cycle as well as the changes taking place in the follicles. First a quick review of the key hormones involved and their regulation. This control system is often referred to as the hypothalamic-pituitary-ovarian axis. Gonadotrophin-releasing hormone (GnRH) from the hypothalamus stimulates secretion of the gonadotropins, FSH and LH, from the anterior pituitary. FSH acts on the granulosa cells of the follicle and LH acts on the thecal cells of the follicle. The follicle then produces estrogen and progesterone. Estrogen and progesterone, in turn, usually feedback on the hypothalamus and pituitary to inhibit their activity, thus reducing FSH and LH secretion. This is a classic negative feedback loop. However, at a key point in the cycle the feedback briefly changes to positive feedback. This switch from negative to positive feedback control causes a sudden 10-fold increase in LH secretion and to a lesser extent more FSH secretion as well.



Hormonal Regulation of Ovulation.

The mechanisms that produce this sudden positive feedback are not well understood.

The ovarian cycle can be divided into two distinct phases, the follicular contribute as well. However, there are other unknown signaling processes involved, because administering just estrogen and progesterone to women in their mid-follicular phase does not achieve this positive feedback. There is more to be discovered and learned about this positive feedback switch.

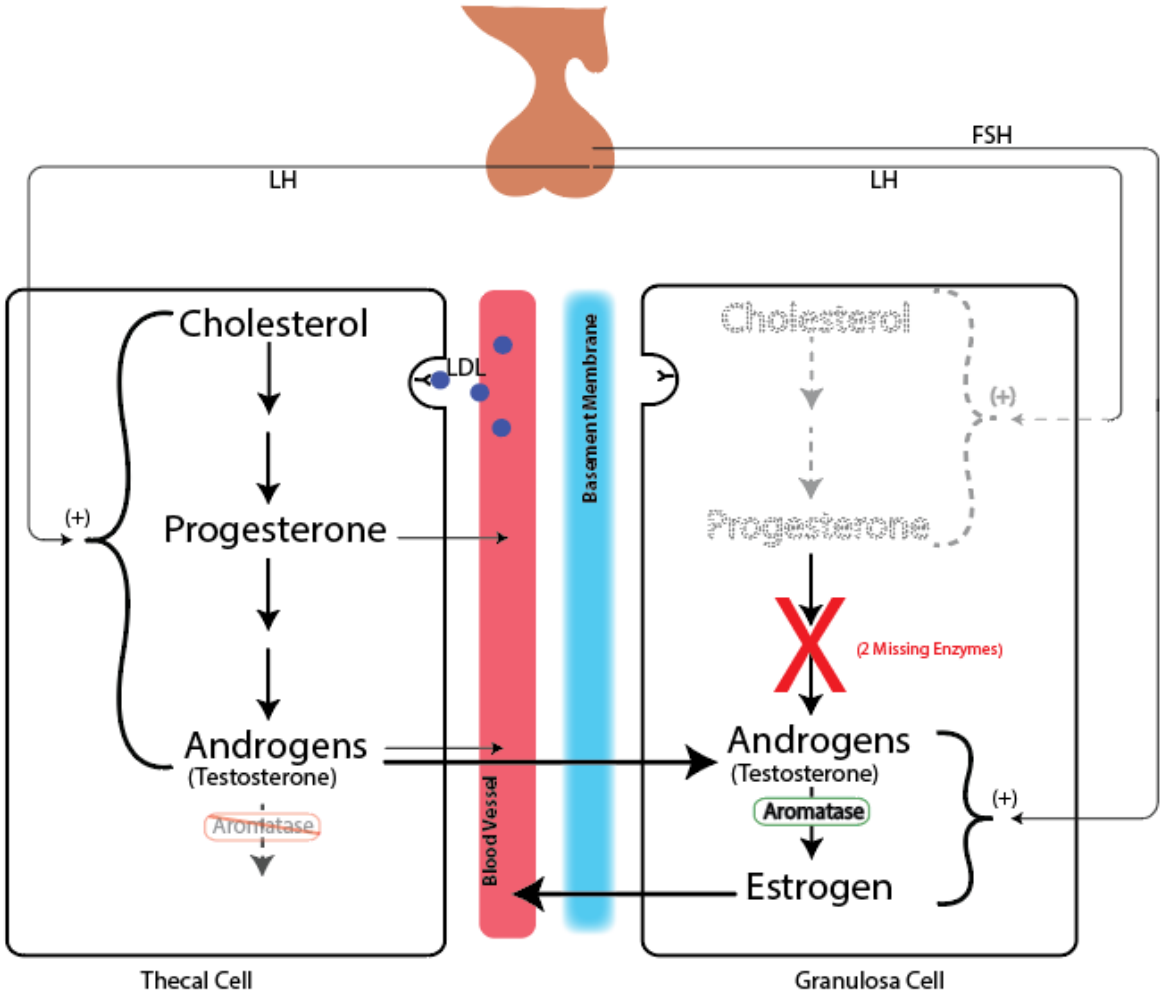
As was also true in the male, inhibin acts on the pituitary to selectively inhibit FSH secretion allowing for differential secretion of the two gonadotropins. In the female, inhibin is produced by the granulosa cells of the follicle. The normal cyclic pattern of hormone secretion observed in the ovarian cycle is coordinated by the negative and positive feedback actions of this system.

The event that separates these two phases is ovulation, thus the follicular phase begins on day 1 of the cycle and ends at ovulation and the luteal phase begins at ovulation and ends at the beginning of the next menses. Each phase lasts approximately 14 days.

Two cell theory of estrogen production:

In the ovary, the oocyte is surrounded by granulosa cells. The granulosa cells lay down a basement membrane and then layers of thecal cells develop beyond this membrane. Thecal cells contain LH receptors. As LH rises in the blood before ovulation, it binds these receptors and stimulates steroidogenesis. This causes the thecal cells to take in more LDLs to access the cholesterol needed to make steroids. The thecal cells metabolize cholesterol to progesterone. Some of the progesterone can enter the circulation, but most is quickly metabolized to androgens. Some androgens can enter the circulation, but most diffuses to the nearby granulosa cells. Thecal cells have the enzymes to perform the biochemical reactions to make androgens from cholesterol, but a key enzyme called “aromatase” is missing in the thecal cells.

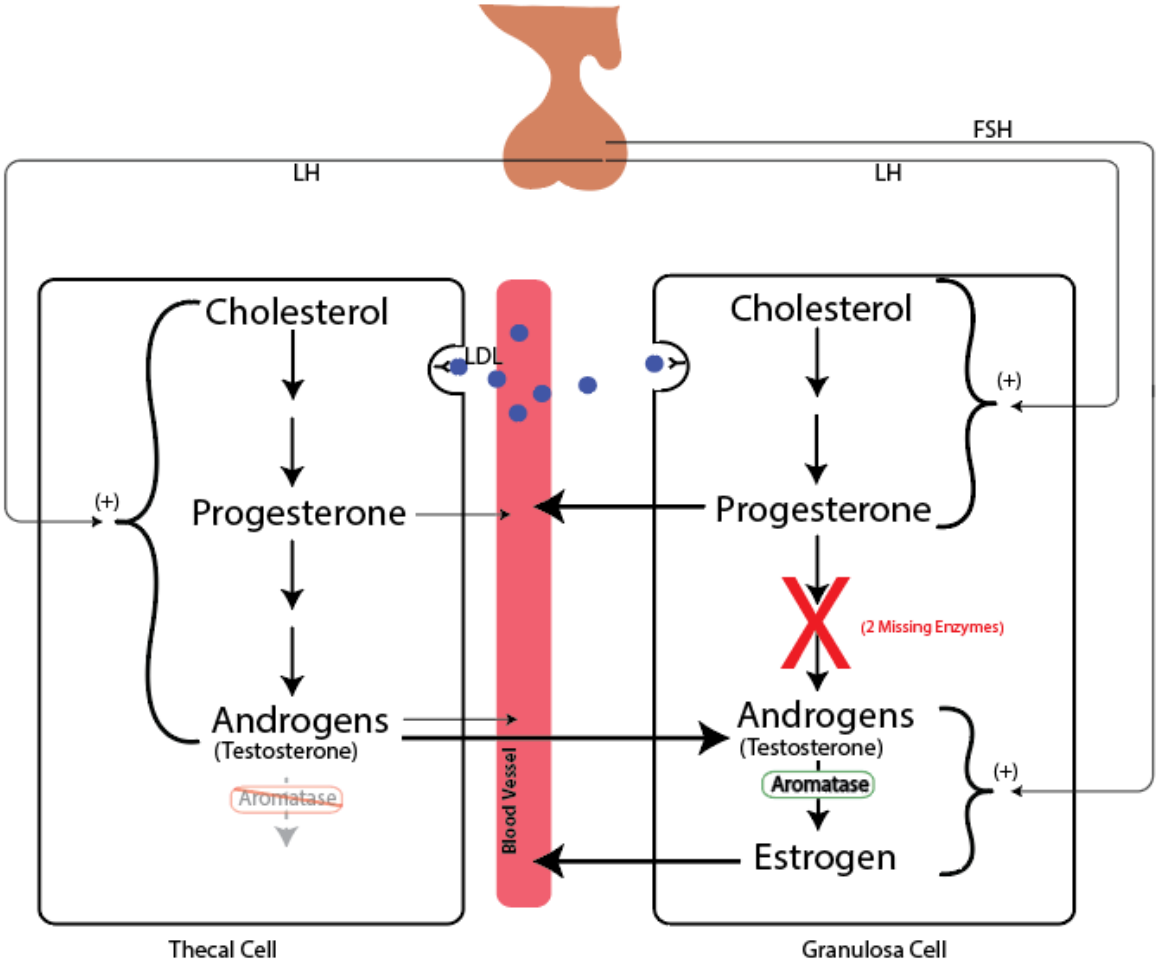
The granulosa cells have very few if any LH receptors before ovulation. These cells do have FSH receptors that respond to rising levels of FSH in a way that upregulates the aromatase enzyme. Therefore, we find that before ovulation we have rising levels of LH and FSH which result in the stimulation of thecal cells to make androgens out of cholesterol (LH) and we find granulosa cells responding to FSH to make estrogen out of androgens. This is called the two cell theory of estrogen production.



Two cell organization for steroidogenesis

Image by JS BYU-I Fall 2013

After ovulation we see some significant changes in the structure and relationship of thecal and granulosa cells. First, we see that the basement membrane is disrupted between these two cells. This allows easier access to LDLs which can provide cholesterol for steroidogenesis. Second, we see the upregulation of LH receptors on granulosa cells. These combine events turn the granulosa cells into cholesterol metabolizing factories. Cholesterol is quickly turned into progesterone but the granulosa cells are missing the enzymes to turn progesterone into androgens. This is why we see progesterone levels rise a lot after ovulation. Estrogen is also being made as before (2 cell estrogen producing theory), but after ovulation is when we see the real change in progesterone production.



Two cell organization for steroidogenesis after ovulation. Cholesterol can access granulosa cells now.

Image by JS BYU-I Fall 2013

Follicular Phase

The follicular phase gets its name from the fact that during this part of the cycle the follicle is developing and preparing for ovulation. During the early follicular phase, estrogen levels are low but are gradually increasing. The estrogen exerts a negative feedback on the hypothalamus and pituitary, inhibiting FSH and LH secretion. Although the FSH levels are low, the follicles are still being stimulated by FSH. The dominant follicle up-regulates its FSH receptors and is therefore more sensitive to the FSH, stimulating its further development. Estrogen secretion by the dominant follicle

increases while in the less mature follicles estrogen secretion declines, eventually contributing to their degeneration. During the final portion of the follicular phase, the increased estrogen levels cause a switch from negative to positive feedback. This results in a sudden increase in GnRH secretion producing a marked rise in both LH and FSH. The rise is much more pronounced for LH and its levels nearly triple. FSH also increases but not as dramatically, probably due to the presence of inhibin which selectively inhibits its secretion. The surge in LH is the event that is responsible for ovulation. Ovulation usually occurs about 12 hours after the peak of the surge. The LH surge appears to stimulate the ovum in the rapidly growing follicle to complete its first meiotic division. Also, LH triggers a cascade of events that weaken the follicular wall and ultimately causes the follicle to rupture, releasing the egg. The rupture also allows blood to be exposed directly to the granulosa cells which brings in cholesterol from circulating LDLs and resulting in a biological switch to produce progesterone.

Luteal Phase

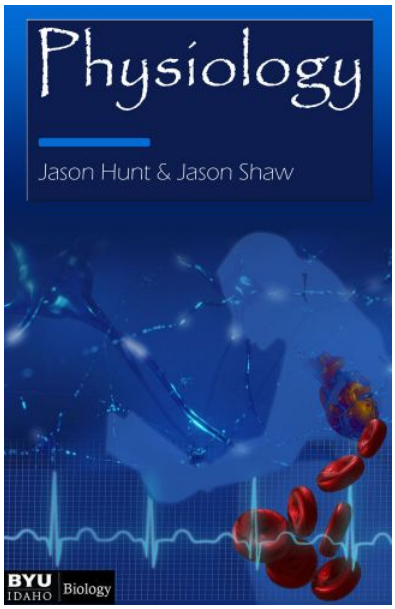
Once ovulation is complete the remaining cells of the follicle, under the influence of LH, are transformed to become the corpus luteum. The second half of the ovarian cycle, the luteal phase, is named for the presence of the corpus luteum. After ovulation, hypothalamus and pituitary control reverts back to negative feedback resulting in a dramatic reduction in LH and FSH secretion. Additionally, the structural changes in the corpus luteum result in a switch from mainly estrogen secretion to mainly progesterone secretion. Progesterone levels increase markedly and reach peak levels about 7 days after ovulation. Estrogen levels follow the same general pattern but its overall concentration is significantly lower. In the absence of fertilization, the corpus luteum survives 10-12 days and begins to regress. This results in a sharp drop in progesterone and estrogen levels resulting in the onset of menses and the end of the cycle. About 2 days prior to menses, as the negative feedback from estrogen and progesterone decreases due to decreasing concentrations, FSH levels increase slightly. It is this small spike in FSH that is thought to be the stimulus that recruits a new cohort of follicles to begin development. If the ovum is fertilized, the developing embryo will begin to produce a hormone called human chorionic gonadotropin (hCG). hCG is nearly identical to LH and stimulates the corpus luteum to continue producing progesterone and estrogen. Under the influence of hCG the corpus luteum continues functioning for about the first trimester (1st 3 months) of gestation. By the end of the 1st trimester the placenta has started producing progesterone and estrogen and the corpus luteum is no longer needed and will begin to regress.

Summary

1. Corpus luteum dies and as a result, estrogen and progesterone levels begin to decline
2. The declining levels of estrogen and progesterone result in an increased FSH secretion from the pituitary gland
3. FSH recruits a cohort of graffian follicles and they start to rapidly proliferate resulting in an increase in estrogen (albeit still low levels) and inhibin.
4. Estrogen and inhibin feedback negatively on FSH secretion and causing the levels of FSH to decline
5. Declining FSH levels cause atresia of all follicles with the exception of one. The one that survives continues to proliferate and secrete estrogen (levels increase)
6. Higher levels of estrogen begin to feedback positively and LH and FSH begin to surge
7. Surging LH induces ovulation. The rupture exposes the granulosa cells to a direct blood supply and therefore cholesterol. LH then causes the granulosa cells to secrete progesterone.
8. High progesterone and inhibin negatively feedback on LH and FSH causing the levels to

decline

9. The remaining corpus luteum gradually begins to degenerate and will die if it is not rescued by hCG.



Hunt, J. & Shaw, J. (n.d.). *BIO 461 Principles of Physiology*. BYU-I Books. https://books.byui.edu/bio_461_principles_o