

Female Reproductive System

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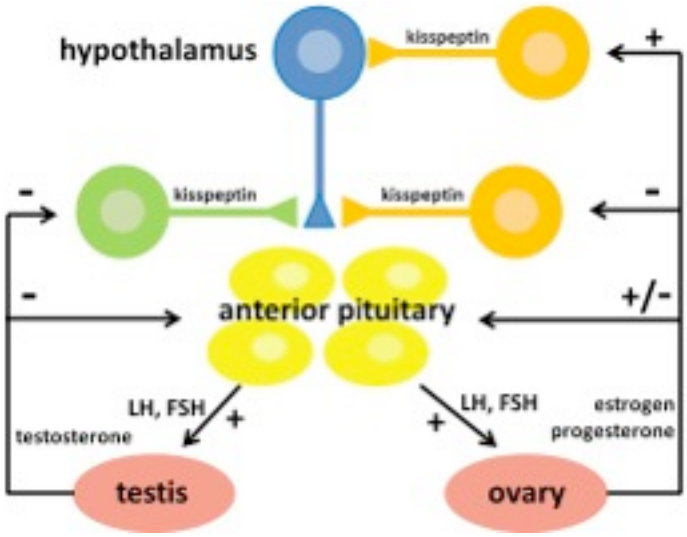
The underlined headings correspond to the 2 Female Reproductive System videos.

1. Hypothalamus-Pituitary-Gonad Axis and Follicle Maturation

The Common Axis

There are many similarities between the hypothalamus-pituitary-gonad axis in males and females. The process of producing sperm or ova is coordinated by the hypothalamus which secretes GnRH (gonadotropin-releasing hormone) in a pulsatile manner. In turn, GnRH stimulates the anterior pituitary to secrete both FSH (follicle-stimulating hormone) and LH (luteinizing hormone) (Fig. 1). In both males and females, androgens (like testosterone) produced in the gonad are needed for development of the ovum or sperm. Production of inhibin B by cells in the testis or ovary decreases FSH secretion while sex hormones like testosterone and estrogen regulate GnRH, LH, and FSH secretion.



The Axis in Females

In the female, the cyclic pattern of hypothalamic secretion controls the menstrual cycle. Starting at puberty, the hypothalamus secretes GnRH which leads to LH and FSH secretion from the anterior pituitary. LH acts on the theca cells of the ovary to secrete androgen. FSH acts on the follicles in the ovary and specifically on the granulosa cells which surround the ovum. These cells contain the enzyme **aromatase** which converts local androgen (from the theca cells) to estrogen. Estrogen exerts a negative feedback blocking secretion of GnRH, LH and FSH (Fig. 1). Granulosa cells also secrete inhibin which selectively suppresses FSH secretion.

left) and

The Ovary

The ovary has two primary functions. In oogenesis, the ovum and its surrounding granulosa cells mature in a structure called a follicle. The other role of the ovary is the secretion of estrogen and progesterone which develops and maintains female secondary sex characteristics and prepares the uterine surface for the initiation of pregnancy (implantation of embryo) (Fig. 2).

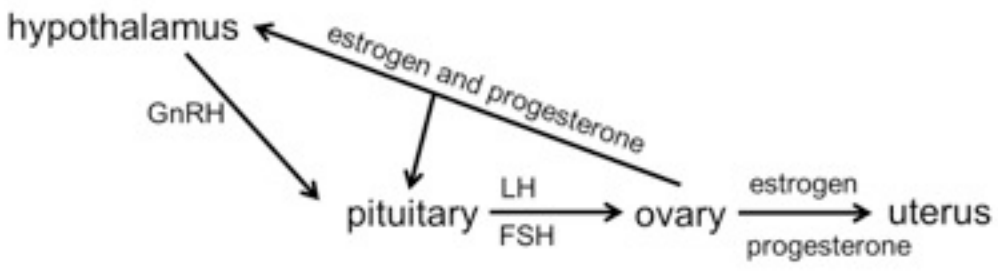


Figure 2. The regulation of the ovary and uterus.

Oogenesis
The ovarian germ cell population changes in number over time. The peak stem cell population occurs at about the fifth month of gestation and is followed by a very rapid fall in numbers such that at birth the germ cell population is about 10-20 million cells. During the prepubertal and reproductive periods there is a further reduction in oocyte number such that only about 400-500 oocytes actually mature to ovulation (i.e., leave the ovary). The others are lost to cell death (called atresia). The loss of oocytes is the fundamental basis of menopause.

Follicle growth
Each oocyte is surrounded by one to several layers of granulosa cells. This structure is called a follicle. The menstrual cycle in the ovary can be divided into follicular and luteal phases. The follicular phase extends from day 1 (beginning of menses) to day 14. The follicle develops in response to FSH. Granulosa cells of the follicle continue to secrete increasing amounts of estrogen which feeds back in a negative manner to regulate FSH. Plasma FSH levels decline. FSH levels are also regulated by a second hormone, inhibin, secreted by the granulosa cells. Inhibin negatively regulates FSH secretion from the pituitary.

Each month several follicles start to mature but only one is chosen to be ovulated (i.e., expelled from the ovary) for transport to the uterus. This chosen follicle expresses the highest number of FSH and LH receptors. It survives and the others die (atresia).

Between days 12-14, there is a rapid rise in estrogen secretion by the granulosa cells. Now estrogen acts in a positive manner resulting in an increase in kisspeptin within the hypothalamus. The surge of LH production in response to increased estrogen is unique to females. Male brains develop in the presence of testosterone which is converted to estrogen. Increased levels of estrogen in the male brain prevent development of a certain group of neurons in the anteroventral periventricular (AVPV) nucleus of the hypothalamus. However, under conditions of low estrogen during prenatal development as is seen in females, neurons gather in the AVPV which synapse with the cell body of GnRH producing neurons and stimulate GnRH release under increased estrogen levels as occurs during follicular development (Fig. 1). This local rise in kisspeptin increases GnRH secretion and consequently a surge in LH secretion. Thirty six to forty eight hours after the LH surge, ovulation of the chosen ovum occurs.
Luteal phase

The luteal phase of the ovary extends from days 14-28. In the ovary, the now empty chosen follicle converts to a hormone secreting tissue called the corpus luteum. The corpus luteum secretes both estrogen and progesterone. In the luteal phase, estrogen inhibits FSH and LH secretion from the pituitary, as well as GnRH. If fertilization does not occur, then 12-14 days after ovulation, the corpus luteum degenerates and ceases estrogen and progesterone production. The decrease in estrogen and progesterone allows for increased GnRH production to begin the cycle all over again.

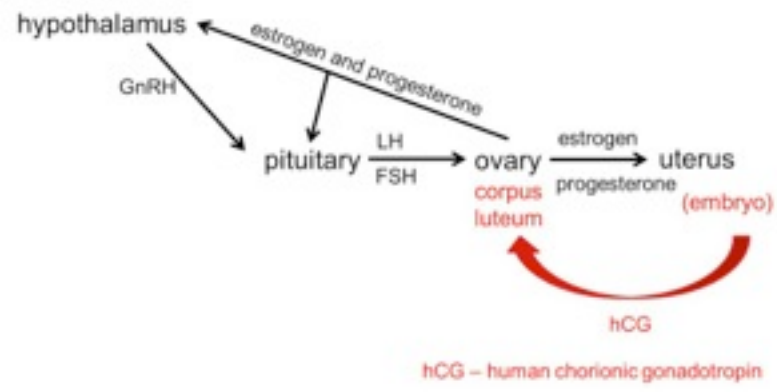
2. The Menstrual Cycle

During the menstrual cycle the hypothalamus, pituitary, ovary, and uterus interact to cause a follicle to mature, egg to be released, and provide a uterus suitable for pregnancy. This is accomplished by the hypothalamus and pituitary exerting control over the ovary while the steroids of the ovary feedback to regulate the hypothalamus and pituitary. The steroids of the ovary are also responsible for initiating and controlling changes that occur in the endometrium of the uterus (Fig. 2).

The Uterus

The menstrual cycle of the ovary causes the uterus to be either proliferative or secretory The uterus proliferative phase (growth phase) is regulated by estrogen during days 1-14 of the menstrual cycle. During this time the uterine wall thickens and uterine glands develop.

The secretory phase of the uterus is regulated by progesterone during days 14-28 of the menstrual cycle. Progesterone prepares the uterus for the possibility of embryo implantation. In the absence of fertilization and implantation, progesterone levels decline late in the menstrual cycle so that by day 28, the uterine glands atrophy and the uterine surface sloughs off. This is due to vascular constriction and enhanced uterine smooth muscle activity. Menses ensues.



Successful implantation and pregnancy requires a continuous production of progesterone. If fertilization and pregnancy occurs, then the newly formed embryo (blastocyst) secretes the hormone, human chorionic gonadotrophin (hCG), which stimulates the corpus luteum to produce estrogen and progesterone during the first trimester of pregnancy (Fig. 3). hCG is used to assess the viability of the fetus and is the basis of the at home pregnancy test. If there is not successful implantation, there is no hCG produced and the corpus luteum degenerates and ceases estrogen and progesterone production. hCG levels increase and peak at 10-12 weeks of pregnancy. Once the hCG levels decrease, 3 months into the

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pregnancy, the corpus luteum regresses. However, estrogen and progesterone levels continue to increase throughout the pregnancy because the placenta produces them.

Mechanisms of action for estrogen
Steroid hormones act as transcription factors in their target tissues. In the uterus and breast, estrogen up-regulates estrogen receptors. In addition, estrogen primes the tissue for progesterone action by increasing the numbers of progesterone receptors expressed. The continual exposure to unopposed estrogen can result in pathological stimulation of these target tissues (cancer of the uterus).

In contrast, progesterone-dependent transcription down-regulates the estrogen receptor (decreases its numbers) thereby facilitating differentiation. Remember that the tissue is sensitive to the hormone only if it expresses the receptor for that hormone.

Oral Contraceptives
Oral contraceptive pills are usually a combination of synthetic estrogen and progesterone. The doses are lower than would be normally found in the body due to a prolonged half-life (4-8 hours versus 20 min). This is accomplished by adding groups such as acetyl or methyl groups which slow metabolism of the synthetic hormones by the liver. They act by inhibiting pituitary secretion of LH (negative feedback) which often prevents ovulation. Some pills, such as progesterone-only pills, are not as effective at preventing ovulation. However, they prevent pregnancy by affecting cervical mucus which prevents sperm from entering the uterus or by making the endometrium unable to facilitate implantation. Periodic withdrawal of steroids is needed to allow for a sloughing of the uterine wall (menstrual flow).