IDP 208 MENSTRUAL CYCLE (summary by Margie Anderson, Prof. of Biol. Sci.).

The purpose of the menstrual cycle is to prepare a woman's reproductive system for pregnancy about once each month. At mid-cycle, an **egg** (ovum) is released (ovulated) from the ovary. If the egg is fertilized by a sperm shortly after ovulation, pregnancy occurs. The egg develops within a **follicle.** Starting out as a **primary follicle** just a little over one thousandth of an inch in diameter at the beginning of the cycle, the follicle grows into a large, fluid-filled sphere as much as ¾ inch across by ovulation. At **ovulation**, the egg -- about 0.1 mm in diameter (the size of a period on this page) -- is released from the follicle. The cells of the follicle left behind in the ovary reorganize into a new structure called the **corpus luteum.** The corpus luteum functions for about 10 days. It degenerates if pregnancy does not occur. If pregnancy does occur, the corpus luteum persists and continues its secretions. Thus, over a single menstrual cycle, the ovary goes through three phases, (1) follicular development (**follicular phase**), (2) **ovulation**, and (3) presence of the corpus luteum (**luteal phase**). (Please refer to the table below and attached figures as you read this summary).

The menstrual cycle also includes functions of the **uterus** that occur in three phases. The uterine phases correspond with the ovarian phases. Menstrual flow occurs in the first days of the cycle (the uterine **menstrual phase**). The average amount of actual blood lost during menstruation is only about half a cup. The remainder of the menstrual discharge consists of components of the inner uterine lining, the **endometrium**. The endometrial tissues and products that would have been used, had fertilization and pregnancy happened, are sloughed away. The endometrium is thinnest at the end of the menstrual phase. Following menstruation, the endometrium thickens again during the uterine **proliferative phase**. It will reach its maximum thickness shortly after ovulation. During the last half of the menstrual cycle, the endometrium secretes substances that produce a lush, hospitable environment for the potential implantation of an embryo. This is the uterine **secretory phase**. If pregnancy does not happen, another cycle is complete, and menstruation occurs again.

The following table summarizes the ovarian and uterine phases of the menstrual cycle. The cycle is typically described as a 28-day (lunar) cycle. However, normal menstrual cycles range from 20-40 days in length.

| **Ovarian phases:** | |
|---|---|
| Follicular | Days 1-14: growth and development of a follicle which contains an ovum (egg); this phase overlaps the uterine *menstrual* and *proliferative* phases. |
| Ovulation | Day 14 |
| Luteal | Days 15-28: the corpus luteum secretes hormones; this phase overlaps the uterine *secretory* phase |
| **Uterine phases:** | |
| Menstrual | Days 1-5: components of the endometrium (inner lining of the uterus) are discharged along with some blood; this phase overlaps the *follicular* ovarian phase |
| Proliferative | Days 5-14: the endometrium grows from ~ 1 mm to ~ 5 mm in thickness and develops new capillaries and glandular structures; this phase overlaps the *follicular* ovarian phase |
| Secretory | Days 15-28: endometrial glands secrete mucus and nutritive substances to produce an environment that would support an embryo, if implantation takes place; this phase overlaps the *luteal* ovarian phase. |

The menstrual cycle is coordinated by hormones released from the brain, pituitary gland, and ovaries. Hormones (from the Greek, "to excite") are released into the blood and carried to distant sites where they exert their effects. Cells in the brain initiate each menstrual cycle by secreting a hormone. **Neuroendocrine cells** of the hypothalamus, a part of the brain located just above the

pituitary gland, secrete **gonadotropin releasing hormone (GnRH).** The neuroendocrine brain cells function like other nerve cells. They make action potentials and graded potentials, but they are specialized to release a hormone into the blood instead of a neurotransmitter at a synapse. Although we don't yet understand the anatomy, we know that the GnRH neuroendocrine cells receive synaptic input from other nerve cells that may signal stress or a variety of other factors that can influence the menstrual cycle. During most of the cycle, the hypothalamic cells secrete GnRH in bursts about once every 1.5 hours.

GnRH travels in small blood vessels that go directly from the hypothalamus to the anterior pituitary gland. In the anterior pituitary, GnRH stimulates secretion of two different hormones, **follicle stimulating hormone (FSH)** and **luteinizing hormone (LH).** These hormones are released into capillaries that lead into larger blood vessels that go to the rest of the body. Even though hormones are carried throughout the circulatory system, they exert their effects only on **target tissues** that possess specific molecular receptors that recognize and bind them. FSH and LH stimulate specific target cells in the ovaries: (i) FSH and LH stimulate the granulosa cells of the ovarian follicles to secrete **estrogen** (the main estrogen produced in the ovary is **estradiol**) during the follicular phase. (ii) LH and FSH stimulate and the corpus luteum of the ovary to secrete **both estrogen and progesterone** during the luteal phase. Thus actions of the ovary are stimulated by a sequence of hormones from hypothalamus → anterior pituitary gland → ovary. We will see that the estrogen and progesterone both exert effects on reproductive structures (such as the uterus and the ovary itself), and they also signal back to the hypothalamus and pituitary gland.

A girl infant is born with all the eggs (ova) she will ever produce -- about 250,000 to 500,000 per ovary. About 400 of these will mature and be ovulated over her reproductive years. With each cycle, several follicles, each containing an ovum, begin to develop. Midway through the follicular phase all but one (or two, in the case of fraternal twins) degenerate. Initially, the follicle consists of the ovum surrounded by a layer of **granulosa cells.** As the follicle develops, the granulosa cells increase in number, and they secrete a gel-like layer around the ovum called the **zona pellucida.** Later an outer layer of cells, the **theca,** forms around the follicle. As the follicle grows in size, a fluid-filled space, the **antrum,** forms at its center. At this stage, the follicle is a fluid-filled sphere. The wall of the sphere is made up of an outer layer of theca cells and an inner layer of granulosa cells. The ovum, in a cloud of granulosa cells, points into the antrum like a little pimple. Both the granulosa cells and the theca cells secrete hormones.

The development of the follicle requires about two weeks, the duration of the follicular phase. At ovulation, the ovum is expelled from the ovary. The **oviducts** extending upward from the uterus to the ovaries are open at their ends close to the ovaries. Like a trapeze artist, the ovum leaps from the ovary through space into the open end of the oviduct. The oviduct possesses cilia that beat downward, creating a current that sweeps the ovum into the oviduct. The trip to the uterus takes about four days. The ovum remains fertile about 10 - 15 hours. Therefore, fertilization, if it is to occur, must occur in the oviduct. After ovulation, the remainder of the follicle left in the ovary develops into the corpus luteum, which is present for the luteal phase of the menstrual cycle.

***The follicular phase* of the ovary overlaps with the *menstrual and proliferative phases* of the uterus.** We will now consider more details of the main hormones coordinating these phases. Starting at the beginning of the menstrual cycle, **LH** (secreted in response to hypothalamic GnRH) travels from the anterior pituitary to the ovary and stimulates the **theca cells** to *proliferate* (divide by mitosis and become more numerous) and also to produce androgens (a collective term for male sex steroids such as testosterone. *Yes, male hormones are made by the female ovary and adrenal*

*glands*). These androgens diffuse out of the theca cells into the granulosa cells. At the same time the theca cells are responding to LH, the **granulosa cells** are being signaled by **FSH** to convert the androgens into estrogen. The end result is that the developing follicle secretes estrogen in response to hormonal signals from the brain and pituitary gland.

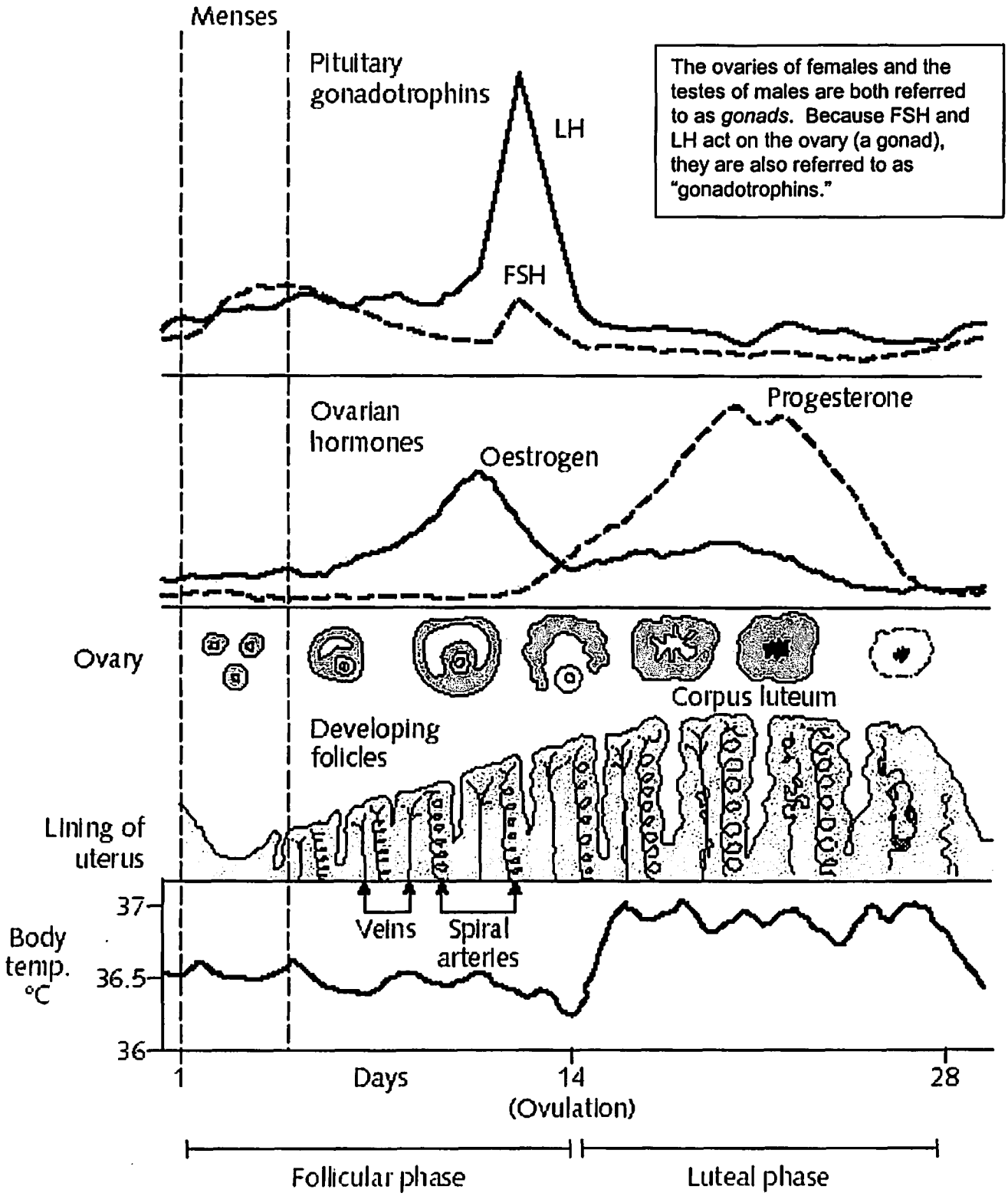
Estrogen from the granulosa cells exerts effects in the ovary and also enters the bloodstream which carries it to other target organs. Its concentration in the blood stays low for the first part of the cycle. In **low concentration**, estrogen signals back on the pituitary and hypothalamus to keep GnRH, FSH, and LH secretion at low levels. The granulosa cells also secrete another hormone, inhibin, in addition to estrogen. Inhibin's effect is to inhibit the secretion of FSH by cells in the pituitary. During the late follicular phase, estrogen secretion increases significantly. The reason is that estrogen secreted by existing granulosa cells stimulates these cells to proliferate. As more cells are made, each one secreting estrogen, a snowball-effect occurs, causing a rapid increase in both the number of granulosa cells and the total amount of estrogen produced.

What is all this estrogen doing? Estrogen performs important functions at three locations: (1) At the uterus, after menstruation is complete, estrogen stimulates the endometrium to thicken. Thickening of the endometrium occurs during the *uterine proliferative phase*. (2) At the ovary, in the mid-to-late follicular phase, the estrogen acting in concert with FSH stimulates the granulosa cells to develop receptors for the hormone LH, which is secreted by the anterior pituitary. (3) At the hypothalamus in the late follicular phase, estrogen in **high concentrations** causes the GnRH-secreting cells to increase the frequency of pulses of GnRH. With increased GnRH coming from the hypothalamus, the LH-secreting cells of the anterior pituitary put out a huge surge of LH. This hormone triggers ovulation.

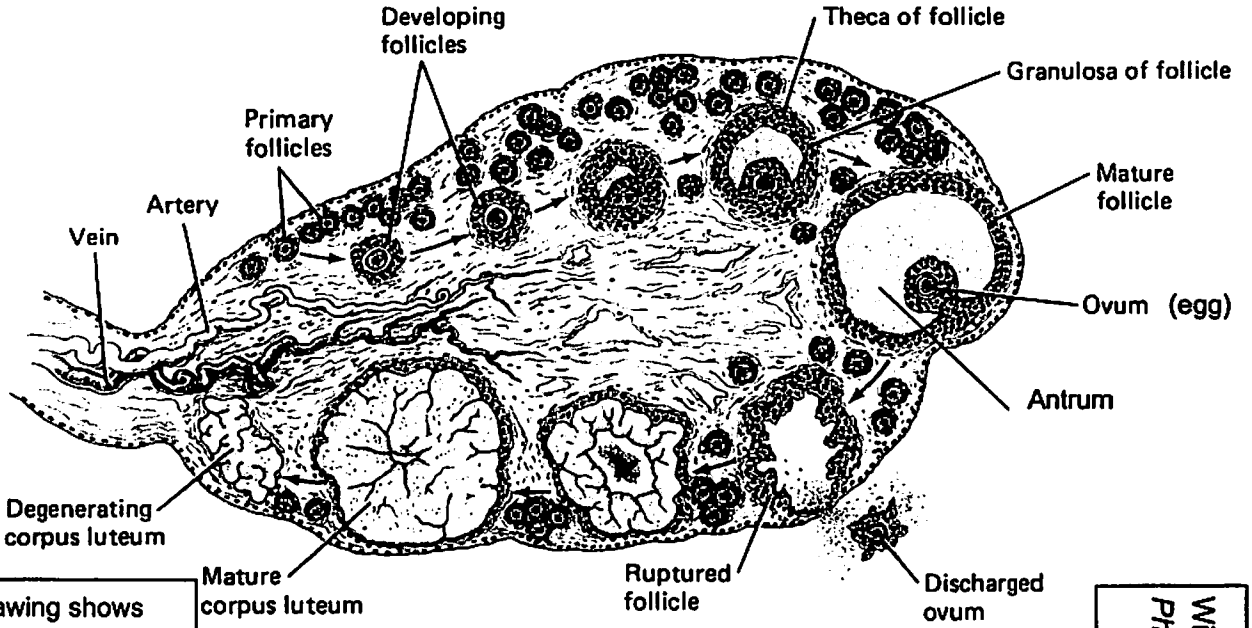
***Ovulation.*** Within hours, LH exerts dramatic effects on the ovary. It ♦stimulates the accumulation of fluid in the antrum of the follicle so that it balloons from the surface of the ovary, and it ♦causes secretion of enzymes which break the membranes at the point where the follicle bulges up against the surface of the ovary so that the ovum can escape. These events cause the expulsion of the egg from the follicle and send it on its trip to the uterus. A woman may feel some discomfort or cramping at the time of ovulation. This is referred to as "mittelschmerz," from the German "middle" (of the cycle) "pain." The LH also ♦causes the granulosa cells to decrease their production of estrogen, and ♦triggers the granulosa cells of the collapsed follicle to transform into luteal cells of the corpus luteum. Within a matter of hours, what was the follicle switches its functions from supporting the development of an egg (ovum) in the follicular phase to supporting a possible pregnancy (if fertilization occurs) in the luteal phase.

***The luteal phase*** **of the ovary overlaps with the** ***secretory phase*** **of the uterus**, and new hormonal actions emerge. The LH-surge is over. The pituitary continues to secrete a small amount of LH which maintains the corpus luteum. The corpus luteum secretes estrogen (not in as great quantity as secreted earlier by the follicle), progesterone and inhibin. Progesterone is the dominant hormone during the last part of the menstrual cycle. Traveling in the blood to the uterus, progesterone stimulates the thickened endometrium to secrete mucus, accumulate nutrients, and develop blood vessels – all in readiness for the possibility of implantation. Thus, progesterone supports the *uterine secretory phase*. Traveling to the hypothalamus and pituitary gland, progesterone and estrogen together strongly inhibit the secretion of GnRH, FSH and LH. Without GnRH, LH and FSH, follicles in the ovary are not stimulated to mature. All is quiet, waiting to see if fertilization and implantation take place.

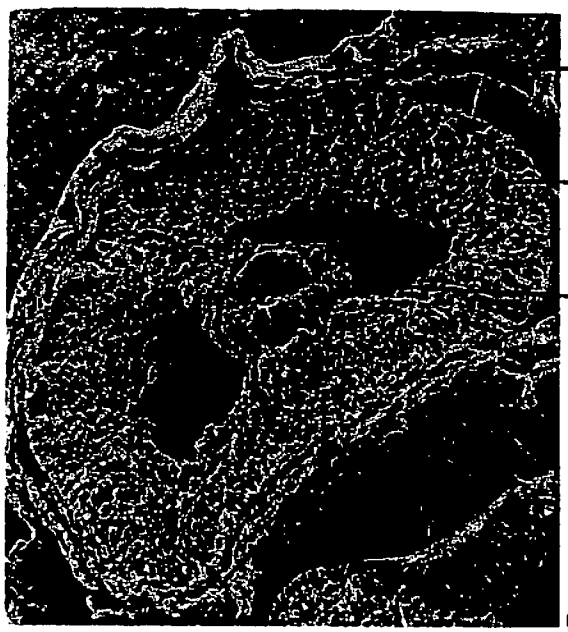
After about ten days, if implantation does not happen, the corpus luteum degenerates. Estrogen and progesterone concentrations drop. Progesterone no longer supports the endometrium, which breaks down and is given off with menstrual blood. Now that the corpus luteum no longer secretes progesterone and estrogen, these two hormones no longer inhibit secretion of GnRH from the hypothalamus and LH and FSH from the anterior pituitary. Renewed secretions of GnRH, LH, and FSH stimulate a new cohort of follicles to develop in the ovary, and a new cycle begins. If implantation happens, exciting and amazing events of embryonic development begin. That's another story.




http://content.answers.com/main/content/img/oxford/Oxford_Body/019852403x.menstrual-cycle.1.jpg




(a) Cross section of ovary

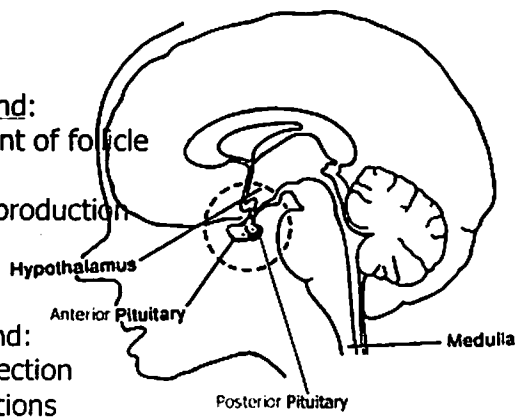



(b) Developing follicle

(a) The drawing shows the structures seen in a section of the ovary. At any time of the month, many follicles and corpora lutea are present in different stages of development. Mature and ovulating follicles appear only during the middle of the menstrual cycle.
(b) This scanning electron micrograph shows the egg (enclosed within the zona pellucida and surrounded by granulosa cells) projecting into the antrum. The wall of the follicle consists of more granulosa cells, which are surrounded by a tissue layer called the theca.

Witherspoon, J.D. *Human Physiology*, p. 324. 1984.

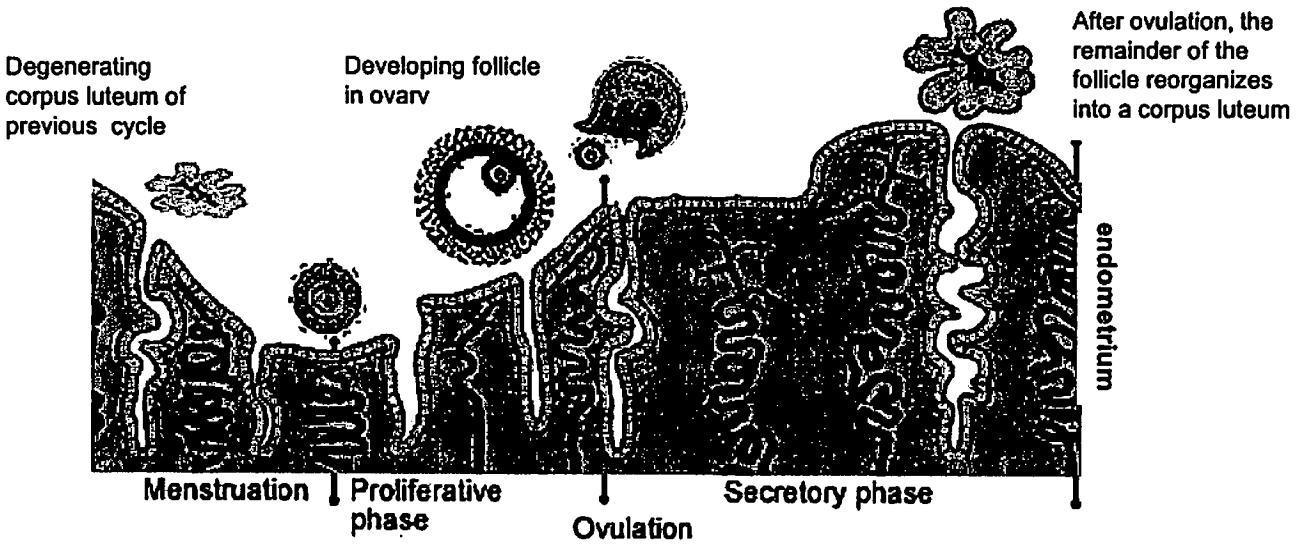
The **pituitary gland** lies above the roof of the mouth, and the **hypothalamus** (a part of the brain) lies above the pituitary gland. The anterior and posterior parts of the pituitary gland secrete several different hormones. Those listed here contribute to reproduction. Hormones secreted by nerve cells in the hypothalamus travel in a special set of blood vessels called *portal vessels* to the anterior pituitary gland. The hypothalamic hormones either stimulate or inhibit the gland cells in the anterior pituitary to secrete their hormones.

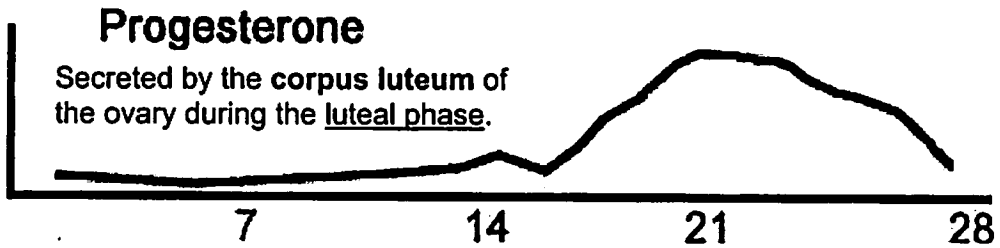



Anterior pituitary gland:
**FSH** – development of follicle
**LH** – ovulation
**prolactin** – milk production

Posterior pituitary gland:
**oxytocin** – milk ejection
(also unterine contractions during birth and encouraging parental care of offspring

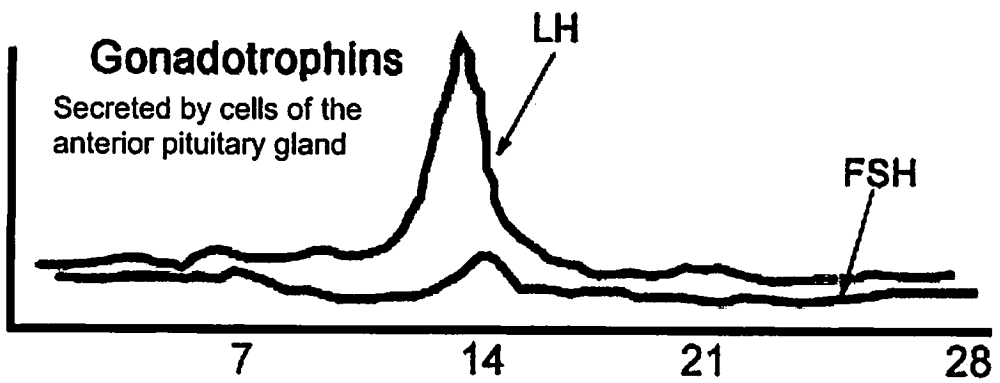
## Changes in the Ovary & Endometrium during the menstrual cycle





Oestrogen = estrogen. Secreted by the **follicle** of the ovary during the follicular phase and the corpus luteum during the luteal phase..




http://www.elu.sgul.ac.uk/rehash/example/reproduction_anatomy_physiology/female/menstrualcycle.htm

FYI: Go to Google, and type in "menstrual cycle". You'll have an opportunity to click on "image results for menstrual cycle." This image, plus many more, are available for your viewing.