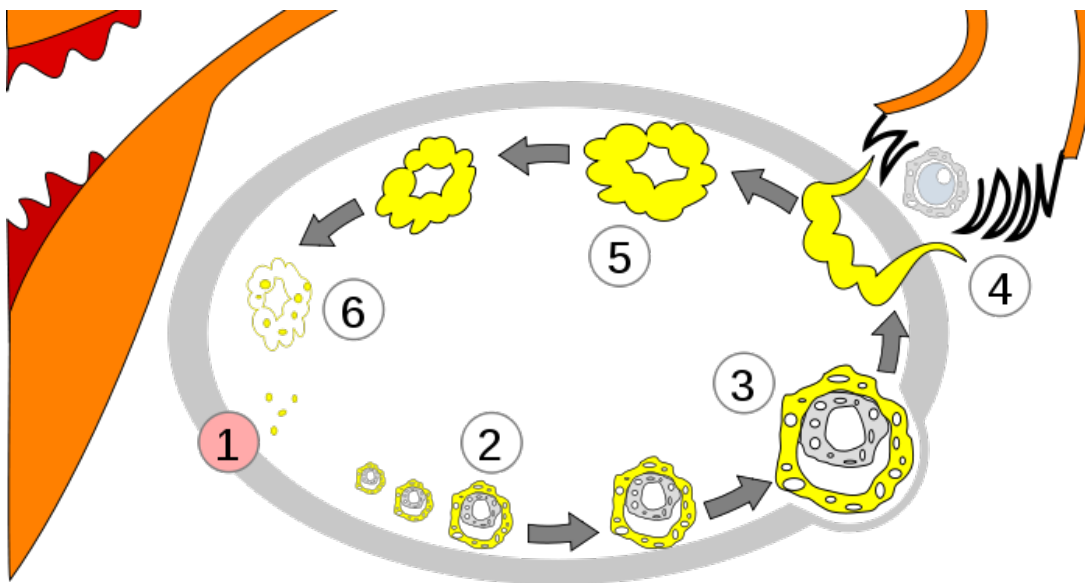


## Physiological Effects of Estradiol and Progesterone: Menstrual and Endometrial Cycle

[See online here](#)

The female reproductive system consists of two ovaries, two fallopian tubes, the uterus, cervix, and external genitalia. Women undergo a monthly cycle of 28 days, in which an ovum is released from either ovary and the endometrium is prepared for the implantation of an embryo, which eventually sheds if fertilization does not occur. This normal physiological mechanism is controlled by a number of hormones secreted by the hypothalamus, pituitary gland, and ovaries. Any aberration in the release of these hormones may result in abnormalities in the menstrual cycle or infertility.

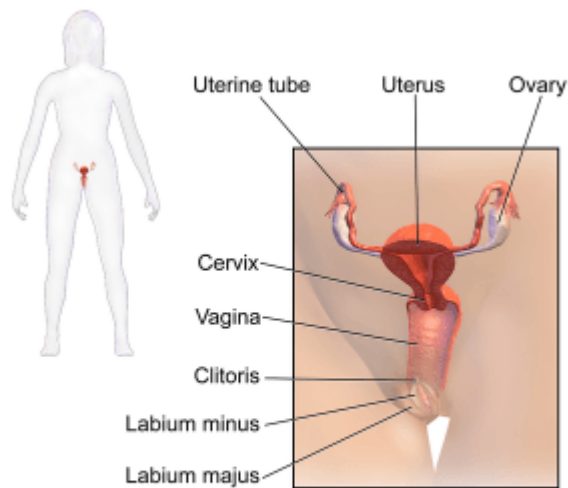


### Role of Estradiol

The ovaries secrete the **hormones, estradiol (estrogen) and progesterone**, which play important roles in the female reproductive cycle.

**Estradiol** is the most common type of estrogen in women of reproductive age. During childhood, the amount of estradiol secreted by the ovaries is minimal. When puberty is attained, there is a 20-fold increase in estradiol levels.

This phenomenon occurs under the influence of the **pituitary gonadotropic hormones**. Estradiol plays an important role in the development of **primary and secondary female sexual characteristics**, some of which are highlighted below.



## The Female Reproductive System

Bild: "Female Reproductive System" von BruceBlaus. Lizenz: [CC BY 3.0](#)

Estradiol brings about an overall increase in the size of female reproductive organs and external genitalia. It causes the deposition of fat in the **mons pubis** and **labia majora** and the enlargement of the **labia minora**.

The **vaginal epithelium** changes from cuboidal to the stratified type, which provides resistance to external stress. Young girls are often prescribed estrogen creams for local application to prevent recurrent genital tract infections.

The size of the uterus increases to three times its size. There is a marked **proliferation of endometrial stroma** and the development of **endometrial glands** during each menstrual cycle.

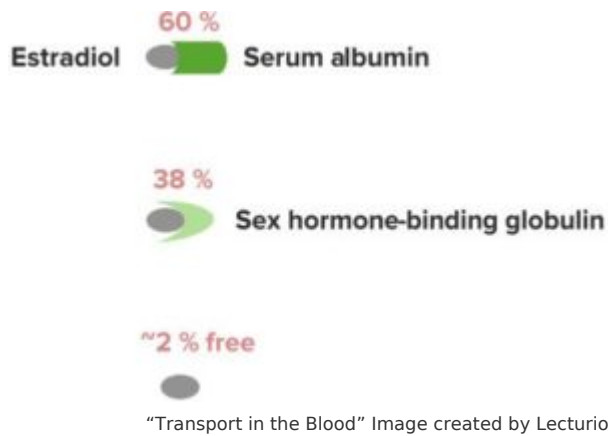
The **glandular tissues in the fallopian tube** proliferate with an increase in the number of ciliated epithelial cells. The cilia become more active and propel the **ovum** towards the uterus. This maximizes the chances of fertilization.

**Breast enlargement** occurs under the influence of estradiol along with the deposition of fat and development of stromal tissues and the ductile system. Estradiol, however, does not cause lactation.

**Osteoblastic activity** increases under the influence of estradiol and causes an overall increase in height during puberty. There is also an early union of epiphyses with the shaft of long bones. The increase in the height in women, therefore, ceases after a few years as compared to men. **Osteoporosis** in older women after **menopause** is due to the deficiency of estrogen. **Hormone replacement therapy** is often indicated in this condition.

The protein levels in the body increase as a result of an **enlargement of the sexual organs**. At the cellular level, estradiol increases RNA transcription, and consequently, protein synthesis.

Estradiol increases **the vascularity of the skin** and gives it a **soft texture**. Hair distribution on the skin is not brought about by estrogens but controlled by the **androgens** produced by the adrenal glands.



Estradiol, like other **adrenocortical hormones**, causes **sodium** and **water** retention; however, this effect is slight and goes unnoticed in women who are not pregnant.

Estrogen receptors are either the traditional cytosolic-nuclear complex type (similar to other steroid hormones) or less commonly, the cell-membrane type.

## Effects of estradiol

Tissue	Effects
Bone	↑ functional capacity of osteoblasts
Endocrine	↑ progesterone responses
Liver	<ul style="list-style-type: none"> <li>• ↑ clotting factors</li> <li>• ↑ steroid-binding proteins               <ul style="list-style-type: none"> <li>• ↓ LDL</li> <li>• ↑ HDL</li> </ul> </li> </ul>
Reproductive organs	<ul style="list-style-type: none"> <li>• ↑ uterine growth</li> <li>• ↑ vaginal and fallopian-tube growth               <ul style="list-style-type: none"> <li>• ↑ breast growth</li> </ul> </li> <li>• ↑ cervical mucus secretion</li> <li>• ↑ luteinizing hormone (LH) receptors on granulosa cells</li> </ul>

## Role of Progesterone

Progesterone, an important **ovarian hormone** playing a role in the female reproductive cycle, is responsible for several other functions as listed below.

It promotes the secretory functions of the **uterine endometrium**, which prepares the endometrium for implantation of the **fertilized ovum** in the second half of the menstrual cycle.

The secretory functions of the **lining of the fallopian tubes** are also enhanced to nourish the dividing zygote after fertilization.

The development of **lobules and alveoli of the breasts** is regulated by progesterone. These lobules and alveoli become secretory in nature; however, they are unable to produce milk without the action of the **hormone, prolactin**.

Progesterone in large amounts may enhance **reabsorption of sodium, chloride, and water** from the distal tubules of the **kidney**.

## Effects of progesterone

Tissue	Effects
Breast	<ul style="list-style-type: none"><li>• ↑ lobular development</li><li>• ↓ milk production</li></ul>
Reproductive organs	<ul style="list-style-type: none"><li>• ↓ endometrial growth</li><li>• ↑ endometrial secretions</li><li>• ↑ thickness of mucosal secretions</li></ul>
Temperature	↑ internal temperature

## Endometrial and Ovarian Cycles

The endometrial cycle lasts 28 days, on average, in women of reproductive age and is characterized by the **shedding of the endometrial lining of the uterus**. This process of the loss of endometrial lining is called **menstruation**.

Another important event occurring during this cycle is the **release of a mature follicle or ovum** from one of the two ovaries. This process is known as **ovulation**. Both menstruation and ovulation occur under the rhythmic control of the **hypothalamic, pituitary, and ovarian hormones**.

The menstrual cycle primarily consists of the **proliferative** and **secretory phases**. This may be followed by menstruation if fertilization does not occur.

### Proliferative phase (estrogen phase)

The **primordial follicle**, in which the **ovum** is surrounded by a single layer of **granulosa cells**, remains inhibited by the **oocyte-maturation inhibiting factor** in childhood.

At puberty, when the **pituitary gland** starts producing **LH** and **follicle-stimulating hormone (FSH)**, the process of follicular growth is initiated. FSH causes an increase in the number of granulosa cell layers around the ovum, converting it to the **primary follicle**. It is responsible for the growth of 5–6 primary follicles each month. The rise in FSH levels precedes that of LH by a few days. Spindle cells from the interstitium of the ovary surround the granulosa cells to form a layer of cells called theca.

**The theca** differentiates into two layers, namely, the **theca interna** and **theca externa**. The latter becomes the outer capsule of the developing follicle. After a few days, the granulosa cells secrete a **follicular fluid** that forms the **antrum**. This follicular fluid secretes estrogen, which increases the FSH receptors on granulosa cells, thereby creating a **positive feedback response**.

After a week of initial growth, one growing follicle outgrows all others. The other follicles undergo **atresia**. The growing follicle starts producing more estrogen, which causes a surge in LH, leading to the release of the ovum from the ovary on approximately day 14 of the cycle.

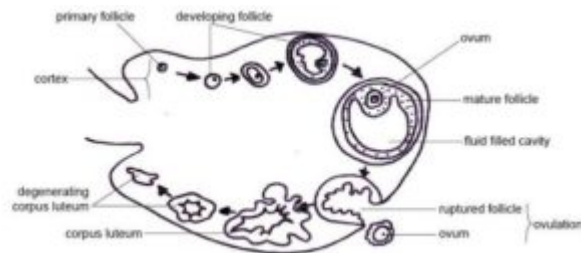
After the previous menstruation cycle, most of the endometrial lining is desquamated and only a deep layer is left behind. Under the influence of estrogen secreted by the ovaries, the **stromal** and **epithelial cells** proliferate.

The **endometrial thickness** is regained within 4–7 days following menstruation. There is an increase in the number of stromal cells, growth of **endometrial glands**, and an increase in **vasculature**. This process continues until **ovulation** occurs, during which, the endometrium is approximately 3–4 mm thick. During ovulation, the **cervical glands**

secrete **thin, stringy mucus** which forms channels to direct **sperm** towards the **uterus for fertilization**.

## Secretory phase (progesterone phase)

After ovulation, a **corpus luteum that consists of granulosa and theca cells** is formed in its place. The corpus luteum secretes high levels of estrogen and progesterone. While estrogen causes further proliferation of the stromal cells of the epithelial lining of the uterus, progesterone is responsible for the secretory development of these cells.



**Image:** "Development Stages of the Ovarian Follicle." by The original uploader was Sunshineconnelly at English Wikibooks - Transferred from en.wikibooks to Commons by Adrignola using CommonsHelper. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

The blood supply to the **endometrium** increases and the **blood vessels** become increasingly tortuous. The '**uterine milk**' secreted by the endometrium nourishes the fertilized ovum. In addition, there is **lipid and glycogen deposition** in the cytoplasm of the stromal cells. The endometrium is thus prepared for the implantation of the embryo.

If **implantation** occurs, the **trophoblasts forming the outer** lining the **blastocyst** digest the endometrial cells and absorb the stored substances. The lining of the endometrium is 5-6 mm thick at the end of the secretory phase. The adjoining figure illustrates the developmental stages of the ovarian follicle.

## Menstruation

The levels of estrogen and progesterone decline two days prior to the end of the menstrual cycle. The hormonal effect on the endometrial lining diminishes. It is followed by the **involution of the endometrium** to 65% of its previous thickness. This causes **vasospasm** of the tortuous blood vessels. High levels of **prostaglandins** released at this stage are also responsible for the vasospastic response.

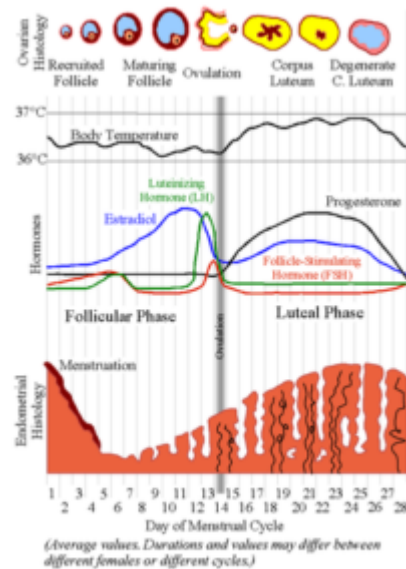


Image: "Menstrual Cycle." by Lyrl - Derived from Image: MenstrualCycle.png, an image made by the user Chris 73. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

These phenomena collectively lead to **necrosis of the endometrium**, especially the **stratum vasculare**. Blood sweeps into the vascular layer of the endometrium, thereby creating **hemorrhagic areas**. Within 48 hours, this hemorrhagic layer is desquamated from the uterus. The contractile effect of prostaglandins initiates **uterine contractions** and causes expulsion of the superficial layers of the endometrium.

Approximately 40 mL of blood and 30 mL of serous fluid are lost during menstruation. The **fibrinolysin** present in blood prevents blood clotting; however, if excessive bleeding occurs, the fibrinolysin becomes insufficient and blood clots may be seen. Normal menstrual flow lasts 3–7 days.

**Leukorrhea** during menstruation is a normal physiological phenomenon that prevents infection. The endometrium becomes resistant to microbes despite being denuded. The image alongside gives a detailed account of the menstrual cycle.

## Regulation of the Menstrual Cycle

The interplay between the ovarian and hypothalamic-pituitary hormones is summarized in this section.

The **hypothalamus** is connected to the **pituitary gland** by the **hypothalamic-hypophyseal portal system**. The former secretes **gonadotropin-releasing hormone (GnRH)** in a pulsatile manner. This, in turn, results in the pulsatile release of **LH** by the pituitary gland. To some extent, **FSH levels** are also influenced by the pulsatile release of GnRH; however, the effect is more prolonged.

**Estrogen** initially has a **suppressive effect on FSH and LH**. Just before ovulation, there is a two-fold and six-fold increase in the levels of FSH and LH secreted by the pituitary gland, respectively. This is known as the **LH surge** and is mandatory for ovulation to occur. Estrogen has a positive feedback effect.

After ovulation, **progesterone** and **estrogen** secreted by the **corpus luteum** have a negative feedback effect and decrease the production of LH and FSH. However, when the

corpus luteum involutes just before menstruation, the levels of estrogen and progesterone begin to fall. This phenomenon reinitiates the production of FSH and LH for the subsequent cycle.

**Inhibin** is another hormone that works synergistically with estrogen and progesterone in lowering the production of FSH. However, it does not play a significant role in lowering the amount of GnRH released by the hypothalamus.

## Menstrual/Ovarian Cycle Disorders

- **Anovulation** (absence of ovulation): Occurs during the first few cycles of puberty or prior to menopause; anovulation is also seen in **polycystic ovarian syndrome** and is the most common cause of primary **infertility** among women
- **Oligo-ovulation**: Irregular ovulatory cycles
- **Amenorrhea** (absence of menstruation): Can either be primary, in which a woman has never menstruated, or secondary, in which there is a cessation of menstruation after the start of normal menstruation
- **Oligomenorrhea**: Scanty menstrual flow with cycle length > 35 days
- **Polymenorrhea**: Frequent menses with each cycle lasting < 22 days
- **Menorrhagia**: Excessive menstrual bleeding
- **Dysmenorrhea**: Lower abdominal pain during the menstrual cycle

## References

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Hall, J., Guyton, A. Guyton & Hall physiology review. Philadelphia: Elsevier Saunders; 2006.

Silverthorn, D., Johnson, B. Human physiology. San Francisco: Pearson/Benjamin Cummings; 2010.

**Correct answers:** 1B, 2B, 3A, 4A

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