Normal menstrual cycle

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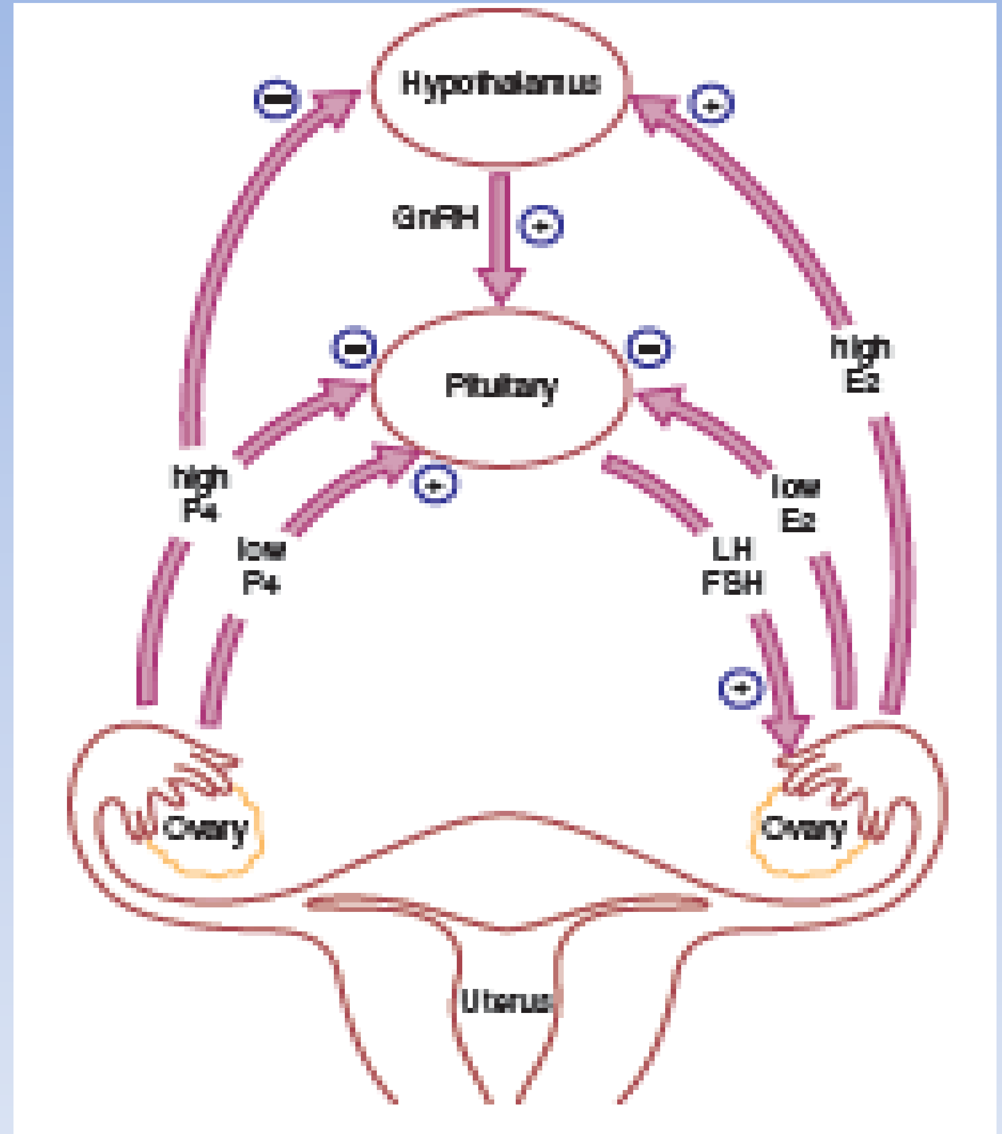
- The external manifestation of a normal menstrual cycle is the presence of regular vaginal bleeding. This occurs as a result of the shedding of the endometrial lining following failure of fertilization of the oocyte or failure of implantation. The cycle depends on changes occurring within the ovaries and fluctuation in ovarian hormone levels, that are themselves controlled by the pituitary and hypothalamus, the **hypothalamo–pituitary–ovarian axis (HPO)**

- **Hypothalamus**
- The hypothalamus in the forebrain secretes the peptide hormone gonadotrophin-releasing hormone **(GnRH**), which in turn controls pituitary hormone secretion. GnRH must be released in a pulsatile fashion to stimulate pituitary secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). If GnRH is given in a constant high dose, it desensitizes the GnRH receptor and reduces LH and FSH release

- **Pituitary gland**
- Low levels of oestrogen have an inhibitory effect on LH production (negative feedback), where as high levels of oestrogen will increase LH production (positive feedback). The high levels of circulating oestrogen in the late follicular phase of the ovary act via the positive feedback mechanism to generate a periovulatory LH surge from the pituitary. low levels of progesterone have a positive feedback effect on pituitary LH and FSH secretion (as seen immediately prior to ovulation) and contribute to the FSH surge. High levels of progesterone, as seen in the luteal phase, inhibit pituitary LH and FSH production.

Inhibin and activin are peptide hormones produced by granulosa cells in the ovaries, with opposing effects on gonadotrophin production. Inhibin inhibits pituitary FSH secretion, whereas activin stimulates it.



- **Ovary**
- Ovaries with developing oocytes are present in the female fetus from an early stage of development. By the end of the second trimester *in utero*, the number of oocytes has reached a maximum and they arrest at the first prophase step in meiotic division. No new oocytes are formed during the female lifetime.
- With the onset of menarche, the primordial follicles containing oocytes will activate and grow in a cyclical fashion, causing ovulation and subsequent menstruation in the event of non-fertilization

- **Follicular phase**
- The initial stages of follicular development are **independent** of hormone stimulation. FSH levels rise in the first days of the menstrual cycle, when oestrogen, progesterone and inhibin levels are low.
- there are two cell types theca and the granulosa cells. LH stimulates production of androgens from cholesterol within theca cells. These androgens are converted into oestrogens by the process of aromatization in granulosa cells, under the influence of FSH.

As the follicles grow and oestrogen secretion increases, there is negative feedback on the pituitary to decrease FSH secretion. This assists in the selection of one follicle to continue in its development towards ovulation – **the dominant follicle**. In the ovary, the follicle which has the most efficient aromatase activity and highest concentration of FSH-induced LH receptors will be the most likely to survive as FSH levels drop, while smaller follicles will undergo **atresia**.

- There are other autocrine and paracrine mediators playing a role in the follicular phase of the menstrual cycle. These include **inhibin and activin**.
- Insulin-like growth factors (**IGF-I, IGF-II**) act as paracrine regulators. Circulating levels do not change during the menstrual cycle, but follicular fluid levels increase towards ovulation, with the highest level found in the dominant follicle.
- In the follicular phase, IGF-I is produced by theca cells under the action of LH. Within the theca, IGF-I augments LH-induced steroidogenesis.

- In granulosa cells, IGF-I augments the stimulatory effects of FSH on mitosis, In the preovulatory follicle, IGF-I enhances LH-induced progesterone production from granulosa cells. Following ovulation, IGF-II is produced from luteinized granulosa cells, and acts in an autocrine manner to augment LH-induced proliferation of granulosa cells.

- **Kisspeptins** are proteins which have more recently been found to play a role in regulation of the HPO axis, via the mediation of the metabolic hormone leptin’s effect on the hypothalamus. **Leptin** is thought to be key in the relationship between energy production, weight and reproductive health. Mutations in the kisspeptin receptor, are associated with delayed or absent puberty,

- **Ovulation**
- By the end of the follicular phase, which lasts an average of 14 days, the dominant follicle has grown to approximately 20 mm in diameter. As the follicle matures, Production of oestrogen increases until they reach the necessary threshold to exert a positive feedback effort on the hypothalamus and pituitary to cause the **LH surge**. This occurs over 24–36 hours, during which time the LH-induced luteinization of granulosa cells in the dominant follicle causes progesterone to be produced, causing a small periovulatory rise in FSH.

- The LH surge is one of the best predictors of imminent ovulation,
- The LH surge has another function in stimulating the **resumption of meiosis** in the oocyte just prior to its release.
- The physical ovulation of the oocyte occurs after breakdown of the follicular wall occurs under the influence of LH, FSH and progesterone

proteolytic enzymes, such as plasminogen activators

- **Luteal phase**
- After the release of the oocyte, the remaining granulose and theca cells on the ovary form the **corpus luteum.**
- The granulosa cells have a vacuolated appearance with accumulated yellow pigment, hence the name corpus luteum (‘yellow body’). The corpus luteum undergoes extensive vascularization in order to supply granulosa cells with a rich blood supply for continued steroidogenesis.
- Progesterone levels are at their highest in the cycle during the luteal phase. This also has the effect of suppressing FSH and LH secretion to a level that will not produce further follicular growth in the ovary during that cycle.

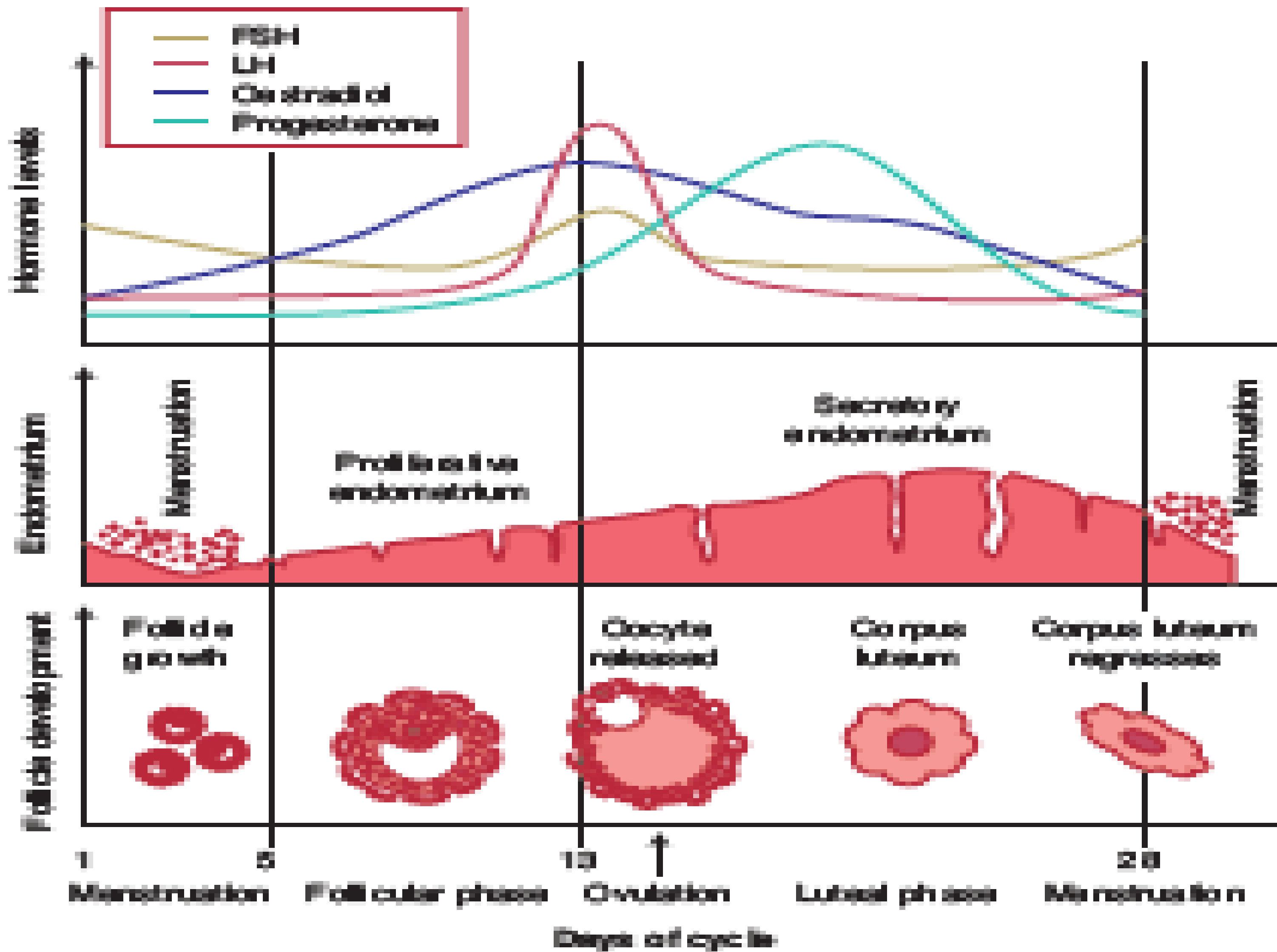
The luteal phase lasts 14 days in most women without great variation. In the absence of beta human chorionic gonadotrophin (bHCG) being produced from an implanting embryo, the corpus luteum will regress in a process known as luteolysis. The withdrawal of progesterone has the effect on the uterus of causing shedding of the endometrium and thus menstruation. Reduction in levels of progesterone, oestrogen and inhibin feeding back to the pituitary cause increased secretion of gonadotrophic hormones, particularly FSH. New preantral follicles begin to be stimulated and the cycle begins anew.

- Menstruation
- The endometrium is under the influence of sex steroids that circulate in females of reproductive age. During the ovarian follicular phase, the endometrium undergoes proliferation (the ‘**proliferative phase’**); during the ovarian luteal phase, it has its ‘**secretory phase’.**

- **The proliferative phase**
- Menstruation will normally cease after 5–7 days, once endometrial repair is complete. After this time, the endometrium enters the proliferative phase, when glandular and stromal growth occur. The epithelium lining the endometrial glands changes from a single layer of columnar cells to a pseudostratified epithelium with frequent mitoses. The stroma is infiltrated by cells derived from the bone marrow . Endometrial thickness increases rapidly, from 0.5 mm at menstruation to 3.5–5 mm at the end of the proliferative phase.

- **The secretory phase**
- After ovulation (generally around day 14), there is a period of endometrial glandular secretory activity ,the endometrial glands will become more tortuous, spiral arteries will grow, and fluid is secreted into glandular cells and into the uterine lumen. Later in the secretory phase, progesterone induces the formation of a temporary layer, known as the **decidua,** in the endometrial stroma. Stromal cells show increased mitotic activity, nuclear enlargement and generation of a basement membrane

- Immediately prior to menstruation, three distinct layers of endometrium can be seen. The **basalis** is the lower 25 per cent of the endometrium, which will remain throughout menstruation and shows few changes during the menstrual cycle. The mid-portion is the **stratum spongiosum** with oedematous stroma and exhausted glands. The superficial portion (upper 25 per cent) is the **stratum compactum** with prominent decidualized stromal cells. On the withdrawal of both oestrogen and progesterone, the decidua will collapse, with vasoconstriction and relaxation of spiral arteries and shedding of the outer layers of the endometrium



FSH
LH
Oestradiol
Progesterone
Hormone levels
Endometrium
Menstruation
Proliferative endometrium
Secretory endometrium
Menstruation
Follicle development
Follicle growth
Oocyte released
Corpus luteum
Corpus luteum regression
1
5
28
Menstruation
Follicular phase
Ovulation
Luteal phase
Menstruation
Days of cycle

Thank you