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CHANGES IN CERVIX DURING MENSTRUAL CYCLE

Mucus membrane of the cervix also shows cyclic changes during different phases of menstrual cycle.

Proliferative Phase

During proliferative phase, the mucus membrane of cervix becomes thinner and more alkaline due to the influence of estrogen. It helps in the survival and motility of spermatozoa.

Secretory Phase

During secretory phase, the mucus membrane of cervix becomes more thick and adhesive because of actions of progesterone.

VAGINAL CHANGES DURING MENSTRUAL CYCLE

Proliferative Phase

Epithelial cells of vagina are cornified. Estrogen is responsible for this.

Secretory Phase

Vaginal epithelium proliferates due to the actions of progesterone. It is also infiltrated with leukocytes. These two changes increase the resistance of vagina for infection.

DEFINITION

Menstrual cycle is defined as cyclic events that take place in a rhythmic fashion during the reproductive period of a woman's life. Menstrual cycle starts at the age of 12 to 15 years, which marks the onset of puberty. The commencement of menstrual cycle is called menarche.

Menstrual cycle ceases at the age of 45 to 50 years. Permanent cessation of menstrual cycle in old age is called menopause.

DURATION OF MENSTRUAL CYCLE

Duration of menstrual cycle is usually 28 days. But, under physiological conditions, it may vary

between 20 and 40 days.

CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, series of changes occur in ovary and accessory sex organs.

These changes are divided into 4 groups:

1. Ovarian changes
2. Uterine changes
3. Vaginal changes
4. Changes in cervix.

All these changes take place simultaneously.

OVARIAN CHANGES DURING MENSTRUAL CYCLE

Changes in the ovary during each menstrual cycle occur in two phases:

A. Follicular phase

B. Luteal phase.

Ovulation occurs in between these two phases.

FOLLICULAR PHASE

Follicular phase extends from the 5th day of the cycle until the time of ovulation, which takes place on 14th day. Maturation of ovum with development of ovarian follicles takes place during this phase.

Ovarian Follicles

Ovarian follicles are glandular structures present in the cortex of ovary. Each follicle consists of the ovum surrounded by epithelial cells, namely granulosa cells. The follicles gradually grow into a matured follicle through various stages.

Different follicles:

1. Primordial follicle
2. Primary follicle
3. Vesicular follicle
4. Matured follicle or graafian follicle.

1. Primordial Follicle

At the time of puberty, both the ovaries contain about 400,000 primordial follicles. Diameter of the primordial follicle is about 15 to 20 μ and that of ovum is about 10 μ. Each primordial follicle has an ovum, which is incompletely surrounded by the granulosa cells

These cells provide nutrition to the ovum during childhood. Granulosa cells also secrete the oocyte maturation inhibiting factor, which keeps ovum in the immature stage. All the ova present in the ovaries are formed before birth. No new ovum is developed after birth.At the onset of puberty, under the influence of FSH and LH the primordial follicles start growing through various stages.

2. Primary Follicle

Primordial follicle becomes the primary follicle, when ovum is completely surrounded by the granulosa cells. During this stage, the follicle and the ovum increase in size. Diameter of the follicle increases to 30 to 40 μ and that of ovum increases to about 20 μ. The follicle is not covered by a definite connective tissue capsule. Changes taking place during development of primary follicle

i. Proliferation of granulosa cells and increase in size of the follicle

ii. Increase in size of the ovum

iii. Onset of formation of connective tissue capsule around the follicle.

Primary follicles develop into vesicular follicles.

3. Vesicular Follicle

Under the influence of FSH, about 6 to 12 primary follicles start growing and develop into vesicular follicles. Changes taking place during the development of vesicular follicle

i. Changes in granulosa cells

ii. Changes in ovum

iii. Formation of capsule.

i. Changes in granulosa cells

a. First, the proliferation of granulosa cells occurs

b. A cavity called follicular cavity or antrum is formed in between the granulosa cells

c. Antrum is filled with a serous fluid called the liquor folliculi

d. With continuous proliferation of granulosa cells, the follicle increases in size

e. Antrum with its fluid also increases in size

f. Ovum is pushed to one side and it is surrounded by granulosa cells, which forms the germ hill

or cumulus oophorus

g. Granulosa cells, which line the antrum form membrana granulosa

h. Cells of germ hill become columnar and form corona radiata.

ii. Changes in ovum

a. First, the ovum increases in size and its diameter increases to 100 to 150 μ

b. Nucleus becomes larger and vesicular

c. Cytoplasm becomes granular

d. Thick membrane is formed around the ovum, which is called zona pellucida

e. A narrow cleft appears between ovum and zona pellucida. This cleft is called perivitelline space.

iii. Formation of capsule

Spindle cells from the stroma of ovarian cortex are modified and form a covering sheath around the follicle. The covering sheath is known as follicular sheath or theca folliculi.

Theca folliculi divides into two layers:

a. Theca interna

b. Theca externa.

Theca interna

Theca interna is the inner vascular layer with loose connective tissue. This layer also contains special type of epithelial cells with lipid granules and some delicate collagen fibers.Epithelial cells become secretory in nature and start secreting the female sex hormones, especially estrogen. Hormones are released into the fluid of antrum.

Theca externa

Theca externa is the outer layer of follicular capsule and consists of thickly packed fibers and spindle shaped cells. After about 7th day of menstrual cycle, one of the vesicular follicles outgrows others and becomes the dominant follicle. It develops further to form graafian follicle. Other vesicular follicles degenerate and become atretic by means of apoptosis.

4. Graafian Follicle

Graafian follicle is the matured ovarian follicle with maturing ovum . It is named after the Dutch physician and anatomist, Regnier De Graaf. Changes taking place during the development of graafian follicle

i. Size of the follicle increases to about 10 to 12 mm. It extends through the whole thickness of ovarian cortex

ii. At one point, the follicle encroaches upon tunica albuginea and protrudes upon surface of the ovary. This protrusion is called stigma. At the stigma, the tunica albuginea becomes thin

iii. Follicular cavity becomes larger and distended with fluid

iv. Ovum attains maximum size

v. Zona pellucida becomes thick

vi. Corona radiata becomes prominent

vii. Small spaces filled with fluid appear between the cells of germ hill, outside the corona radiata. These spaces weaken the attachment of the ovum to the follicular wall

viii. Theca interna becomes prominent. Its thickness becomes double with the formation of rich capillary network

ix. On the 14th day of menstrual cycle, graafian follicle is ready for the process of ovulation.

OVULATION

Ovulation is the process by which the graafian follicle ruptures with consequent discharge of ovum into the abdominal cavity. It is influenced by LH. Ovulation occurs on 14th day of menstrual cycle in a normal cycle of 28 days. The ovum enters the fallopian tube.

Stages of ovulation

1. Rupture of graafian follicles takes place at the stigma

2. Follicular fluid oozes out

3. Germ hillock is freed from wall

4. Ovum is expelled out into the abdominal cavity along with some amount of fluid and granulosa cells

5. From abdominal cavity, the ovum enters the fallopian tube through the fimbriated end.

Ovum becomes haploid before or during ovulation by the formation of polar bodies. After

ovulation, the ovum is viable only for 24 to 48 hours. So it must be fertilized within that time. Fertilized ovum is called zygote. Zygote moves from fallo pian tube and reaches the uterus on 3rd day after ovula tion. It is implanted in the uterine wall on 6th or 7th day If fertilization does not occur, ovum degenerates.

- Generally, only one ovum is released from one of the ovaries.

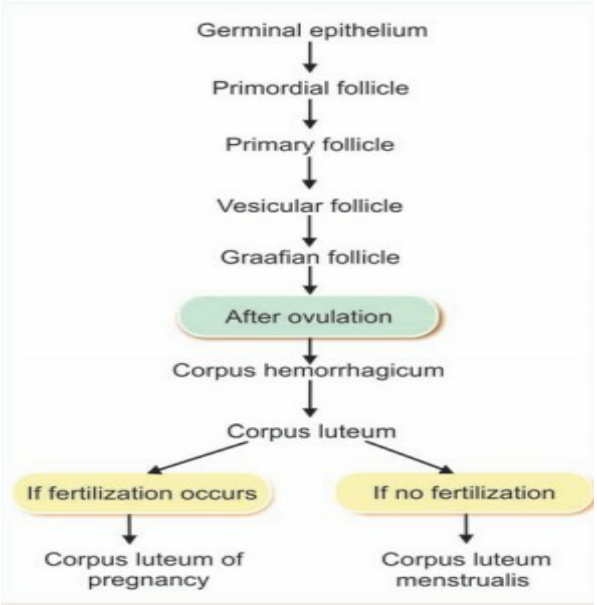
LUTEAL PHASE

Luteal phase extends between 15th and 28th day of menstrual cycle. During this phase, corpus luteum is developed and hence this phase is called luteal phase

Ovarian follicles

Corpus Luteum

Corpus luteum is a glandular yellow body, developed from the ruptured graafian follicle after the release of ovum. It is also called yellow body.



Development of Corpus Luteum

Soon after the rupture of graafian follicle and release of ovum, the follicle is filled with blood. Now the follicle is called corpus hemorrhagicum. The blood clots slowly. Corpus hemorrhagicum does not degenerate immediately. It is transformed into corpus luteum.Follicular cavity closes gradually by the healing of the wound. Blood clot is gradually replaced by a serous fluid containing fibrin. Corpus luteum obtains a diameter of 15 mm and remains in the ovary till the end of the cycle.

Structure of Corpus Luteum

In the corpus luteum, granulosa cells and theca interna cells are transformed into lutein cells called granulosa lutein cells and theca lutein cells. The process which transforms the granulosa and theca cells into lutein cells is called luteinization.Granulosa lutein cells contain fine lipid granules and the yellowish pigment granules. The yellowish pigment granules give the characteristic yellow color to corpus luteum. Theca lutein cells contain only lipid granules and not the yellow pigment.Follicular cavity is greatly reduced with irregular outline. It is filled with the serous fluid and remnants of blood clots.

Functions of Corpus Luteum

1. Secretion of hormones

Corpus luteum acts as a temporary endocrine gland. It secretes large quantity of progesterone and small amount of estrogen. Granulosa lutein cells secrete progesterone and theca lutein cells secrete estrogen. LH influences the secretion of these two hormones.

2. Maintenance of pregnancy

If pregnancy occurs, corpus luteum remains active for about 3 months, i.e. until placenta develops. Hormones secreted by corpus luteum during this period maintain the pregnancy. Abortion occurs if corpus luteum becomes inactive or removed before third month of pregnancy, i.e. before placenta starts secreting the hormones.

Fate of Corpus Luteum

Fate of corpus luteum depends upon whether ovum is fertilized or not.

1. If the ovum is not fertilized

If fertilization does not take place, the corpus luteum reaches the maximum size about one week after ovulation. During this period, it secretes large quantity of progesterone with small quantity of estrogen. Then, it degenerates into the corpus luteum menstrualis or spurium. The cells decrease in size and the corpus luteum becomes smaller and involuted. Afterwards, the corpus luteum menstrualis is transformed into a whitish scar called corpus albicans. The process by which corpus luteum undergoes regression is called luteolysis.

2. If ovum is fertilized

If ovum is fertilized and pregnancy occurs, the corpus luteum persists and increases in size. It attains a diameter of 20 to 30 mm and it is transformed into corpus luteum graviditatis (verum) or corpus luteum of pregnancy. It remains in the ovary for 3 to 4 months. During this period, it secretes large amount of progesterone with small quantity of estrogen, which are essential for the maintenance of pregnancy. After 3 to 4 months, placenta starts secreting these hormones and corpus luteum degenerates.

UTERINE CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, along with ovarian changes, uterine changes also occur simultaneously.Uterine changes occur in three phases:

1. Menstrual phase

2. Proliferative phase

3. Secretory phase.

MENSTRUAL PHASE

After ovulation, if pregnancy does not occur, the thickened endometrium is shed or desquamated. This desquamated endometrium is expelled out through vagina along with blood

and tissue fluid. The process of shedding and exit of uterine lining along with blood and fluid is called menstruation or menstrual bleeding. It lasts for about 4 to 5 days. This period is called menstrual phase or menstrual period. It is also called menses, emmenia or catamenia. The day when bleeding starts is considered as the first day of the menstrual cycle.Two days before the onset of bleeding, that is on 26th or 27th day of the previous cycle, there is a sudden reduction in the release of estrogen and progesterone from ovary. Decreased level of these two hormones is responsible for menstruation.

Changes in Endometrium during

Menstrual Phase

i. Lack of estrogen and progesterone causes sudden involution of endometrium ii. It leads to reduction in the thickness of endometrium, up to 65% of original thickness

iii. During the next 24 hours, the tortuous blood vessels in the endometrium undergo severe constriction.

Endometrial vasoconstriction is because of three reasons:

a. Involution of endometrium

b. Actions of vasoconstrictor substances like prosta glandin, released from tissues of involuted endometrium

c. Sudden lack of estrogen and progesterone (which are vasodilators)

iv. Vasoconstriction leads to hypoxia, which results in necrosis of the endometrium

v. Necrosis causes rupture of blood vessels and oozing of blood

vi. Outer layer of the necrotic endometrium is separated and passes out along with blood

vii. This process is continued for about 24 to 36 hoursviii. Within 48 hours after the reduction in the secretion of estrogen and progesterone, the superficial layers of endometrium are completely desquamated

ix. Desquamated tissues and the blood in the endometrial cavity initiate the contraction of uterus

x. Uterine contractions expel the blood along with desquamated uterine tissues to the exterior through vagina. During normal menstruation, about 35 mL of bloodalong with 35 mL of serous fluid is expelled. The blood clots as soon as it oozes into the uterine cavity. Fibrinolysin causes lysis of clot in uterine cavity itself, so that the expelled menstrual fluid does not clot. However, in the pathological conditions involving uterus, the lysis of blood clot does not occur. So the menstrual fluid comes out with blood clot. Menstruation stops between 3rd and 7th day of menstrual cycle. At the end of menstrual phase, the thickness of endometrium is only about 1 mm. This is followed by proliferative phase.

PROLIFERATIVE PHASE

Proliferative phase extends usually from 5th to 14th day of menstruation, i.e. between the day when menstruation stops and the day of ovulation. It corresponds to the follicular phase of ovarian cycle.At the end of menstrual phase, only a thin layer(1 mm) of endometrium remains, as most of the endometrial stroma is desquamated.

Changes in Endometrium during

Proliferative Phase

i. Endometrial cells proliferate rapidly

ii. Epithelium reappears on the surface of endometrium within the first 4 to 7 days

iii. Uterine glands start developing within the endometrial stroma

iv. Blood vessels appear in the stroma

v. Proliferation of endometrial cells occurs continuously, so that the endometrium reaches the thickness of 3 to 4 mm at the end of proliferative phase.

All these uterine changes during proliferative phase occur because of the influence of estrogen released from ovary. On 14th day, ovulation occurs under the influence of LH. This is followed by secretory phase.

SECRETORY PHASE

Secretory phase extends between 15th and 28th day of the menstrual cycle, i.e. between the day of ovulation and the day when menstruation of next cycle commences.After ovulation, corpus luteum is developed in the ovary. It secretes a large quantity of progesterone along with a small amount of estrogen. Estrogen causes further proliferation of cells in uterus, so that the endometrium becomes more thick. Progesterone causes further enlargement of endometrial stroma and further growth of glands.Under the influence of progesterone, the endometrial glands commence their secretory function.

Many changes occur in the endometrium before commencing the secretory function.

Changes in Endometrium during

Secretory Phase

i. Endometrial glands become more tortuous. Because of increase in size, the glands become tortuous to get accommodated within the endometrium

ii. Cytoplasm of stromal cells increases because of the deposition of glycogen and lipids

iii. Many new blood vessels appear within endometrial stroma. Blood vessels also become tortuous

iv. Blood supply to endometrium increases

v. Thickness of endometrium increases up to 6 mm.

Actually, secretory phase is the preparatory period, during which the uterus is prepared for implantation of ovum. All these uterine changes during secretory phase occur due to the influence of estrogen and progesterone. Estrogen is responsible for repair of damaged endometrium and growth of the glands. Progesterone is responsible for further growth of these structures and secretory activities in the endometrium. If a fertilized ovum is implanted during this phase and if the implanted ovum starts developing into a fetus, then further changes occur in the uterus for the survival of the developing fetus. If the implanted ovum is unfertilized or if pregnancy does not occur, menstruation occurs after this phase and a new cycle begins.

CHANGES IN CERVIX AND VAGINA DURING MENSTRUAL CYCLE

Mucus membrane of the cervix also shows cyclic changes during different phases of menstrual cycle.

Proliferative Phase

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Secretory Phase

During secretory phase, the mucus membrane of cervix becomes more thick and adhesive because of actions of progesterone.

VAGINAL CHANGES DURING MENSTRUAL CYCLE

Proliferative Phase

Epithelial cells of vagina are cornified. Estrogen is responsible for this.

Secretory Phase

Vaginal epithelium proliferates due to the actions of progesterone. It is also infiltrated with leukocytes. These two changes increase the resistance of vagina for infection.

REGULATION OF MENSTRUAL CYCLE

Regulation of menstrual cycle is a complex process that is carried out by a well organized regulatory system. The regulatory system is a highly integrated system, which includes hypothalamus,

anterior pituitary and ovary with its growing follicle. In the whole scenario, the growing follicle has a vital role to play.

HORMONES INVOLVED IN REGULATION The regulatory system functions through the

hormones of hypothalamo-pituitary-ovarian axis. Hormones involved in the regulation of menstrual cycle are:

1. Hypothalamic hormone: GnRH

2. Anterior pituitary hormones: FSH and LH

3. Ovarian hormones: Estrogen and progesterone.

Hypothalamic Hormone – GnRH

GnRH triggers the cyclic changes during menstrual cycle by stimulating secretion of FSH and LH from anterior pituitary. GnRH secretion depends upon two factors:

i. External factors like psychosocial events, which act on hypothalamus via cortex and many other brain centers

ii. Feedback effects of ovarian changes via ovarian hormones.

Anterior Pituitary Hormones – FSH and LH

FSH and LH modulate the ovarian and uterine changes by acting directly and/or indirectly via ovarian hormones. FSH stimulates the recruitment and growth of immature ovarian follicles. LH triggers ovulation and sustains corpus luteum. Secretion of FSH and LH is under the influence of GnRH.

Ovarian Hormones – Estrogen and Progesterone

Estrogen and progesterone which are secreted by follicle and corpus luteum, show many activities during menstrual cycle. Ovarian follicle secretes large quantity of estrogen and corpus luteum secretes large quantity of progesterone. Estrogen secretion reaches the peak twice in each cycle; once during follicular phase just before ovulation and another one during luteal phase . On the other hand, progesterone is virtually absent during follicular phase till prior to ovulation. But it plays a critical role during luteal phase. Estrogen is responsible for the growth of follicles. Both the steroids act together to produce the changes in uterus, cervix and vagina.Both the ovarian hormones are under the influence of GnRH, which acts via FSH and LH. In addition, the secretion of GnRH, FSH and LH is regulated by ovarian hormones.

REGULATION OF OVARIAN CHANGES

Follicular Phase

1. The biological clock responsible to trigger the cyclic events is the pulsatile secretion of GnRH, at about every 2 hours (due to some mechanism that is not understood clearly)

2. Pulsatile release of GnRH stimulates the secretion of FSH and LH from anterior pituitary

3. LH induces the synthesis of androgens from theca cells of growing follicle

4. FSH promotes aromatase activity in granulosa cells of the follicle resulting in the conversion of androgens into estrogen. It also promotes follicular development

5. Estrogen is responsible for development and growth of graafian follicle. It also stimulates the secretory activities of theca cells

6. Estrogen also exerts a double feedback control on GnRH

i. Initially, when estrogen secretion is moderate, it exerts a negative feedback control on GnRH so that GnRH secretion is inhibited. This leads to decrease in secretion of FSH and LH (negative feedback)

ii. During later period of follicular phase, when a large amount of estrogen is secreted by the maturing follicle, it exerts a positive feedback effect on GnRH secretion. Now, GnRH secretion is increased, resulting in secretion of large quantity of FSH and LH. This in turn, facilitates the growth of graafian follicle

7. In addition, estrogen shows the following actions:

i. Increases the number of FSH and LH receptors on the granulosa cells of follicles and increases the sensitivity of these cells for FSH and LH

ii. Facilitates the faster growth of graafian follicle

8. LH is necessary to provide the final touches for the growth of graafian follicle. It stimulates the secretion of estrogen. At the same time, it stimulates the theca cells to secrete progesterone.

Ovulation

LH is important for ovulation. Without LH, ovulation does not occur even with a large quantity of FSH. The need for excessive secretion of LH for ovulation is known as ovulatory surge for LH or luteal surge.

Prior to ovulation, a large quantity of LH is secreted due to positive feedback effect of estrogen on GnR.

Role of LH

Ovarian changes during luteal phase depend mainly on

LH. Luteinizing hormone:

1. Induces development of corpus luteum from the follicle (devoid of ovum) by converting the granulosa cells into lutein cells

2. Stimulates corpus luteum to secrete progesterone and estrogen

3. Necessary for the maintenance of corpus luteum.

Role of FSH

FSH also plays a role during luteal phase. Follicle-stimulating hormone:

1. Maintains the secretory activity of corpus luteum

2. Stimulates lutein cells to secrete inhibin, which in turn inhibits FSH secretion. If the ovum is not fertilized or if implantation of ovum does not take place, the changes in the level of the hormones produce some effects on corpus luteum which are:

1. Progesterone and estrogen secreted from corpus luteum, inhibit the secretion of FSH and LH from anterior pituitary by negative feedback

2. Granulosa lutein cells secrete another hormone called inhibin (which is also secreted by Sertoli cells of testes in males: Inhibin also inhibits

the secretion of FSH and LH by negative feedback

3. In the absence of FSH and LH, the corpus luteum becomes inactive

4. Finally, the corpus luteum regresses by means of luteolysis; so progesterone and estrogen are not available

5. Absence of progesterone and estrogen induces the secretion of GnRH from hypothalamus

6. GnRH stimulates the secretion of FSH and LH from anterior pituitary

7. FSH and LH stimulate the new immature follicles, resulting in the commencement of next cycle.

REGULATION OF UTERINE CHANGES

Uterine changes during menstrual cycle are influenced by estrogen and progesterone.

Proliferative Phase

During proliferative stage, the repair of the damaged endometrium occurs mainly by estrogen.

Estrogen stimulates:

1. Proliferation of cells in endometrial stroma

2. Development of uterine glands and appearance of blood vessels in the endometrial stroma.

Secretory Phase

Secretory phase of uterine changes, coincides with luteal phase of ovarian cycle. Under the influence of FSH and LH from anterior pituitary, the corpus luteum secretes large amount of progesterone and small amount of estrogen. Progesterone is responsible for endometrial changes along with estrogen during this phase.

Progesterone stimulates:

1. Growth of endometrial glands and makes them more tortuous

2. Growth of blood vessels and makes them also tortuous, leading to increase in blood flow to endometrium

3. Secretory activities of endometrial glands.Thus, during the secretory phase, the structure, blood flow and secretory functions of uterus are influenced by estrogen and progesterone secreted by corpus luteum.

Menstrual Phase

If pregnancy does not occur, menstrual phase occurs:

1. During the last two days of secretory phase, i.e. two days prior to onset of menstruation, the secretion of large quantity of progesterone and estrogen from corpus luteum inhibits the secretion of FSH and LH from anterior pituitary, by negative feedback

2. In the absence of LH and FSH, the corpus luteum becomes inactive and starts regressing

3. Sudden withdrawal (absence) of ovarian hormones progesterone and estrogen occurs

4. It leads to menstrual bleeding.

Lack of ovarian hormones causes the release of gonadotropins once again from anterior pituitary. It results in the onset of development of new follicles in ovary and the cycle repeats.