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PHARMACOLOGY

PHS 212

A.

CYCLIC CHANGES IN THE VAGINA

The most striking changes in the vagina, is the marked basal **cell proliferation** and **thickening of the stratum granulosum** during the follicular phase of the menstrual cycle during the proliferative or follicular phase of the cycle, which corresponds to the development of the ovarian follicles, the uterus showed growth of endometrial glands, stroma and endothelial cell proliferation with capillary sprouts. Shortly after ovulation and parallel to the formation of the corpora lutea, the endometrium enters the secretory or luteal phase, which is characterised by coiling of endometrial glands, glandular secretion and the differentiation of the spiral artery.

The vaginal epithelium is subject to normal, cyclic changes, that are influenced by oestrogen: with increasing circulating levels of the hormone, there is proliferation of epithelial cells along with an increase in the number of cell layers.As cells proliferate and mature, they undergo partial cornification.Although hormone induced changes occur in the other tissues and organs of the female reproductive system, the vaginal epithelium is more sensitive and its structure is an indicator of estrogen levels.

The superficial cells exfoliate continuously and basal cells replace the superficial cells that die and slough off from the stratum corneum Under the stratus corneum is the stratum granulosum and stratum spinosum.The cells of the vaginal epithelium retain a usually high level of glycogen compared to other epithelial tissue in the body.The surface patterns on the cells themselves are circular and arranged in longitudinal rows he epithelial cells of the uterus possess some of the same characteristics of the vaginal epithelium.

2. CYCLIC CHANGES IN THE CERVIX

Cervical mucus appears to have an important function in the process of human reproduction. In response to stimulation by estrogen, cervical glands produce increasing amounts of a characteristic mucoid secretion.At the peak of this secretory activity, prior to ovulation, these glands produce copious amounts of a thin, isotonic mucus which is easily penetrated by the sperm. 5 , 7, 15, 16 Progesterone, on the other hand, is known to bring about both quantitative and qualitative alterations in the cervical secretion. During the luteal phase of the menstrual cycle, cervical mucus has been shown to become scanty in amount, as well as viscous and cellular. During the pro-gestational phase also, such properties as spinnbarkeit and crystallisation of the cervical mucus, which characterise estrogen stimulation, are markedly reduced or absent and consequently sperm migration is inhibited. Since endogenous progesterone causes an inhibition of sperm migration through cervical mucus, exogenously administered progestins, as prescribed for oral contraception, might be expected to have a similar effect.

3. CYCLIC CHANGES IN THE BREAST

Each month, women go through changes in the hormones that make up the normal menstrual cycle. The hormone estrogen is produced by the ovaries in the first half of the menstrual cycle. It stimulates the growth of milk ducts in the breasts. The increasing level of estrogen leads to ovulation halfway through the cycle. Next, the hormone progesterone takes over in the second half of the cycle. It stimulates the formation of the milk glands. These hormones are believed to be responsible for the cyclical changes that many women feel in their breasts just before menstruation. These include swelling, pain, and soreness.

During menstruation, many women also have changes in breast texture. Their breasts may feel very lumpy. This is because the glands in the breast are enlarging to get ready for a possible pregnancy. If pregnancy does not happen, the breasts go back to normal size. Once menstruation starts, the cycle begins again.

B. Menstrual Cycle

The menstrual cycle is the hormonal driven cycle; Day 1 is the first day of your period (bleeding) while day 14 is the approximate day you ovulate and if an egg is not fertilised, hormone levels eventually drop and at about day 25; the egg begins to dissolve and the cycle begins again with

the period at about day 30. Most periods vary somewhat, the flow may be light, moderate or heavy and can vary in length from about 2 to 7 days; with age, the cycle usually shortens and becomes more regular. Menstruation begins day 1 and normally ends days 3-5 of the menstrual cycle. The average age for a girl to get her first period in the US is 12, but the range of age is about 8 to 15 years old. Women usually have periods until about ages 45 to 55. The average length of the menstrual cycle is 28–29 days, but this can vary between women and from one cycle to the next. The length of your menstrual cycle is calculated from the first day of your period to the day before your next period starts. Girls get their first period (menarche), on average, between the ages of 11 and 14 years. By this stage, other sexual characteristics have developed, such as pubic hair and budding breasts.

Hormones and the menstrual cycle

The menstrual cycle is complex and is controlled by many different glands and the hormones that these glands produce. A brain structure called the hypothalamus causes the nearby pituitary gland to produce certain chemicals, which prompt the ovaries to produce the sex hormones oestrogen and progesterone.

The menstrual cycle is a biofeedback system, which means each structure and gland is affected by the activity of the others.

Phases of the menstrual cycle

The four main phases of the menstrual cycle are:

- menstruation
- the follicular phase
- ovulation
- the luteal phase.

MENSTRUATION

Menstruation is the elimination of the thickened lining of the uterus (endometrium) from the body through the vagina. Menstrual fluid contains blood, cells from the lining of the uterus (endometrial cells) and mucus. The average length of a period is between three days and one week. Sanitary pads or tampons are used to absorb the menstrual flow. Both pads and tampons need to be changed regularly (at least every four hours). Using tampons has been associated with an increased risk of a rare illness called ***toxic shock syndrome (TSS)***.

• FOLLICULAR PHASE

The follicular phase starts on the first day of menstruation and ends with ovulation. Prompted by the hypothalamus, the pituitary gland releases follicle stimulating hormone (FSH). This hormone stimulates the ovary to produce around five to 20 follicles (tiny nodules or cysts), which bead on the surface.

Each follicle houses an immature egg. Usually, only one follicle will mature into an egg, while the others die. This can occur around day 10 of a 28-day cycle. The growth of the follicles stimulates the lining of the uterus to thicken in preparation for possible pregnancy.

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 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 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.

a. 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.

b. 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 (Fig. 80.1). 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 release of a mature egg from the surface of the ovary. This usually occurs mid-cycle, around two weeks or so before menstruation starts.During the follicular phase, the developing follicle causes a rise in the level of oestrogen. The hypothalamus in the brain recognises these rising levels and releases a chemical called gonadotropin-releasing hormone (GnRH). This hormone prompts the pituitary gland to produce raised levels of luteinising hormone (LH) and FSH.

Within two days, ovulation is triggered by the high levels of LH. The egg is funnelled into the fallopian tube and toward the uterus by waves of small, hair-like projections. The life span of the typical egg is only around 24 hours. Unless it meets a sperm during this time, it will die.When you want to have a baby you can improve your chance of getting pregnant if you know about ovulation and the ‘fertile window’ in the menstrual cycle.

Process of Ovulation

Mechanism of ovulation is not known clearly.

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. Ovumisexpelledoutintotheabdominalcavityalong

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 fertilised within that time.

Fertilised ovum is called zygote. Zygote moves from fallopian tube and reaches the uterus on 3rd day after ovulation. It is implanted in the uterine wall on 6th or 7th day.

• LUTEAL PHASE

During ovulation, the egg bursts from its follicle, but the ruptured follicle stays on the surface of the ovary. For the next two weeks or so, the follicle transforms into a structure known as the corpus luteum. This structure starts releasing progesterone, along with small amounts of oestrogen. This combination of hormones maintains the thickened lining of the uterus, waiting for a fertilised egg to stick (implant).

If a fertilised egg implants in the lining of the uterus, it produces the hormones that are necessary to maintain the corpus luteum. This includes human chorionic gonadotropin (HCG), the hormone that is detected in a urine test for pregnancy. The corpus luteum keeps producing the raised levels of progesterone that are needed to maintain the thickened lining of the uterus.

If pregnancy does not occur, the corpus luteum withers and dies, usually around day 22 in a 28-day cycle. The drop in progesterone levels causes the lining of the uterus to fall away. This is known as menstruation. The cycle then repeats.

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 colour 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.