FEMALE REPRODUCTIVE SYSTEM

Female reproductive system includes 2 ovaries, 2 oviducts, the uterus, the vagina, the external genitalia and the mammary gland.

There are two main function of female reproductive system - reproductive (the formation of ovum) and endocrine (the production of hormones - estrogens and progesterone that are responsible for the development of the female secondary sex characters, and regulate cyclical changes in the uterus and maturation of the oocytes).

OVARIES

A single layer of cuboidal epithelium covers the surface of the ovary. It is peritoneal mesothelium. Fibrous connective tissue forms a thin capsule, the tunica albuginea, immediately beneath the epithelium.

The ovary is divided into an outer cortex and an inner medulla. The medulla is composed of loose connective tissue, which contains nerves and blood vessels (mostly wide veins).

The cortex consists of connective tissue stroma in which the ovarian follicles are situated. Ovarian follicles are structural and functional units of the ovaries. Ovarian follicles consist of one primary oocyte and surrounding follicular cells.

There are three basic types of follicles, according phase of their development:

- Primordial follicles;
- Growing follicles or developing follicles;
- Mature or Graafian follicles.

The growing follicles are further subdivided as primary, secondary.

The primordial follicles are located in the cortex just beneath tunica albuginea. One layer of flattened follicular cells surrounds the primary oocyte in period of little growth.

Oogenesis takes place in two organs of female reproductive system. It begin in ovary and finish in oviduct. The first mitotic stage of oogenesis begin in ovary in period of early embryonic development. At this stage oogonia divide mitotically to produce primary oocytes in the fetal ovary. In period of embryonic development, the primary oocytes enter

prophase of the first meiotic division. First meiotic division is then arrested at the diplotene stage of first meiotic prophase and the primary oocytes consisting of в составе primordial follicles remain in this condition or period of long growth throughout the remainder of gestation, childhood and puberty. The first meiotic prophase is not completed until just before ovulation.

Long growth takes place from gestation to puberty maturation and is independent of gonadotropin stimulation.

During puberty and reproductive life span, small groups of primordial follicles undergo cyclic growth and maturation each menstrual cycle. It is accompanied by the process of the primordial follicle transformation into the Graafian follicle. It is a short follicular growth that is regulated by FSH and lasts for about 14 days.

Normally, only one primordial follicle reaches full maturity and only one secondary oocyte is released from the ovary during each menstrual cycle.

By the sixth month of gestation about 7 million oocytes and oogonia are present in the ovaries. By the time of birth this number is reduced to about 2 million. Of these only about 400.000 survive until puberty. During the reproductive life span, a woman produces only about 400 mature ova.

Most ovarian follicles undergo a degenerative process called follicular atresia in which follicular cells and oocytes die and are destroyed by phagocytic cells.

The primary follicle

The early primary follicle is the first stage of follicular maturation. The oocyte enlarges. As the oocyte grows, it secretes glycoproteins of zona pellucida that is extracellular coat between the oocyte and the adjacent follicle cells. The flattened follicular cells become a cuboidal or columnar shape. Follicular cells form a single layer, and the follicle is called a unilaminar primary follicle or early primary follicle.

The continued proliferation of follicular cells will result in the formation of a stratified epithelium or stratum granulosum, surrounding the oocyte. The follicle cells are now identified as granulosa cells. Stromal cells surrounding the follicle form a sheath of connective tissue cells, known as the theca folliculi, just external to the

basal lamina. The follicle is now called a multilaminar primary follicle or late primary follicle.

The secondary follicle

Under influence of FSH small fluid-filled spaces appear between the granulosa cells. The fluid is called liquor folliculi. It contains high concentrations of estrogens, producing by granulosa cells. Estrogens provide the reconstitution of the endometrium. Such follicle is called secondary follicle. The spaces enlarge and coalesce or fuse to form the foilicular antrum, which is the defining feature of the secondary or antral follicle. The oocyte is now located eccentric in the secondary follicle in the cumulus oophorus, where granulosa cells surround it. The eccentrically positioned oocyte undergoes no further growth, because the granulosa cells secret peptide called oocyte maturation inhibitor into the antral fluid.

The theca folliculi differentiates into a theca interna and a theca externa. The theca interna is the inner, highly vascularized layer of loose connective tissue containing cuboidal secretory cells. In response to LH stimulation, they synthesize and secrete the androgens that are the precursors of estrogen. The theca externa is the outer layer of dense connective tissue.

Mature (Graafian) follicle

A mature (Graafian) follicle contains a large antrum and an oocyte embedded within the cumulus oophorus. The cells of the cumulus oophorus immediately surrounding the oocyte remain with it after ovulation and are referred to as the corona radiata. The mature (tertiary, preovulatory or Graafian) follicle further increases in size till 14^{th} day of a 28 day ovarian menstrual cycle.

Blood - ovarian barrier

There is blood - ovarian barrier into ovaries. It separates capillary bed of the theca interna from the oocyte. It includes:

- endothelium with basal membrane,
- connective tissue of the theca interna,
- the basement membrane between the granulosa layer and the theca interna,

- granulosa layer,
- corona radiate and
- zona pellucida.

Hormonal regulation of cells of follicle

In humans, LH stimulates the cells of theca interna to secrete androgens, which serve as estrogen precursors. Androgens are transported to the smooth endoplasmic reticulum (sER) in the granulosa cells. In response to FSH, the granulosa cells catalyze the conversion of androgens to estrogens. Estrogens stimulate the granulosa cells to proliferate and thereby increase the size of the follicle. A surge in the release of FSH or LH is induced in the adenohypophysis approximately 24 hours before ovulation. The granulosa cells no longer produce estrogens in response to LH. Triggered by this surge, the first meiotic division of the primary oocyte resumes resulting in the formation of the secondary oocyte and the first polar body.

Ovulation

The first meiotic division is completed завершается after the increase in LH secretion but before the full exit of the oocyte from the follicle. Trough about 1 or 2 minutes, the secondary oocyte, surrounded by the corona radiata is expelled from the ruptured Graafian follicle. This process is called ovulation. Ovulation takes place in the middle of the menstrual cycle (i.e., on the 14th day of a 28-day cycle) and is induced by a surge in the LH level.

There are several factors, providing the process of ovulation:

1) increase in the volume and pressure of the follicular fluid;

2) proteolytic activity of the follicular wall enzymes;

3) hormonally directed deposition of glycosaminoglycans between the oocyte–cumulus complex and the stratum granulosum;

4) contraction of the smooth muscle cells in the theca externa layer.

The oocyte then will be caught by the dilated end of the oviduct. The oocyte enters the infundibulum of the uterine tube, where it is may be fertilized. As the secondary oocyte leaves the follicle at ovulation, the second meiotic division (equatorial division) is in progress. This division is arrested останавливается at the second

metaphase and is not completed unless secondary oocyte is penetrated by aspermatozoon. If fertilization occurs, the secondary oocyte completes the second meiotic division and forms a mature ovum with the maternal pronucleus containing a set of 23 chromosomes. After fertilization, the new diploid cell zygote appear. Zygote begins to undergo cleavage and is transported to the uterus. This a trip lasts about 5 days. If the oocyte is not fertilized within the oviduct the first 24 hours after ovulation, it begins to degenerate.

Normally, only one follicle completes maturation and ruptures to release its oocyte at the middle of the menstrual cycle, on the 14th day of a 28-day cycle. Rarely, oocytes are released from other follicles that have reached full maturity during the same cycle, leading to the possibility of multiple births.

Atresia

Most of the follicles degenerate and disappear through a process called ovarian follicular atresia with formation of atretic follicles in ovary. Large numbers of follicles undergo atresia during fetal development, early postnatal life, and puberty. After puberty, groups of follicles begin to mature during each menstrual cycle, but normally, only one follicle completes its maturation. Thus, at any stage of its maturation a follicle may undergo atresia.

In atresia the granulosa cells and oocyte undergoes degeneration. The zona pellucida becomes folded and collapses within the cavity of the follicle. Macrophages are involved in the phagocytosis of the zona pellucid, granulosa cells and the remnants of the degenerating oocyte.

Although granulosa cells and the oocytes undergo degeneration during atresia of the follicles, enlargement of the theca interna cells occurs in some atretic follicles. These thecal cells are called interstitial cells. These cells, presenting in ovary from childhood through menopause are the source of ovarian androgens and finally estrogens.

The Corpus luteum

After ovulation, the remainders of the follicle in the ovary form a temporary endocrine gland called the corpus luteum (yellow body). It is localized in the cortical region and secretes progesterone.

When the follicle ruptures, a bleeding from the capillaries of theca interna into the follicular lumen leads to the formation of a central clot. The follicle filled with blood is called the corpus haemorrhagicum.

Further corpus luteum is formed instead of the corpus hemorrhagicum under influence of LH. Process of corpus luteum formation includes:

1) rapidly growth of blood and lymphatic vessels from the theca interna into the granulosa layer;

2) luteinization that is the process when the theca interna cells differentiate into theca lutein cells and granulosa cells differentiate into granulosa lutein cells. They increase in size, become filled with lipid droplets and start accumulated the lipochrome (yellow pigment called lutein). At the ultrastructural level, the theca lutein cells and granulosa cells demonstrate features of steroid-secreting cells and begin to produce progesterone. This hormone stimulates the growth and secretory activity of the uterus lining endometrium, to prepare it for the implantation of the germ. The cyclic development of ovarian follicles is also blocked by the progesterone.

3) degeneration of corpus luteum when it transforms into a corpus albicans - whitish scar tissue within the ovaries. The corpus albicans slowly disappears over a period of several months.

If fertilization and implantation do not occur, the corpus luteum remains active only for 14 days; in this case it is called the corpus luteum of menstruation. If fertilization and implantation occur, the chorionic gonadotropin producing by the placenta will be stimulate the corpus luteum to increase in size to form the corpus luteum of pregnancy, which is active for about 6 months of gestation. The corpus luteum of pregnancy is essential for the maintenance of pregnancy in the first few months. After the fourth month, the corpus luteum of pregnancy is no longer needed, as the placenta begins to secrete progesterone.

Very few follicles pass the way from primordial follicles to the yellow body.

The series of changes from formation of an ovarian follicle to degeneration of the corpus luteum constitute an ovarian cycle.

Hormonal Regulation of the Ovarian Cycle

During each menstrual cycle, the ovary undergoes cyclic changes, including a follicular phase and a luteal phase, which are separated by ovulation. At the beginning of the follicular phase, a small number (10 to 20) of primary follicles begin to develop under the influence of FSH of the adenohypophysis. During the first 8 to 10 days of the cycle, FSH is the principal hormone influencing the growth of the follicles. It stimulates the granulosa and thecal cells, which begin to secrete steroid hormones, principally estrogens into the follicular lumen. The quantity of estrogens in circulating blood inhibits further production of FSH by the adenohypophysis. Follicles that have not reached a state of FSH-independent development undergo degeneration. As a result of this hormonally controlled development, only one of the maturing follicles normally has full maturation and is released from the ovary.

Ovulation is induced by a sharp increase in the level of LH.

The luteal phase begins immediately after ovulation, as the corpus luteum is formed. Estrogens and large amounts of progesterone are secreted by the corpus luteum. Under the influence of both hormones, but primarily progesterone, the endometrium begins the preparation for implantation. LH appears to be responsible отвечает for the development and maintenance of the corpus luteum during cycle.

The oviduct (Fallopian or uterine tubes).

The uterine tube is a muscular tube. The uterine tubes transport the ovum from the ovary to the uterus and provide the necessary environment for fertilization and initial development of the zygote to the morula stage.

Each uterine tube is can be divided into four segments:

1) The infundibulum is the funnel-shaped segment of the tube adjacent to the ovary. At the distal end, it opens into the peritoneal cavity. Fringed extensions called fimbriae extend from the infundibulum toward the ovary;

2) The ampulla is the longest segment of the tube, that is the site of fertilization;

3) The isthmus is the narrow, medial segment of the uterine tube adjacent to the uterus;

4) The uterine part lying within the uterine wall and opens into the cavity of the uterus.

The wall of the oviduct is composed of 3 tunics:

I) mucosa consisting of:

1) simple columnar epithelium;

2) lamina propria – loose connective tissue

II) muscular tunuc consisting of:

1) inner circular layer and

2) outer longitudinal layers of smooth muscle tissue;

III) serosa.

The mucosa exhibits thin longitudinal folds that project into the lumen of the uterine tube. These folds are most numerous in the ampulla. In cross sections, the lumen of the ampulla resembles a labyrinth.

The epithelium lining the mucosa of oviduct contains 2 types of cells:

1) Ciliated cells that are most numerous in the infundibulum and ampulla. The wave of the cilia is directed toward the uterus;

2) Nonciliated or peg гвоздь cells that are secretory cells producing the fluid with nutritive material for the ovum and the early embryo.

Both ciliary movements and peristaltic muscular activity of uterine tube are involved in the movements of the oocyte and early embryo toward the uterus.

UTERUS

The uterus is a hollow pear-shaped organ. It is divided into body and cervix. The upper, rounded part of the body is the fundus. The lumen of the cervix, the endocervical canal, has a constricted opening, or os, at each end. The internal os communicates with the cavity of the body, the external os with the vagina.

The uterine wall is composed of three layers.

1. Endometrium - the mucosa of the uterus.
2. Myometrium - the thick muscular layer.

3. Perimetrium - the external serous layer.

Endometrium

The endometrium consists of epithelium and lamina propria containing simple tubular glands that sometimes branch near the myometrium. Epithelium of endometrium is simple columnar containing ciliated and secretory cells. The secretory cells produce the mucous.

The loose connective tissue of the lamina propria rich by fibroblasts, abundant amorphous ground substance and tissue fibers of reticular type.

Functionally the endometrium can be subdivided into 2 layers:

1) the functional layer

2) the basal layer

Myometrium

The myometrium is the thickest layer of the uterine wall, being composed of bundles of smooth muscle fibers separated by connective tissue. The muscle fibers run in various directions and distinct layers are difficult to define. However, three layers, external, middle and internal are usually described. The fibers in the external layer are predominantly longitudinal. In the internal layer some bundles are longitudinal and others are circular. In the middle layer there is a mixture of bundles running in various directions.

The central muscle layer contains numerous large blood vessels and called the stratum vasculare. Contractions of the myometrium are responsible for expulsion of the fetus at the time of childbirth.

During pregnancy, the myometrium goes through a period of great growth. The growth takes place due to the hypertrophy of smooth muscle cells, which may reach more than 500 мкм in length, and due to the hyperplasia, when the number of smooth muscle cells increase through division.

Perimetrium

The peritoneal surface of the uterus is covered by a serosa, consisting of a mesothelium and a thin layer of areolar tissue, covers only the upper part of the uterus.

The surface of the uterus not covered by peritoneum is covered by connective tissue, or adventitia.

Menstrual cycle

The endometrium undergoes cyclical changes in its secretory activity and structure, which constitute the menstrual cycle. The menstrual cycle prepares the uterus endometrium for the implantation of embryo. Changes of endometrium are controlled by ovarian hormones estrogens and progesterone, and correlated with the cyclic growth and maturation of ovarian follicles.

The duration of the menstrual cycle is variable but average is 28 days according the ovarian cycle.

The menstrual cycle includes 3 phases: 1) menstrual phase (days 1-4 of the cycle); 2) proliferative phase (days 5-14 of the cycle); 3) secretory phase (days 15-28 of the cycle).

Menstrual and proliferative phase constitute the follicular phase, but the secretory phase is luteal phase.

Menstrual phase of the menstrual cycle

During the menstrual or desquamation phase, the functional layer of endometrium sloughs off as a result of ischemia and necrosis caused by contraction of the coiled arteries supplying endometrium. This occurs if fertilization does not take place and the corpus luteum atrophies causing the levels of estrogenes and progesterone to fall in ovaries.

Bleeding from the vessels within the uterus mucosa accompanies by a menstrual flow from the vagina. The menstrual cycle is defined as beginning on the day when menstrual flow appears. The basal layer remain during menstruation and serves as the source for the regeneration of the functional layer for next proliferative phase of the menstrual cycle.

Proliferative phase of the menstrual cycle

The proliferative or postmenstrual phase follows the menstrual phase. For this phase the epithelium, uterine glands and connective tissue of the functional layer are reconstitute by active proliferation and differentiation of the cells in the bases of the

glands and connective tissue cells that remained in the basal layer of endometrium. Coiled arteries grow into the regenerating stroma.

At the end of the proliferative phase, the endometrium is 2-3 mm thick, and the glands are straight tubules with narrow lumens. The proliferative phase is also known as the follicular phase because it coincides with development of ovarian follicles and with production of estrogens by their granulosa cells. Thus during the proliferative phase the changes in the endometrium are driven by ovarian estrogens.

Secretory phase of the menstrual cycle

The secretory phase or premenstrual phase begins shortly after ovulation occurs. It is influenced by progesterone produced by the corpus luteum of ovary. Due to it this phase is called luteal phase. At this phase the endometrium becomes thickest (6-7 mm) and the uterine glands are coiled and have large lumen to produce mucous secrete necessary for implantation of embryo if fertilization occur.

Highly coiled arteries are also called spiral extend from the basal layer into the functional layer of the endometrium. They arise from arcuate arteries of myometrium. The arcuate arteries also give rise to straight arteries that supply the basal layer of endometrium.