CONTENTS

ABBREVIATIONS

a-GnRH — Gonadotropin-releasing hormone agonist
ACTH — Adrenocorticotropic hormone
AMH — Anti-mullerian hormone
AUB — Abnormal uterine bleeding
APS — Antiphospholipid syndrome
VVC — Vulvovaginal candidiasis
PID — Pelvic inflammatory disease
IUI — Intrauterine insemination
IUD — Intrauterine device
LGR-IUS — Levonorgestrel releasing intrauterine system
HSV — Herpes simplex virus
HPV — Human papillomavirus
HR-HPV — High-risk human papillomavirus
ART — Assisted reproductive technology
VTE — Venous thromboembolism
GABA — Gamma-amino-butyric acid
GnRH — Gonadotrophin-releasing hormones
EHP — Endometrial hyperplastic processes
SHBG — Sex hormone binding globulin
DHEA — Dehydroepiandrosterone
DHEA-S — Dehydroepiandrosterone sulfate
DUB — Dysfunctional uterine bleeding
DMPA — Depot medroxyprogesterone acetate
DRSP — Drospirenone
E1 — Estrone
E2 — Estradiol
E3 — Estriol
CHD — Coronary heart disease
ICSI — Intracytoplasmic sperm injection
BMI — Body mass index
STI — Sexually transmitted infections
IGF — Insulin-like growth factor
CEE — Conjugated equine estrogen
COCP — Combined oral contraceptive pill
CC — Clomiphene citrate
LH — Luteinizing hormone
LGR-IUS — Levonorgestrel releasing intrauterine system
HDL — High density lipoproteins
LDL — Low density lipoproteins

MHT — Menopausal hormone therapy
MPA — Medroxyprogesterone acetate
MRI — Magnetic resonance imaging
NSAIDs — Non-steroidal anti-inflammatory drugs
PVI — Papillomavirus infection
PMDD — Premenstrual dysphoric disorder
PMD — Premenstrual disorders
PMS — Premenstrual syndrome
PCR — Polymerase chain reaction
SDC — Separate diagnostic curettage
RCT — Randomized clinical trial
MS — Multiple scrlerosis
CC — Cervical cancer
SSRIs — Selective serotonin reuptake inhibitors
SERMs — Selective estrogen receptor modulators
PCOS — Polycystic ovarian syndrome
STH — Somatotropic hormone
TSH — Thyroid-stimulating hormone
US — Ultrasonography
FOC — Functional ovarian cyst
GF — Growth factors
FSH — Follicle stimulating hormone
CIBD — Chronic inflammatory bowel disease
hCG — Human chorionic gonadotropin
C — Cholesterol
CE — Chronic endometritis
hMG — Human menopausal gonadotropin
Cx — Cervix
IVF — In vitro fertilization
EE — Ethinyl estradiol
ASCCP — American society of colposcopy and cervical pathology
ASCUS — Atypical squamous cells of undetermined significance
BRCA — Breast cancer gene
CIN — Cervical intraepithelial neoplasia
FIGO — International federation of gynecology and obstetrics
HSIL — High-grade squamous intraepithelial lesion
LEEP — Loop electrosurgical excision procedure
LLETZ — Large loop excision of the transformation zone
LSIL — Low-grade squamous intraepithelial lesion
NIH — National institutes of health
WHI — Women’s health initiative

Chapter 1
INTRODUCTION TO GYNECOLOGY

1.1. INTRODUCTION TO GYNECOLOGY

Gynecology is the science of a woman, a term has Greek origin and is composed of two words: gyne — woman and logos — study.

Gynecology is a diverse and extensive field of medicine that includes reproductive medicine (reproduction of the progeny, assistance in childbirth — obstetrics), physiology and pathology of the genital organs, interaction with all the regulatory functional systems of the body (nervous, humoral, endocrine, immune, cardiovascular, hemostasis, etc.). Many female (gynecological) diseases precede disorders of reproductive function (infertility, pregnancy loss, complications of childbirth and postpartum period), perinatal complications and losses, as well as the occurrence of neuroendocrine, autoimmune and malignant diseases.

Historically, the study of this complex, multidimensional discipline begins with obstetrics (the beginning of life — conception, implantation, placentation, pregnancy development, childbirth, and postpartum period). Therefore, the first volume of this textbook is devoted to physiological obstetrics.

However, pregnancy is associated with overcoming the immunological tolerance of the semi-foreign "graft" (fetus), complications due to maternal somatic diseases, fetal developmental disorders, complex interactions in the maternal-placenta-fetus system. Therefore, the second volume — "Pathological obstetrics" — reveals the possibilities of prevention, treatment, and correction of gestational complications (with the help of surgical interventions described in volume III "Operative obstetrics").

The present, fourth volume — "Gynecology" — combines disorders, pathological conditions, female diseases that are not directly associated with the obstetric practice.

Mention of female diseases is found in the written records of the Hindu civilization as early as III century BC. In addition to realizing the need for

assistance in childbirth, there were instructions on the need to remove tumors, birth canal lacerations, and female infertility were described. The first scientific studies addressed the description of the structure of the uterus, fallopian tubes, ovaries, and testicles (R. de Graaf). De Graaf suggested that "homunculi" are formed upon a fusion of male and female germ cells, which grow and develop inside the mother for at least 10 lunar months.

For many centuries, physicians have tried not only to alleviate the suffering of childbirth, but also to treat infertility, preserve pregnancy, and promote its onset.

Gradually, gynecology separated from general medicine as a very difficult and multifaceted profession. Gynecological surgery developed: Wertheim's surgery for cervical cancer, which has remained almost unchanged since 1900 and until the present time, removal of ovarian tumors (A.Ya. Krassovsky), myomatous nodules (V.A. Karavaev, K.F. Slavyansky).

In the XIX century, gynecology became an independent separate profession. The study of gynecological disorders has become more active, the number of gynecological surgeries has increased (Russian obstetricians-gynecologists A.Ya. Krassovsky, V.F. Snegirev et al.). Complex surgical interventions in case of "acute abdomen" (ectopic pregnancy, tumour torsion, uterine bleeding)have been performed, based on the development of methods of general anesthesia, a scientific approach to surgical and conservative methods of treatment.

Knowledge of topographic anatomy (N.I. Pirogov, 1853), development of aseptics and antiseptics (I. Semmelweis, 1847; D. Lister, 1978), development of morphology (R. Virchow), bacteriology (L. Pasteur, R. Koch, I. Mechnikov), physiology (K. Bernard) and other fields of science and medical practice were of great significance for the evolution of gynecology.

A great contribution to the development of operative gynecology was made by Russian obstetricians-gynecologists — A.Ya. Krassovsky, V.F. Snegirev, D.O. Ott, K.F. Slavyansky, A.I. Lebedev and others.

One of the founders of Russian gynecology is V.F. Snegirev (1847–1946) — an outstanding surgeon, teacher, founder of the gynecological clinic of Moscow University and Gynecological Institute for advanced medical training (1896), author of the classic treatise "Uterine bleeding" (1884). The main principle of national gynecological care was expressed in the report of V.F. Snegirev at the First All-Russian Congress of obstetricians and gynecologists in 1903: "The immediate task of gynecologists is to help our Russian woman, the cradle of our people, to ease the burden of our mother's situation, to prevent the physical and spiritual degeneration of the people; so that at

30 years of age a woman is not exhausted and tired. The same should be done for her, that is done for a woman of high socioeconomic class; to open wide the doors for her civilian activity; to take care of raising her ethical and moral level, so that honour and respect surround her. And to do this, apply the principle: a woman — the cradle of the human race — should have more rights and fewer responsibilities. Then she, as a mother, will preserve her health, restore her strength and power."

This ***principle of gynecological care is based on the training of qualified general practitioners,*** who will inevitably face problems of women's health; continuous training of specialists in obstetrics and gynecology; a humanistic attitude to such a responsible discipline; love and respect for the profession of an obstetrician and gynecologist.

Chapter 2

HORMONAL REGULATION OF FEMALE REPRODUCTIVE SYSTEM. NORMAL MENSTRUAL CYCLE

Reproductive endocrinology studies hormones and neuroendocrine biologically active substances that are produced in and/or affect the tissues of the reproductive system. These tissues include the hypothalamus, anterior pituitary, ovaries, endometrium, and placenta.

Hormones are the products of cellular secretion of endocrine organs, which can affect target tissues distant from the site of secretion by entering the peripheral bloodstream (*endocrine secretion*).

In reproductive physiology, there are also additional forms of intercellular interaction. *Paracrine* interaction (typical for ovarian cells) is the transmission of a chemical signal between adjacent cells. *Autocrine* action occurs when a cell produces biologically active substances that affect its own function.

The action of neurotransmitters released by neurosecretory cells into the bloodstream and transported to other tissues is called *neuroendocrine secretion*. An example is the secretion of gonadotropin-releasing hormone (GnRH) into the hypophyseal portal vessels, which affects the cells of the anterior pituitary.

The principles of reproductive system regulation can be schematically represented as five levels that interact on the principle of positive or negative feedforward and feedback loops.

The first level of this regulatory system is represented by: *the cerebral cortex, limbic system, hippocampus, amygdala, and some other extrahypothalamic structures*. In response to the impulses of the external and internal environment, these structures synthesize and secrete neurotransmitters and neuropeptides (norepinephrine, dopamine, gamma-aminobutyric acid — GABA, acetylcholine, serotonin, etc.), which affect the neural secretory nuclei in the hypothalamus, stimulating the production of releasing hormones.

The second level of reproductive system regulation is the hypothalamus (in particular, the ventromedial and dorsomedial arcuate nuclei), which secretes stimulating (releasing hormones) and blocking (inhibiting hormones) neurohormones. GnRH (gonadotropin-releasing hormone) is a decapeptide with a cyrhoral rhythm of secretion (approximately every hour), it reaches the portal hypothalamic-hypophyseal blood vessels along the axons of nerve cells, stimulates the synthesis and secretion of FSH and LH in the anterior pituitary lobe.

The third level of regulation includes anterior pituitary lobe (adenohypophysis), which produces following hormones: FSH, LH, prolactin, adrenocorticotropic hormone (ACTH), somatotropic hormone (STH), thyroid-stimulating hormone (TSH).

The fourth level of regulation includes *organs of peripheral endocrine system:* ovaries, adrenal glands, thyroid gland.

Inside the ovary, LH and FSH bind to the theca cells and granulosa cells, stimulating folliculogenesis and production of steroid hormones (estrogens, progestogens, and androgens), peptides (activin, inhibin, and follistatin), and growth factors.

In addition to their main functions, the substances secreted by the ovaries function as the hypothalamic-pituitary-ovarian system regulators, working on the hypothalamus and pituitary by the negative feedback mechanism and thereby reducing the secretion of GnRH and gonadotropins.

Ovarian steroids are also important for preparing the endometrium for implantation and developing the placenta in case of pregnancy onset.

The fifth level consists of target organs that have receptors for sex hormones in their tissues — the uterus, fallopian tubes, vaginal mucosa, mammary glands, and many other organs (skin, adipose tissue, bones, and central nervous system).

Neuroendocrine regulation of female reproductive function is described in more detail in volume I "Physiological obstetrics".

2.1. BIOSYNTHESIS OF HORMONES AND MECHANISMS OF THEIR ACTION

There are two groups of hormones: peptides and steroids. Each of these groups is characterized by its own way of biosynthesis and mechanism of action.

Peptide hormones of the female body: LH, FSH, hCG. Gonadotropins LH and FSH are synthesized and secreted by the cells of the anterior pituitary gland and stimulate steroidogenesis, follicle development, and ovulation.

Human chorionic gonadotropin (hCG) that has a similar structure is produced by the trophoblast and plays a crucial role in maintaining pregnancy.

LH, FSH, and hCG are heterodimers consisting of a common glycoprotein α-subunit and a β-subunit unique for each hormone, which provides specificity. Despite the fact that α- and β-subunit glycoproteins can be found in the free form circulating in the bloodstream, separately they do not have biological activity. However, measuring their blood levels is used in screening tests for such conditions as pituitary adenoma or pregnancy.

Steroid hormones of the female body. Sex steroid hormones are produced by the ovaries, adrenal glands, and placenta.

Steroid hormones production is based on cholesterol. All steroid-producing tissues, except the placenta, are able to produce cholesterol from acetate.

Estrogens are produced by aromatization of androgens with aromatase. In addition to the ovaries, aromatase is synthesized in significant amounts by adipose tissue, skin, and brain. It is noteworthy that a sufficient amount of estrogen can be produced by peripheral aromatization to trigger endometrial bleeding in the postmenopausal period, especially in women who are overweight and obese.

Circulating estrogens in women of reproductive age include estrone (E1), estradiol (E2), and estriol (E3).

Estrone is the main estrogen during the postmenopausal period, it is produced by the ovaries.

Estradiol is the main estrogen produced by the ovaries during the reproductive years. Estradiol level is maintained both by direct synthesis by granulosa cells of the developing follicle, and by conversion of less active estrone.

Estriol is the predominant estrogen during pregnancy, produced primarily by the placenta.

However, both estrone and estriol can also be produced by converting androstenedione.

Progesterone is also secreted by the ovaries, namely: luteinized cells of corpus luteum during the second phase of the menstrual cycle. Acting on all organs of the female reproductive system and on the mammary glands, progesterone prepares the body for the possible onset of pregnancy.

The ovaries also produce *androgen hormones* in response to stimulation of theca cells by luteinizing hormone. The main products are relatively weak androgens *androstenedione* and *dehydroepiandrosterone* (DHEA), and a small amount of *testosterone* is also secreted.

Although the adrenal cortex produces mainly mineralocorticoids and glucocorticoids, it also provides about half of the daily production of androstenedione and DHEA, and virtually all of sulfated DHEA (DHEA-S).

In women, 25% of circulating testosterone is secreted by the ovaries, 25% by the adrenal glands, and the remaining 50% is produced by converting androstenedione into testosterone.

Most of the steroids in the peripheral blood are bound to transport proteins. These proteins can be either specific proteins (e.g., sex hormone-binding globulin — SHBG, thyroxine-binding globulin, or corticosteroid-binding globulin), or non-specific proteins such as albumin. Only 1–2% of estrogens and androgens are present in a free, unbound form.

Only unbound steroid fraction is biologically active, although the low affinity of albumin for sex hormones allows steroids associated with this protein to exhibit some effects.

Free hormones level is in balance with the level of bound ones. In other words, the level of free, biologically active hormones is inversely related to the level of bound hormones, and bound hormone level is directly proportional to the transport proteins level. As a result, even small changes in the level of transport proteins expression can lead to significant changes in steroid hormones function.

Sex hormone-binding globulin (SHBG) is mainly produced by the liver, although it has also been found in the brain, placenta, and endometrium. SHBG level increases with hyperthyroidism, pregnancy, and after estrogen administration. In contrast, androgens, progestins, growth factors (GF), insulin, and corticoids lower the SHBG level. Weight gain, especially "central obesity" (when fat tissue grows mainly on the abdomen), significantly suppresses SHBG expression, that, in its turn, reduces bound hormones level and increases their activity.

Clinically, it is difficult to measure the unbound hormones level, and the results should be interpreted with caution.

Steroids are metabolized mainly in the liver, to a lesser extent — in the kidneys and intestines.

Estradiol hydroxylation leads to estrone or catechol-estrogens formation. These estrogens then conjugate with glucuronides or sulfates, forming water-soluble compounds that can be excreted with urine.

2.2. PEPTIDES AND THEIR ROLE IN THE REGULATION OF THE REPRODUCTIVE SYSTEM

Inhibin, activin, and *follistatin* are peptides secreted by granulosa cells in response to FSH stimulation.

Inhibin inhibits FSH secretion. Activin is produced by pituitary and granulosa cells and, conversely, stimulates FSH production by the anterior pituitary

cells. It also enhances FSH effect on the ovaries. Follistatin reduces FSH activity by suppressing activin.

Anti-mullerian hormone (AMH) is a peptide produced by granulosa cells of primordial follicles (less than 6 mm). AMH maintains oocyte maturation and follicle development. AMH level reflects the number of growing follicles in the ovary.

AMH level decreases with age (due to a decrease in the number of follicles), and with an increase in FSH and estradiol concentration.

Relaxin — a peptide secreted by preovulatory follicles and a corpus luteum. It is suggested that it facilitates follicle rupture during ovulation.

Growth factors are polypeptides acting through paracrine and autocrine effects. The most significant growth factors are insulin-like growth factors, epidermal growth factor, tumor necrosis factor α, and IL-1.

Insulin-like growth factors (IGF) are the most numerous group of growth factors. IGF II is produced by theca cells, granulosa, and luteal cells. IGF II increases gonadotropic action (FSH and LH) by stimulating granulosa cell proliferation, aromatase activity, and progesterone production.

2.3. MENSTRUAL CYCLE

Menstruation is cyclic uterine bleeding that occurs due to rejection of the uterine mucosa (endometrium) in case of failed pregnancy influenced by the action of hormones (mainly hypothalamic-pituitary-ovarian system hormones).

Menstruation occurs for a number of reasons, namely:

- reduced levels of estrogens and especially progesterone at the end of the two-phase cycle;
- vascular changes in the endometrium (first vasodilation with significant blood congestion, then vascular spasm, which is accompanied by ischemic, necrotic and destructive changes in endometrial tissue);
- appearance of proteolytic enzymes in a large quantity in the functional layer of the endometrium.

Menstrual cycle is the period from the first day of one menstruation to the first day of subsequent menstruation.

The first menstruation (*menarche*) usually occurs at the age of 11–14 years. After menarche onset, menstruation repeats cyclically every 28±7 days, and physiologically discontinues during pregnancy and lactation. At the age of 45–51 years, menopause occurs, and menstruation stops.

The duration of menstruation is about 4±6 days, the average volume of menstrual blood is 20–60 ml. About 70% of blood loss during menstruation occurs in the first 2 days.

Menstrual secretions consist of dark altered blood, mucus, vaginal epithelial cells, endometrial fragments, prostaglandins, enzymes, and bacteria.

Menstrual cycle duration is individual for each woman and can change during her reproductive life. The menstrual cycle is most stable at the age of 20 to 40 years and is most variable in the first 2 years after menarche (the beginning of menstruation) and in 3 years preceding menopause.

There are two functional phases in the ovarian menstrual cycle: preovulatory follicular and postovulatory luteal.

They correspond to the phases of endometrial changes: proliferative and secretory.

For most women, the luteal phase is stable and lasts for 13–14 days on average. Therefore, the variability of normal duration of menstrual cycle depends more on the change in follicular phase duration.

2.4. OVARY

Ovarian morphology. The ovary of an adult is a glandular organ of oval shape, 2–5 cm long, 1.5–3 cm wide and 1.5–1.5 cm high.

The ovary consists of three parts: external *cortical zone*, where the follicles and germinal epithelium are located; *medulla* containing connective tissue, interstitial cells and smooth muscle cells; *ovarian hilum*, through which arteries and nerves enter, and veins and lymphatic vessels exit.

The ovary performs two interrelated functions: formation of mature oocytes and production of steroid and peptide hormones that create an environment favorable to fertilization of an ovum and its subsequent implantation into the endometrium.

During each cycle, the endocrine function of the ovary correlates with the appearance and disappearance of follicles and corpus luteum.

Ovarian embryology. The ovary grows from three main cellular sources: (1) primordial germ cells, which originate from the yolk sac endoderm and differentiate into primary oogonies; (2) coelomic epithelial cells, from which granulosa cells evolve; (3) mesenchymal cells of the gonadal ridges, subsequently forming the ovarian stroma.

Primordial germ cells appear in the yolk sac by the 3rd week of gestation. During the 6th week of gestation, these cells migrate to the gonadal ridges, forming primary sex cords. After the primordial cells reach the gonads, they continue to multiply by mitotic division. From the 12th week of gestation, these oogonia enter meiosis and become primary oocytes. Primary oocytes, surrounded by a layer of granulosa cells, form a primordial follicle.

Ovarian reserve. All oogonia either develop into primary oocytes or undergo atresia. Currently, the prevailing theory is that new oocytes cannot be formed after birth, unlike male germ cells, which are formed continuously during adulthood.

Recent studies show that ovarian stem cells are able to form mature oocytes, which gives hope for great success in preserving and maintaining female fertility, but these data are preliminary and still quite contradictory.

The maximum number of oogonia (6–7 million oogonia) is acquired by the 20th week of gestation. By the time of birth, there are 1–2 million oogonia in the ovary. By the beginning of adolescence, there are less than 400 thousand, of which less than 500 oocytes will undergo ovulation. Thus, most of the oogonium undergoes atresia.

Follicular atresia is an active process of apoptosis that occurs under the control of hormones of the reproductive system. The process of apoptosis begins in utero and continues throughout life.

Oocytes maturation. As noted earlier, the primary oogonium enters the meiosis and turns into a primary oocyte or the oocyte of the I order. These oocytes become arrested in the prophase of the first meiotic division. Every month, the process of meiosis resumes in part of the oocytes. Meiosis I is completed only in the oocyte intended for ovulation in response to an increase in LH level. Meiosis II begins, which this time is suspended in the metaphase of the second meiotic division. Meiosis II is completed only if ovum is fertilized.

Stromal cells. Stroma of ovary includes interstitial cells, smooth muscle cells, and connective tissue cells. Connective tissue helps to maintain the ovarian structure. A group of interstitial cells surrounding the developing follicle differentiate into theca cells. Under the influence of gonadotropin, theca cells enlarge and accumulate intracellular lipids, which is typical for steroid-producing cells.

Hilus cells are another group of interstitial cells located in the ovarian hilum, whose structure and function are similar to testicular Leydig cells. Hyperplasia or neoplastic lesions in the hilus cells can lead to excessive testosterone secretion and, as a result, to virilization. The normal function of these cells is unknown, but due to their proximity to blood vessels and nerves, it is suggested that they can transmit system signals to the other parts of the ovary.

Hormonal activity of the ovaries. Properly functioning ovary produces and secretes estrogens, androgens, and progesterone in a strictly defined sequence, controlled primarily by the pituitary gonadotropins FSH and LH.

The most significant products of ovarian secretion are progesterone and estradiol. However, the ovary also secretes estrone, androstenedione, testosterone, and 17α-hydroxyprogesterone.

Sex steroid hormones play a crucial role in the menstrual cycle, preparing the uterus for implantation of a fertilized ovum. If implantation does not occur, steroids production decreases, endometrium undergoes involution and menstruation begins.

Gonadal peptides and menstrual cycle. From a variety of gonadal peptides, three (inhibin, activin, and follistatin) modulate gonadotropic activity.

As their names imply, inhibin reduces and activin stimulates gonadotropic function. Follistatin suppresses FSHβ gene expression by binding to this site, thereby preventing activin from interacting with its receptor.

Follicles development begins with the primordial follicles that were formed in the antenatal period. These follicles contain an oocyte surrounded by a layer of granulosa cells and arrested at the first meiotic division. The follicles are separated from the ovarian stroma by a thin basement membrane.

Preovulatory follicles do not contain blood vessels. Thus, they are critically dependent on diffusion and on the subsequent development of intercellular gap junctions used to obtain nutrients and release metabolic waste. Transport of steroid precursors from the theca layer to granulosa cells also occurs due to diffusion.

At the stage of primary follicle, granulosa cells of the developing follicle become cuboid and increase in size, forming a pseudostratified layer.

Intercellular gap junctions are formed between granulosa cells and developing oocyte, which contributes to the passage of nutrients, ions, and regulatory factors from cell to cell. Gap junctions also allow cells, without gonadotropin receptors, to receive signals from cells that can express the receptors. As a result, hormone-mediated effects spread throughout the follicle.

During this stage, the oocyte begins to secrete glycoproteins, forming a cell-free layer called *zona pellucida*.

Zona pellucida contains at least three proteins: ZP1, ZP2, and ZP3. In modern physiological models, the acrosome receptors of the sperm cell head recognize ZP3. This interaction releases acrosome contents and promotes its penetration through the pellucid zone and, as a result, ovum fertilization. Acrosomal enzymes induce changes in ZP2, which leads to the seal of the layer. This prevents the ovum from being fertilized by more than one sperm cell.

The development of a secondary (or preantral) follicle involves the final maturation of the oocyte and a further increase in the number of granulosa cells. The stroma around the layer of granulosa cells differentiates into theca interna and theca externa.

Tertiary follicles, or antral follicles, are formed by further development of selected follicles. Follicular fluid accumulates between granulosa cells, eventually forming a fluid-filled follicular cavity.

Follicular fluid consists of plasma filtrate and factors secreted by granulosa cells. There is a higher concentration of these factors, including estrogens and growth factors in the follicular fluid than in plasma, which plays a crucial role in follicle development.

Further accumulation of antral (follicular) fluid leads to a rapid increase in the size of follicle and formation of preovulatory (Graafian) follicle.

The early stages of follicle development (up to the secondary follicle) do not need to be stimulated by gonadotropin, so they are called "gonadotropin-independent" stages of development. Final follicle maturation requires an adequate level of circulating LH and FSH, so the final stage is called "gonadotropin-dependent".

2.5. PHASES OF THE MENSTRUAL CYCLE

Follicular phase. By the end of the menstrual cycle, levels of estrogen, progesterone, and inhibin drop abruptly, leading to an increase in FSH level, which is responsible for "awakening" and activating a group of follicles including a follicle intended for ovulation.

In the middle of the follicular phase, the follicles produce estrogen and inhibin, their level increases, that reduces FSH level by a negative feedback mechanism.

It is believed that this drop in the FSH level promotes the selection of the follicle, which becomes dominant. This is associated with the fact, that the remaining follicles express fewer FSH receptors, so they become less sensitive to FSH when its concentration decreases.

In response to FSH stimulation, granulosa cells multiply, increase the expression of aromatase, and, in the presence of estradiol, expression of LH receptors on granulosa cells increases.

With the appearance of LH receptors in the late follicular phase, granulosa cells start to produce a small amount of progesterone. Progesterone suppresses the proliferation of granulosa cells, which slows down follicle growth.

Ovulation. By the end of the follicular phase, the estradiol level rises significantly. An acute rise in estradiol level changes the negative feedback to a positive feedback both in the hypothalamus and pituitary, which leads to LH release. The reasons for this change are not fully understood, but it is associa-

ted with changes in neurons that express kisspeptin (a protein that enhances GnRH and LH production).

A small preovulatory increase in progesterone concentration causes an elevation of the FSH level, which occurs simultaneously with an LH surge.

A surge in LH level affects both granulosa cells and theca cells of the preovulatory follicle, completing the processes of the follicular phase and triggering the expression of genes responsible for ovulation and luteinization. In addition, the LH surge initiates the re-entry of the oocyte into the meiosis, prostaglandin production and luteinization of granulosa cells.

The average duration of LH surge is 48 hours, and ovulation occurs approximately 30 to 40 hours after the beginning of LH elevation.

For an ovulatory surge of LH, serum estradiol level must exceed 200 pg/ml for approximately 50 hours and remain such until the LH level begins to rise. This regulation by the positive feedback mechanism is facilitated by a low progesterone level in the serum.

The follicle enlarges to 20 mm in diameter due to the active production of follicular fluid by granulosa cells. Enzymes in the fluid affect the basement membrane, facilitating follicle rupture and oocyte release. It is proven that follicle rupture is not associated with an increase in its hydrostatic pressure, but occurs as a result of collagen destruction in its wall.

Luteal phase. After ovulation, the remaining follicular cells turn into the corpus luteum or yellow body. The process of morphological and functional cell transformation under the influence of LH is called luteinization.

Granulosa cells and theca cells proliferate and hypertrophy, forming luteal cells. During the formation of corpus luteum, the basement membrane that separates granulosa cells from theca cells disappears, which promotes the vascularization of previously avascular granulosa cells. Vascularization gives luteal cells access to low-density lipoproteins (LDL) circulating in the blood, which are a source of cholesterol precursors for steroid synthesis.

Under the influence of LH, corpus luteum produces estradiol, progesterone, and inhibin A. They, in turn, inhibit FSH production to prevent follicle development during the luteal phase.

Corpus luteum exists and actively functions for 10 days, and then regresses in 3–4 days if pregnancy does not occur. Blood supply of corpus luteum decreases, and luteal cells undergo apoptosis and are replaced by connective tissue — corpus albicans is formed.

Due to corpus luteum disappearance, levels of progesterone, estradiol and inhibin drop, and menstruation begins. In cycles when fertilization occurs, an

increase in HCG levels supports corpus luteum and progesterone production until 8–12 weeks of gestation.

The rise of the progesterone level in the luteal phase of the cycle prepares the uterus for a possible pregnancy. Progesterone causes endometrial decidualization, suppresses uterine contractions, increases cervical mucus viscosity, induces breast tissue growth and increases body temperature.

For the existence and hormonal activity of corpus luteum, permanent LH secretion is necessary, full dominant follicle development, which is ensured by FSH secretion. If fertilization has occurred, chorionic gonadotropin (hCG) supports the existence of corpus luteum. Serum level of progesterone rises to a maximum about 8 days after the ovulatory surge of LH.

Progesterone provides endometrial maturation and inhibits the growth of new follicles. Morphological changes of the endometrium in the luteal phase are so characteristic that they allow determining the correspondence of the endometrium structure to the day of the menstrual cycle.

Implantation usually occurs on 22–23 day of the menstrual cycle, when secretory activity of the endometrial apocrine glands is maximum.

A defect of the luteal phase of the menstrual cycle may result from a functional deficiency of corpus luteum.

2.6. ENDOMETRIUM

Endometrium consists of two layers: basal, adjacent to the myometrium, and functional, directed to the uterus lumen.

The basal layer practically does not change during the menstrual cycle and serves as a reserve source for the regeneration of the functional layer after endometrium rejection during menstruation.

The functional layer is divided into a more superficial thin compact layer with an abundant cell stroma and a deep spongy layer with glands and loosely organized stroma and interstitial tissue.

After the menstruation, glandular and stromal cells of the functional layer rapidly proliferate affected by estrogen. This period of rapid growth, the proliferative phase, corresponds to the follicular phase in the ovary.

After the menstruation, the thickness of the endometrium is 1–2 mm. By the time of LH surge, the endometrium is approximately 12 mm thick.

After ovulation, the endometrium is transformed into secretory tissue, which corresponds to the secretory phase in the endometrium and coincides with the luteal phase in the ovaries. Glycogen-rich vacuoles appear in the cells lining the glands, which, under the effect of progesterone, move to the glan-

dular lumen and release their secretions. The glands become more sinuous; a large number of spiral arteries also appear.

If the implantation of blastocyst does not occur, progesterone level drops, and the endometrial glands begin to degrade. Polymorphonuclear leukocytes and monocytes from nearby vessels infiltrate the endometrium. The spiral arteries contract, which leads to local ischemia. Lysosomes secrete proteolytic enzymes that accelerate tissue destruction.

Prostaglandins are present in endometrial tissues, especially prostaglandin F2α, which is responsible for arteriolar vasospasm. Prostaglandin F2α also provides myometrial contraction, which aids the rejected endometrium movement along the genital tract.