MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

BUKHARA STATE MEDICAL INSTITUTE

NEUROENDOCRINE SYNDROMES IN GYNECOLOGY

Educational and methodical manual for students of the VI course medical and medical-pedagogical faculties of medical universities

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The theoretical part

Neuroendocrine syndromes are conditions in which pathological changes develop simultaneously in the nervous and endocrine systems. Neuroendocrine gynecological syndromes have a common pathogenesis - a violation of the hypothalamic-pituitary system, as the most important link in the regulation of generative functions of the female body, however, each of these syndromes in the presence of a common pathogenesis is characterized by a predominance of symptoms that determine the specific manifestations of the syndrome**.**

Premenstrual syndrome

Premenstrual syndrome (PMS) is a complex symptom complex characterized by various psychoemotional, vegetative–vascular and metabolic-endocrine disorders manifested in the luteal phase of the menstrual cycle.

PMS is one of the most common neuroendocrine syndromes, the frequency of which, according to various authors, ranges from 25-75%. It should be noted that the prevalence of PMS, which affects women from menarche to menopause, has a certain age gradation. Thus, according to T.A. Serova (2000), N. Frederickson (1997), the frequency of PMS at the age of 30 is about 20%, and after 30 years, PMS occurs in almost every second woman.

There are **the following risk factors** for the development of PMS:

* Caucasian race;
* engaging in intellectual work;
* late reproductive age;
* presence of stressful situations;
* frequent pregnancies or lack of pregnancies;
* miscarriages and/or artificial abortions in the anamnesis;
* the presence of gynecological operations in the anamnesis;
* inflammatory diseases of the genitals in the anamnesis;
* traumatic brain injuries, neuroinfections;
* other neuroendocrine diseases, in particular, obesity;
* insufficient physical activity;
* unbalanced nutrition (lack of calcium, potassium, trace elements, vitamins B and C, polyunsaturated fatty acids, antioxidants in the diet);
* lack of a rational work and rest regime.

Etiology and pathogenesis of premenstrual syndrome. The etiology and pathogenesis of PMS are not completely clear. Since the first description of this syndrome, it has been attributed to the number of endocrine diseases, but until now the question is debated whether PMS is mental, especially in the case of predominance of affective disorders, or an endocrine disorder.

Historically, the hormonal theory, proposed in 1931 by Robert Frank, was the first to appear, according to which PMS is a consequence of absolute or relative hyperestrogenism in the luteal phase of the menstrual cycle. An absolute or relative increase in the level of estrogens in the blood serum causes sodium retention, which, in turn, leads to the accumulation of intercellular fluid, which is clinically manifested in peripheral edema, mastalgia, bloating, weight gain, arthralgia. Irritability and headache and some other neurological and mental manifestations of PMS can be explained by swelling of the brain.

It is believed that the decisive factor in the genesis of PMS is not the level of sex hormones, which does not differ from that of healthy women, but fluctuations in their content during the menstrual cycle (Fig.1). Estrogens and progesterone have been proven to have a significant modulating effect on the central nervous system through gene mechanisms (interaction with nuclear receptors), direct influence on the membrane of neurons and their synaptic function, and not only in the centers responsible for the activity of the reproductive system, but also in the limbic parts of the brain that regulate emotions, behavior and sleep.

The role of hyperprostaglandinemia in the pathogenesis of PMS is also significant. Since prostaglandins are universal tissue hormones that are synthesized in almost all organs and tissues, a violation of their production can manifest a wide variety of clinical effects (migraine headaches, nausea, vomiting, bloating, diarrhea and various vegetative-vascular reactions).

Currently, much attention in the pathogenesis of PMS is paid to disorders of the metabolism of neurotransmitters in the central nervous system (opioid peptides - enkephalins and endorphins, as well as serotonin, dopamine, catecholamines, γ-aminobutyric acid, etc.) and related peripheral neuroendocrine processes.

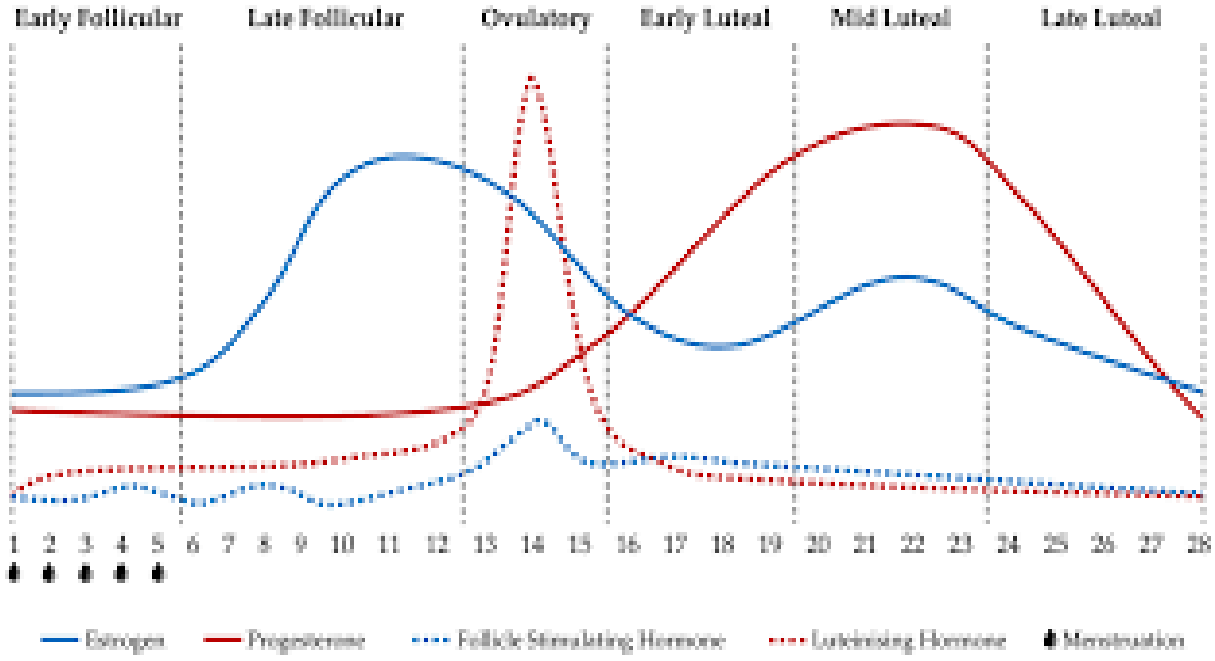

Fig.1. Fluctuations in hormone levels during the menstrual cycle

Thus, according to the latest, most modern theory, PMS is considered as a functional disorder of the central nervous system due to the action of unfavorable external factors against the background of congenital or acquired lability of the hypothalamic-pituitary-ovarian system.

Clinic of premenstrual syndrome. The course of PMS is characterized by an individual variety of clinical manifestations and cyclical nature characteristic in all cases, i.e. the manifestation of symptoms in the second phase of the menstrual cycle (MC).

Depending on the number of symptoms of PMS, their duration and intensity according to the classification of N.N. Kuznetsova (1970), it is proposed to distinguish between its mild and severe forms:

* mild form of PMS - the appearance of 3-4 symptoms 2-10 days before the onset of menstruation with significant severity of 1-2 of them;

* severe form of PMS - the appearance of 5-12 symptoms 3-14 days before the start of menstruation with a significant severity of 2-5 of them.

According to the same classification , three stages of PMS are distinguished during the development of the disease:

Compensated stage - PMS symptoms do not progress over the years, appear in the second phase of the MC and stop with the onset of menstruation.

Subcompensated stage – cases in which the severity of the disease worsens over time, and the symptoms of PMS disappear only with the cessation of menstruation.

Decompensated stage - the manifestations of PMS continue for several days after the end of menstruation.

As part of the PMS, about 150 symptoms are currently being considered. When trying to classify them , depending on the lesion of one or another function or system of the body , the following symptom complexes are distinguished:

Psychoemotional disorders:

* emotional lability, irritability, excitement
* depression, tearfulness
* apathy
* memory degradation
* impaired concentration
* fatigue, weakness
* sleep disorders
* feeling of fear, feeling of longing, suicidal thoughts
* libido disorders
* hypersensitivity to sounds and smells
* olfactory and auditory hallucinations.

Neurological symptoms:

* headache (migraine)
• dizziness
* movement coordination disorders
* hyperesthesia
* increased frequency or occurrence of epilepsy attacks

* cardialgia or arrhythmia attacks
* increased frequency or occurrence of asthma attacks
* phenomena of vasomotor rhinitis.

Violations of the water-electrolyte balance:

* peripheral edema
* weight gain
* breast enlargement/mastalgia
* bloating
* change in the specific gravity of urine, violation of diuresis.

Gastrointestinal symptoms:

* changes in appetite up to anorexia or bulimia
* changing taste preferences
* nausea, vomiting
* flatulence.

Skin manifestations:

* vulgar acne
* changes in the fat content of the skin
* excessive sweating
* urticaria
• itching
* hyperpigmentation.

Musculoskeletal manifestations:

* pain in bones, joints, muscles, lumbalgia
* decreased muscle strength.

Depending on the prevalence of certain symptoms in the clinical picture, there are 4 forms of PMS:

The main clinical forms and symptoms of PMS (Smetnik V.P., Komarova Yu.A., 1988)

Psychovegetative	Edematous
• * irritability • * depression • * tearfulness • * touchiness • * aggressiveness • * numbness of the hands • * drowsiness • * forgetfulness	• * swelling of the face, shins, fingers • * bloating • * itchy skin • * weight gain by 4-8 kg • * mastalgia/mastodynia • * increase in size (≥ 2 sizes) of shoes • * local edema (for example, edema of the anterior abdominal wall or feet, knees)
Cephalgic	**Crisis**
• * headaches by type of migraines • * tension headaches (extracranial)	• * increased blood pressure • * feeling of compression behind the sternum • * numbness and cold of the extremities • * increased heart rate with unchanged ECG

• * vascular headaches (intracranial) • * combined forms of headaches	• * chills • * * increased urination with the end of the attack and so

It is extremely rare to observe atypical forms of PMS, which include:

* hyperthermic (cyclic increase in body temperature to 37.2-38 °C in the absence of signs of inflammatory processes in the body•

* * hypertensive (cyclic daytime drowsiness)

* cyclic allergic reactions up to Quincke's edema

* ulcerative gingivitis and stomatitis

* cyclic iridocyclitis (inflammation of the iris and ciliary body).

Diagnosis of premenstrual syndrome. Diagnosis of PMS primarily involves daily recording of symptoms for at least two consecutive menstrual cycles. This allows not only to identify the relationship of symptoms with the dynamics of the menstrual cycle, which is important for clarifying the diagnosis, but also to determine which of them are subjectively the most severe for the patient.

Hormonal studies include the determination of serum concentrations of gonadotropins, prolactin, female (estradiol, progesterone) and male (testosterone, dehydroepiandrosterone sulfate) steroids or derivatives of the latter in urine (17-ketosteroids). It is also possible to assess the hormonal status by functional diagnostic tests.

The state of the hormone-producing function of the ovaries is indirectly studied by ultrasound examination of the genitals on the basis of determining their morphological characteristics (biometrics, quality and ratio of stroma and follicular apparatus, state of folliculogenesis), as well as the state of the uterus (thickness and features of the endometrium, structure of the myometrium).

In the presence of cerebral symptoms, extended ***computer tomography or magnetic resonance tomography*** of the head is advisable to exclude structural changes in the brain, as well as electroencephalography to determine the functional state of the central nervous system.

In the edematous form of PMS, ***methods are used to detect retention or redistribution of fluid in the body:*** measurement of diuresis, examination of excretory kidney function, determination of body weight and body mass index, which is calculated by the formula: Body mass index = weight (kg) / height (m)2.

With soreness and swelling of the mammary glands, ***ultrasound and / or mammography*** is used for differential diagnosis of mastodynia in PMS with dyshormonal breast diseases accompanied by mastalgia.

If necessary, related specialists are involved in the examination – a therapist, a neurologist, a psychiatrist, an endocrinologist, a mammologist.

Treatment of premenstrual syndrome. The first stage of treatment of any form of PMS is psychotherapy with an explanation of the nature of the disease, auto-training, compliance with the daily and rest regime (full sleep for at least 8 hours, moderate physical activity), as well as diets (restriction of fluid intake, exclusion of coffee, chocolate, spicy, smoked, salted, alcohol, smoking, restriction

of animal fats and carbohydrates). General massage and collar area massage are also recommended. Today, it is statically proven that women who regularly exercise are significantly less susceptible to the development of PMS. The therapeutic and preventive effect of physical activity is pathogenetically justified due to its positive effect on metabolic processes in the body, in particular, the serotonergic effect of dosed physical exercises increases the production of endorphins.

The use of ***vasoactive drugs*** is advisable in almost all variants of the course of PMS, which, due to their angioprotective effect, improvement of microcirculation, positive inotropic effect on the myocardium, stabilize regional hemodynamics. These include: Trental (Pentoxifylline), which is prescribed per os no 100 mg 2-3 times a day or intravenously at 100-200 mg / day; Sermion (Nicergoline) - 5-10 mg 2-3 times a day orally in the second phase of MC.

Venotonics and drugs that affect blood rheology (Escuzan, Ginkorn fort, Memoplant) increase the tone of veins, as well as small arteries and arterioles, reduce vascular permeability, preventing filtration of low-molecular proteins, electrolytes and water into the intercellular space. These drugs are taken in average therapeutic doses in the second phase of the cycle for 2-6 months.

Given the significant role of prostaglandins in the genesis of PMS, the use of prostaglandin synthesis inhibitors is rational. To do this, nonsteroidal anti-inflammatory drugs are used: Indomethacin, Ibuprofen, Naproxen, Nimegesic, Naiz, etc. in average therapeutic doses during the manifestation of clinical symptoms.

In recent years, modern antidepressants have been widely used for the treatment of PMS, combining a mild thymoanaleptic effect (relieving anxiety, tension, improving mood and general mental well-being) with good tolerability. These drugs successfully stop both permanent and paroxysmal psychovegetative symptoms in 65-70% of women with PMS. The most effective selective serotonin reuptake inhibitors are: fluoxetine (Prozac, Profluzac) - 20 mg, sertraline (Zoloft) - 50 mg, fluvoxamine (fevarin) - 50 mg, citalopram (Cipramil) - 20 mg. Most often, in patients with PMS, one tablet of the drug is a sufficient dose, while the intake is carried out cyclically: in the first phase, the dose decreases slightly, reaching its maximum value by the time of the most pronounced manifestation of PMS symptoms. The full therapeutic effect usually occurs after 2-4 months. The course of treatment is 4-6 months, but maintenance therapy is possible for up to 12 months.

Antioxidants that control the level of free radical oxidation reactions and prevent the accumulation of their toxic products in the body take an active part in various metabolic links (in particular, in the respiratory chain of mitochondria), synthesis and metabolism of many biologically active substances, affect the state of the regulatory systems of the cell and its structure, which makes it possible to use them also as adaptogens. The most powerful natural antioxidants are vitamins C, A, E, trace elements zinc, copper and selenium.

For the relief of cyclic mastalgia, a combined homeopathic drug Mastodinone, the main active component of which is Agnus castus (prutnyak), which has a

dopaminergic effect and reduces the secretion of prolactin, can be effective. It is applied 30 drops or 1 tablet 2 times a day for at least 3 months.

Of the greatest interest are drugs that have a selective estrogen-receptor modulating effect, which, first of all, is characteristic of phytoestrogens contained in Remens, Klimadinon, Mulimen preparations. They are prescribed 15-30 drops 2-3 times a day in the second phase of the MC or in a continuous mode.

One of the most common methods of treating PMS is the suppression of cyclic (endocrine and biochemical) changes occurring in the body. For this purpose, monophasic combined oral contraceptives are used (Fig.2).

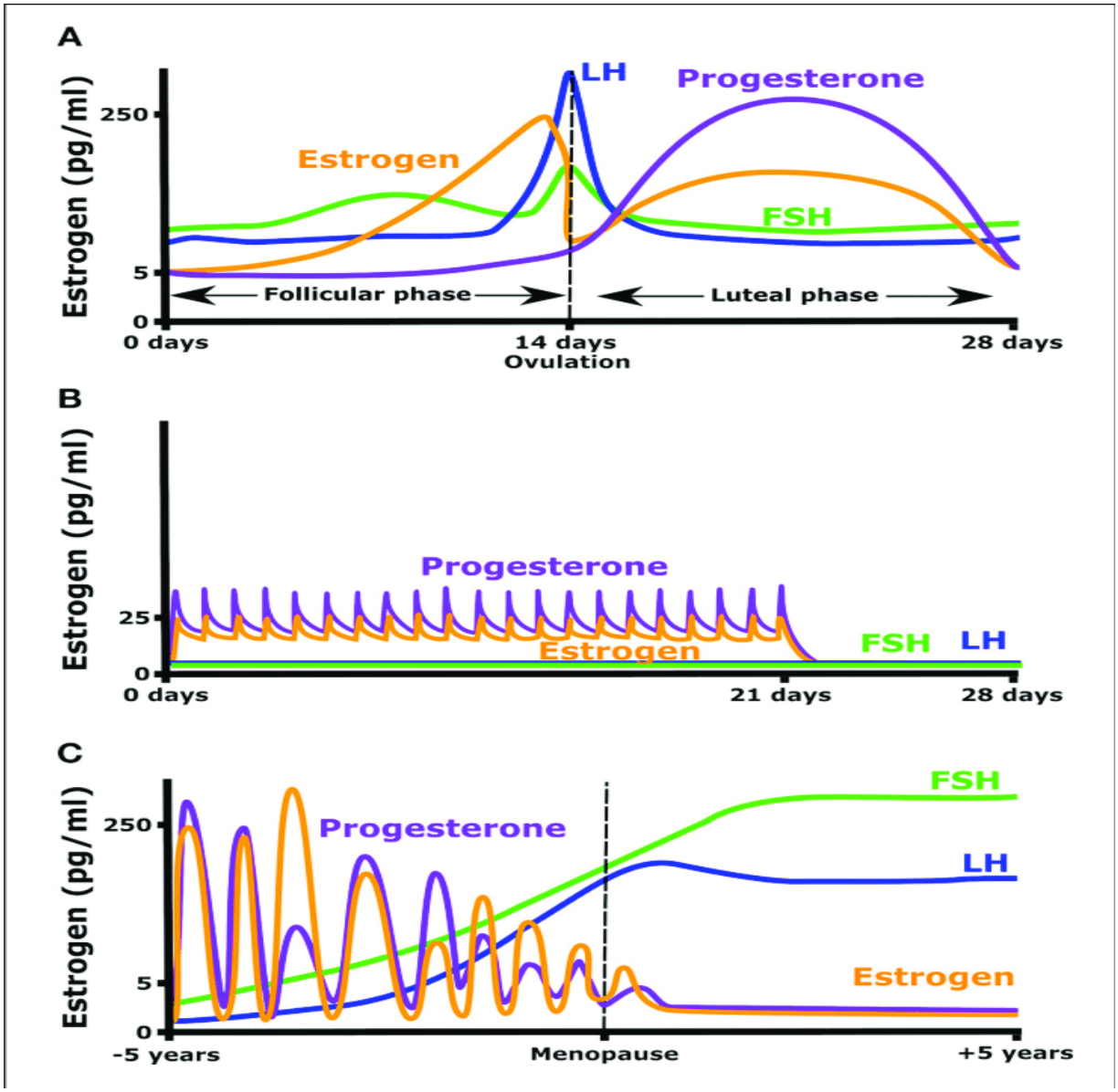

Fig.2. The effect of hormonal drugs on the menstrual cycle

When choosing these drugs, it is necessary to pay attention to the gestagenic component, the absence of its side effects (estrogenic, androgenic, corticosteroid, etc.), which is due to the interaction of gestagens with receptors of other steroid hormones. A drug containing drospirenone in its composition is preferable.

Drospirenone is a unique progestogen that also has antiandrogenic and antimineralocorticoid activity, since it is a derivative of spironolactone, an aldosterone blocker.

When using this drug, a significant decrease in the severity of PMS symptoms such as fluid retention, mastodynia and mastalgia was revealed. The beneficial effect on symptoms such as mood lability and irritability, apparently, is due to the antiandrogenic effect of drospirenone, as well as the relief of the cyclical appearance of acne in some women.If a woman has contraindications for taking oral steroids, it is advisable to introduce the Mirena intrauterine system, which provides controlled diffusion of levonorgestrel 20 mg / day without significant systemic absorption for 5 years.

Gestagenotherapy is indicated in the complex of treatment of PMS with insufficiency of the luteal phase of the cycle. It is advisable to give preference to progesterone derivatives devoid of androgenic, estrogenic and corticosteroid activity and, conversely, with inherent antiandrogenic and antiestrogenic properties, which ensures their good tolerability and the necessary spectrum of action. They are prescribed in average therapeutic doses in the second phase of the cycle (from the 11th to the 25th or from the 16th to the 25th day of the MC) - Dufaston (Dydrogesterone) 10 mg twice a day; Utrozhestan (Progesterone) 100-200 mg / day per os.

The course of treatment of PMS, as a rule, is quite long and can occupy the luteal phases of several consecutive MC.

Forecast. More often favorable. It is necessary to explain to the patient that lifestyle changes (diet, exercise, massage) will lead to an improvement in well-being and quality of life. In addition, patients should be notified that PMS symptoms return with discontinuation of therapy, may increase with age or after childbirth and are absent during pregnancy and menopause.

Menopausal syndrome

Menopausal syndrome is a symptom complex that develops in some women in the process of biological transformation of the body during the transition period and complicates the natural course of the menopausal period.

In the menopausal period , the following stages are distinguished:

* premenopause – the period preceding menopause (about 2-5 years)
* menopause – the last menstrual bleeding
* postmenopause is a period of life that occurs 2 years after menopause.

Menopause includes all of the above periods of a woman's life and is characterized by a gradual decrease and complete shutdown of the generative, menstrual and hormonal function of the ovaries. It is a long period of transition from reproduction to old age.

Perimenopause is a period characterized by endocrinological and clinical manifestations of estrogen deficiency. It includes premenopause (2 years before the cessation of menstruation) and 2 years after the last menstruation. The duration of premenopause varies, but is usually 4-6 years. 1.5-2 years after the last menstruation, postmenopause begins, which continues throughout later life.

Etiology and pathogenesis of menopausal syndrome. The modern concept of the pathogenesis of menopausal syndrome attaches great importance to age-related changes in hypothalamic structures. As you know, gradually over the years, the number of primordial follicles decreases, and by the age of 40 there are from 5 to 10 thousand of them. Accordingly, the secretion of estrogens decreases. In addition, the qualitative composition of the produced estrogens changes. In the menopausal period, estriol is considered to be the most active fraction of estrogens. A decrease in the concentration of estrogens leads to an increase in gonadotropins (more than 10 times) by the feedback mechanism (Fig.5). The ratio of LH and FSH is changing. At the reproductive age, this ratio is equal to one, in the menopausal period, FSH is released more (ratio 0.43). The

loss of trophic effects of estradiol on the genitourinary system and bones leads to the development of complications, which include atrophic vaginitis, urinary disorders and osteoporosis. With the onset of menopause, atherogenic changes in the lipid spectrum develop, contributing to the development of atherosclerosis.

Clinical manifestations of menopausal syndrome. Menopausal syndrome is characterized by vegetative-vascular, neuropsychiatric and metabolic-trophic symptoms that occur in 70-80% of women against the background of a decrease in hormonal function of the ovaries and are more often manifested in perimenopause due to estrogen deficiency. The frequency, nature and severity of menopausal disorders largely depends on external factors (work and rest regime, nutrition, bad habits, etc.), concomitant extragenital diseases that aggravate the course of menopausal syndrome.

Complaints of patients can be divided into three groups:

* neurovegetative - hot flashes, sweating, dizziness, paresthesia, tingling in the heart, tachycardia. All this, as a rule, happens at the moment of high tide.

* psycho-neurotic - impaired memory, sleep, bad mood up to depression.

* somatic - atherosclerosis, systemic osteoporosis, atrophic changes on the part of internal organs.

The pathogenesis of vasomotor symptoms of menopause has not been definitively established. The immediate cause of hot flashes is considered to be the expansion of peripheral vessels, which leads to increased blood flow and an increase in skin temperature. The development of tides is based on the dysfunction of the thermoregulatory center located in the hypothalamus and maintaining body temperature in the normal range (thermoregulatory zone). In women with hot flashes, there is a narrowing of the boundaries of the thermoregulatory zone. At the same time, even a slight increase in body temperature, which exceeds the upper limit of the specified range, causes sweating and peripheral vasodilation, accompanied by a feeling of a rush. Norepinephrine and serotonin levels play an important role in thermoregulation, changes in which are noted with a decrease in estrogen levels. An increase in the content of norepinephrine in the brain and a lack of serotonin cause a narrowing of the boundaries of the thermoregulatory zone. During hot flashes, a sharp rise in the levels of norepinephrine metabolites correlates with an increase in body temperature and heat transfer. A decrease in serotonin levels occurs in parallel with a decrease in estrogen levels during

menopause. Other neurotransmitters, for example, β-endorphins, may also have a certain value.

Tides develop more often in spring and autumn, less often in winter and summer. The tides last from a few seconds to 1-2 minutes. There are three forms according to the number of tides:

* up to 10 tides per day - a light form.
* 10-20 - moderate severity.
* persistent disability is a severe form.

In addition to hot flashes , the following symptoms may occur:

* violation of the menstrual cycle in 90% of women begins already about 4 years before menopause.
* urological disorders (50%) due to atrophy of the urethra and neck of the bladder are manifested by urinary incontinence (coughing, laughing, walking fast), frequent cystitis and pyelonephritis.
* sexual disorders: decreased libido, vaginal dryness, dyspareunia.
* emotional disorders: irritability, mood swings, depression, phobias.
* osteoporosis, accompanied by an increased risk of bone fractures.
* complications of atherosclerosis, first of all, coronary heart disease.
* dementia; in women, Alzheimer's disease develops 2-3 times more often than in men and estrogen deficiency is given importance in its pathogenesis.

The time of occurrence and the degree of severity of these symptoms are subject to significant individual fluctuations, but at the same time they are subject to a certain chronological pattern in the sequence of their manifestation.

Atrophic vaginitis is characterized by a sharp thinning of the vaginal mucosa, the cessation of proliferative processes in the vaginal epithelium. Clinically, this is manifested by vaginal dryness, itching, dyspareunia. In healthy women of reproductive age, the pH values of the vaginal contents are in the range of 3.5-5.5, which is provided by lactobacilli that convert glucose into lactic acid. The latter is formed from glycogen located in the cells of the multilayer squamous epithelium, falling after peeling into the lumen of the vagina. Lactobacilli, in addition to lactic acid, produce other antibacterial components, including hydrogen peroxide. Lactobacilli, low pH, as well as immunoglobulins produced by the paraurethral glands, are a kind of protection against recurrent vaginal infection (protective environmental environment).

Against the background of estrogen deficiency in postmenopause, glycogen production in epithelial cells decreases, the number of lactobacilli decreases significantly or disappears completely. As a result, the pH of the vaginal contents increases, which contributes to a decrease in its protective properties and the appearance of a variety of aerobic and anaerobic pathogenic flora in the vagina.

In the pathogenesis of osteoporosis, a leading role is played by a decrease in the level of estrogens and testosterone, which have an anabolic effect and contribute to the retention of calcium by bone tissue.

It is known that bone tissue after the cessation of growth of the body continues to be constantly updated, remodeling occurs in it with a certain

periodicity in different parts of the skeleton - resorption of the "old" bone by osteoclasts and the formation of new bone tissue by osteoblast cells.

In women, on average up to 35 years old, i.e. up to the age of the most active ovarian function, these processes are carried out with a noticeable advantage of formation over resorption, which leads to the achievement of the so-called peak bone mass. Then the process of resorption begins to prevail, and from that time on, women begin to lose about 0.5% of bone tissue per year. After menopause, the rate of bone loss increases to 1-3% per year.

The loss of bone mass in menopause is primarily accompanied by bone damage with a predominance of spongy matter (vertebral bodies, distal parts of the forearm bones, etc. Senile osteoporosis develops after the age of 70 and is characterized by a predominant lesion of tubular bones with an increase in fractures of the femoral neck (Fig.8). In accordance with changes in bone density, with a decrease of 10%, the risk of fractures of the vertebral column and the proximal part of the femur increases 2-3 times. The decrease in the density of the spongy substance of the vertebrae in early postmenopause is directly related to the initial volume of bone tissue: the higher the density of the latter, the greater the absolute loss. Bone loss is especially great in early postmenopause, when the mass of the spongy substance of the vertebral processes decreases by 5% per year, and the cortical layer - by 1.5%.

In the development of age-related osteoporosis, parathyroid hormone acts as a mediator. The content of calcitonin, the formation of which is stimulated by estrogens, also decreases. Changes in mineral homeostasis and bone tissue deficiency develop against the background of a decrease in the function of the parathyroid glands, endocrine kidney function and other manifestations of age-related involution.

Diagnostics. Based on the presence of clinical symptoms and the cessation of menstruation in women.

Treatment of menopausal syndrome. Treatment is indicated for moderate to severe forms. Treatment should be carried out in stages.

The first stage is non-drug therapy:

* morning gymnastics
* physical therapy
* general massage
* proper nutrition (vegetables, fruits, vegetable fats should prevail in the diet)
* physiotherapy treatment (collar with novocaine on Shcherbak, galvanization of the brain, electroanalgesia - procedures 7-8 times)
* spa treatment - hydrotherapy, balneotherapy, radon baths.

The second stage is non-hormonal drug therapy*:*

* vitamins A, C, E improve the condition of the intermediate brain and help well with the appearance of the first symptoms
* neuroleptic drugs - drugs of the phenothiazine series - meterazine, stagerazine, triftazine, frenolone. They act at the level of the intermediate brain, affect subcortical structures.
* tranquilizers - diazepam, elenium.

The third stage is hormone replacement therapy (MGT).

The principles of hormone replacement therapy in the perimenopausal period are based on the sequential administration of estrogens and progestins in a cyclic mode to alleviate menopausal symptoms and maintain regular cycles. The strategy of hormone replacement therapy provides for the selection of the lowest, but necessarily adequate dose regimen, taking into account the urgent need to prevent proliferative effects on the endometrium and mammary glands by the indispensable use of progestins in a cyclic or continuous mode.

With pronounced signs of aging of the urogenital system, estrogens with specific colpo- and urotropic activity – estriol and its analogues - are the means of choice. When prescribing MGT to patients with local urogenital disorders, the goal is to restore the normal functional state of hormone-dependent tissues of the urogenital system and stimulate the mechanisms of natural biological protection in the lower parts of the genitourinary system.

In the treatment of menopausal syndrome, only natural estrogens are used, identical in chemical structure to estrogens synthesized in the female body:

1. Estradiol and derivatives (17ß-estradiol; estradiol valerate; estradiol benzonate; conjugated equine estrogens).
2. Estrone (conjugated equine estrogens).
3. Estriol (estriol; estriol succinate).

There are 3 main MGT modes:

1. Monotherapy with estrogens or progestogens
2. Combination therapy (estrogen-progestogenic) in a cyclic mode
3. Combination therapy (estrogen-progestogenic) in a monophasic continuous mode.

With an intact uterus, the choice of therapy and drug regimen depends on the phase of the menopausal period.

In perimenopause, with an intact uterus, combined cyclic therapy is prescribed. Recommended medications:

* estradiol valerate 2 mg and levonorgestrel 0.15 mg, course 6-12 months;
* estradiol valerate 2 mg and norgestrel 0.5 mg, course 6-12 months;
* estradiol valerate 1-2 mg and medroxyprogesterone acetate 10 mg, course 6-12 months;
* 17ß -estradiol 2 mg and norethisterone acetate 1 mg, course 6-12 months;
* estradiol valerate 2 mg and cyproterone acetate 1 mg, a course of 6-12 months

(indicated for symptoms of hyperandrogenism in menopause).

In postmenopause, combined continuous therapy is used:

* tibolone 2.5 mg - 1 tablet per day;
* 17ß-estradiol 2 mg and norethisterone acetate 1 mg - 1 tablet 1 time a day.

With contraindications to systemic MGT, it is recommended:

* estradiol 0.05-0.1 mg, 1 patch glued to the skin 1 time a week - 6-12 months;
* apply estradiol 0.5-1 mg 1 time a day to the skin of the abdomen or buttocks, the course is 6 months.

The duration of the MGT course is variable and depends on the time of development and the nature of the clinical manifestations of the menopausal symptom complex. Short courses of MGT with a positive effect can be used in women with hot flashes, psychological disorders, dyspareunia, and urination disorders. With pronounced systemic disorders and in order to prevent their development in women at risk, the duration of MGT is usually 6-8 years. Under these conditions, the protective effect of estrogens is carried out in terms of a favorable effect on the blood lipid spectrum and glucose tolerance. The development of atherosclerosis is prevented, and the risk of developing disorders from the cardiovascular system is reduced from 65 to 33%.

In recent years, femostone has been widely used for MGT, in which the estrogenic component is represented by micronized 17ß-estradiol, and the progestogenic component is represented by didrogesterone. Didrogesterone, which is the D-isomer of progesterone, has high specificity to progesterone receptors (approximately 1.5 times higher than progesterone) and very low affinity to all other types of receptors (estrogenic, androgenic, glucocorticoid and mineralocorticoid), therefore it does not have undesirable additional estrogenic, androgenic (or antiandrogenic), glucocorticoid and mineralocorticoid properties. Didrogesterone is an absolutely metabolically neutral progestogen, and therefore this drug has no negative effect on metabolic parameters and the cardiovascular system. Moreover, it has been shown to have a positive effect on all components of the metabolic syndrome: obesity, arterial hypertension, dyslipidemia and impaired carbohydrate metabolism. It has been established that, despite the similarity with endogenous progesterone in molecular structure and pharmacological properties, it is effective at lower doses when administered orally compared with progesterone.

For the treatment of osteoporosis are used:

* calcitonin 50 IU subcutaneously or intramuscularly after 1 day or 50 IU intranasally 2 times a day, the course is from 3 weeks to 3 months. with minimal symptoms of osteoporosis or as a supportive therapy. With severe osteoporosis and vertebral fractures, it is recommended to increase the dosage to 100 IU per day subcutaneously or intramuscularly 1 time a day for 1 week, then 50 IU daily or every other day for 2-3 weeks;

* diphosphonates (ethidronic acid) 5-7 mg / kg of body weight for 2 weeks. every 3 months.;

* calcium carbonate (1000 mg) in combination with colecalciferol (800 IU). The drug is indicated both for the prevention of osteoporosis and fractures, and for the complex therapy of osteoporosis in combination with calcitonin or bisphosphonate. The intake of calcium carbonate with colecalciferol is indicated for life.

Among the antiresorptive agents, MGT is the most effective for the prevention and treatment of osteoporosis. MGT during the first year of therapy only helps to stop the processes of resorption, but in the next 2-3 years the mass of bone tissue begins to increase. With severe postmenopausal osteoporosis, MGT can be combined with other drugs (for example, bisphosphonates) or the latter can be used as monotherapy with contraindications to hormone therapy and in old age.

The mechanism of the protective effect of estrogens on bone tissue:

* activation of calcitonin synthesis;

* blockade of parathyroid hormone activity by reducing its synthesis or reducing the sensitivity of osteoclasts;

* reduction of bone tissue sensitivity to the absorbable action of vitamin D3 metabolites;

* activation of the processes of hydroxylation of vitamin D3 in the kidneys and its transformation into the active form of 1,25-dihydroxycholecalciferol;

* increased absorption of calcium in the intestine;

* reduction of the catabolic effect of thyroxine by enhancing the synthesis of thyroglobulin.

The protective effect of progestogens on bone tissue is manifested in the form of direct action through specific receptors on osteoblasts and indirectly by blocking receptors to glucocorticoids and reducing their inhibitory effect on bone tissue.

Forecast. Postmenopausal estrogen replacement therapy can reduce the risk of bone fractures, Alzheimer's disease, as well as colon and rectal cancer by 50%.

Post - castration syndrome

Post-castration syndrome is a complex of vegetative-vascular, neuroendocrine and neuropsychic symptoms that occur after total or subtotal ovariectomy (castration) in combination with or without removal of the uterus.

Pathogenesis. In post-castration syndrome, the triggering and pathogenetically leading factor is hypoestrogenism with its characteristic multiplicity of manifestations.

Disorders in the hypothalamic-pituitary region are accompanied by maladaptation of subcortical structures that regulate cardiac, vascular and temperature reactions of the body, since the synthesis of neurotransmitters responsible for the functioning of subcortical structures decreases with estrogen deficiency.

The consequence of a decrease in the level of sex hormones with the cessation of the action of inhibin is a significant increase in the levels of LH and FSH to the corresponding postmenopausal. Disorganization of adaptation processes can lead to increased levels of TSH, ACH. Prolonged estrogen deficiency affects the state of estrogen-receptive tissues, including the genitourinary system: atrophy of muscle and connective tissue increases with a decrease in the number of collagen fibers, vascularization of organs decreases, the epithelium thinns. The lack of sex hormones leads to the gradual progression of osteoporosis.

The clinical picture of post-castration syndrome includes psychoemotional, neurovegetative, as well as metabolic and endocrine disorders.

Psychoemotional disorders can occur from the first days of the postoperative period. Asthenic (37.5%) and depressive (40%) manifestations are most pronounced, phobic, paranoid and hysterical are less common.

Vegetoneurotic disorders form from 3-4 days after ovariectomy and are characterized by mixed sympathetic-tonic and vagotomic manifestations with predominance of sympathetic-tonic activity. Thermoregulation is disrupted in 88%

of patients and is manifested by hot flashes, chills, a feeling of crawling goosebumps, there may be poor tolerance of hot weather. 45% of patients have disturbed sleep, less often there is a fear of confined spaces. Cardiovascular manifestations in the form of tachycardia, subjective complaints of palpitations, compressive pains in the heart and increased systolic blood pressure are detected in 40% of patients.

The reverse development of clinical manifestations without correction during the year occurs in 25% of patients, in patients of reproductive age more often - in 70% of cases. This is due to the inversion of the main source of sex hormones, which are the adrenal glands.

After removal of the ovaries, the risk of myocardial infarction increases 2-3 times, mortality from cardiovascular diseases increases.

Removal of the uterus is associated with a higher risk of arterial hypertension as a result of a decrease in the level of prostacyclines secreted by the uterus as vasodilating, hypotensive agents, endogenous inhibitors of platelet aggregation.

Diagnosis of post-castration syndrome. The diagnosis is established on the basis of anamnesis and clinical picture.

Treatment of post-castration syndrome. Complex therapy is recommended, including non-drug, medication and hormonal treatment. Non-drug therapy should begin early, including morning, therapeutic gymnastics, general massage, walks before going to bed. The diet should be dominated by fruits and vegetables, vegetable fats, limited carbohydrate content. Hydrotherapy at home, pouring cold water, coniferous, sage, hot foot baths are shown. Balneotherapy includes the use of mineral and radon waters. Galvanization of the brain, the cervical-facial region or electrophoresis of novocaine on the area of the upper cervical sympathetic ganglia is quite effective.

The main method of treatment of post-castration syndrome is hormone replacement therapy, which is used in the following modes:

1. Monotherapy with pure estrogens without the addition of progestogens. It is indicated in patients with a removed uterus (history of hysterectomy). Drugs are suitable for this regime: estrophem, proginova, premarin, ovestin, skin patches and gels.

In women with a preserved uterus, a combination of purely estrogenic HRT drugs with progestogens is necessary, most appropriate with didrogesterone - dufastone. Scheme of application: estrogens + dufaston 10-20 mg per day during the last 12-14 days of the cycle. The duration of treatment can be 21 days, followed by a 7-day interval for withdrawal bleeding, or it can be maintained in a continuous mode, when in the days allotted for withdrawal bleeding, the patient continues to receive a reduced dose of estrogens.

2. Cyclic combined estrogen-progestogen therapy in the mode of a 28-day menstrual cycle: the patient receives estrogens on a regular basis, progestogens only 10-14 days. Cyclic two-phase preparations - femoston, klimonorm, klimen, cyclo-proginova, divina, prempak-S.

3. Monophasic combined estrogen-progestogen therapy in continuous mode.

The drug that meets the conditions of the named regime is cliogest. This group also includes livial (2.5 mg tablets), continuous intake of which, for 28 days, is usually not accompanied by bleeding due to the progestogen effect on the endometrium characteristic of the drug. This makes it possible to prescribe livial to patients who are in a long period of postmenopause. It is also prescribed immediately after surgical menopause or not earlier than a year after natural menopause.

1. The regime of prolonged administration of estrogens. An example is the drug divitren. The cycle of taking divitren is 91 days: 70 days only estradiol valerate 2 mg / day, the next 14 days - estradiol valerate 2 mg / day and medroxyprogesterone acetate 20 mg / day, the last 7 tablets do not contain hormones (placebo).

Examinations when prescribing HRT:

* study of anamnesis taking into account contraindications
* vaginal examination, ultrasound of the pelvic organs.
* examination, palpation of mammary glands, mammography
* smear for oncocytology
* measurement of blood pressure, body mass index
* coagulogram, cholesterol level, liver tests
* determination of estrogen levels either in blood serum or by colpocytology
* Plasma FSH: level>15ME/L confirms that complaints and symptoms are associated with ovarian insufficiency.

Absolute contraindications for MGT:

* breast or endometrial cancer
* coagulopathy
* impaired liver function
* thrombophlebitis
* uterine bleeding of unspecified genesis.

The duration of treatment is determined individually, but should not be less than 2-3 years, during which the vegetative-vascular symptoms usually disappear.

In addition to hormonal treatment, symptomatic therapy is carried out: sedatives, tranquilizers, regulators of neurotransmitter metabolism in the central nervous system, vitamins, hepatoprotectors, disaggregant and anticoagulant therapy (aspirin, curantil, trental), taking into account coagulogram data.

The prognosis depends on the age, premorbid background, the volume of surgery and the course of the postoperative period, the timeliness of initiation of therapy and prevention of metabolic disorders. Patients should be under constant medical supervision.

Prevention of post-castration syndrome provides for the prevention and early diagnosis of diseases of the internal genitalia, which are indications for total or subtotal ovariectomy.

Analytical part

Task No. 1.

A 26-year-old woman complained about the appearance a week before menstruation of swelling and tenderness of the mammary glands, bloating and constipation, depression, headaches and irritability; which stop with its onset. These complaints mark the last 6 months after stress.

Questions:

1. Diagnosis.
2. Methods of examination.
3. Treatment and tactics of the doctor.

Answers:

1. PMS edematous form compensated stage.
2. Mammography in the first phase of the menstrual cycle, consultation with a neurologist.
3. Compliance with the regime of the day and rest (full sleep for at least 8 hours, moderate physical activity), as well as diets (restriction of fluid intake, exclusion of coffee, chocolate, spicy, smoked, salted, alcohol, smoking, restriction of animal fats and carbohydrates). In order to improve diuresis, veroshpiron 25 mg 2-3 times a day 3-4 days before the onset of symptoms, antihistamines tavegil, diazolin 1 tab. 3 times a day. Inhibitors of prostaglandin synthesis - naprosin, indomethacin 1 tab. 3 times a day in the second phase of the cycle, progestogens from the 16th to the 25th day of the cycle - dufaston 10 mg 2 times a day or utrozhestan 200-300 mg.

Task No. 2.

A 48-year-old woman complained of hot flashes, excessive sweating, palpitations, headaches, irritability, anxiety, depression, which in the last 3-4 months began to bother her more often.

Questions:

1. Diagnosis.
2. Methods of examination.
3. Treatment and tactics of the doctor.

Answers:

1. Menopausal syndrome.
2. Blood pressure measurement, ECG, neuropathologist consultation.
3. The main therapy consists in the appointment of HRT - Femostone 1/5 to 1 tab. per day 3-6 cycles. Combination therapy, including HRT drugs and Magne B6, seems to be more preferable in women with a predominance of affective psychoemotional disorders in menopause. Therapy should be carried out 2 times a year - in spring and autumn for 2-3 months. In addition, it is recommended to observe the

regime of the day and rest, proper nutrition (vegetables, fruits, vegetable fats should prevail in the diet), physiotherapy (collar with novocaine on Shcherbak, galvanization of the brain, electroanalgesia - procedures 7-8 times), neuroleptic drugs - meterazine, meterazine, triftazine, frenolone.

Task No. 3.

A 54-year-old woman complains of vaginal dryness and dyspareunia. Menopause for 3 years. Three months ago, she was diagnosed with endometrial atrophy.

Questions:

1. Diagnosis.
2. Methods of examination.
3. Treatment and tactics of GP.

Answers:

1. Menopausal syndrome.
2. Analysis of urogenital secretions for the degree of purity, Pap smear.
3. Locally vaginal candles "Estriol". The choice of dosage form (tablets, vaginal creams, suppositories) is largely determined by the individual acceptability of the method of administration. The appointment of estrogens promotes the restoration of the ecology of the vagina, prevents the development of recurrent vaginal and urinary infections and plays an important role in the treatment of urinary incontinence, especially stress and associated with the instability of detrusor muscles.

Test questions

1. The average duration of the menstrual cycle is:

A. 22 days
B. 25 days
C. 28 days
D. G. 35 days
E. 38 days.

2. The establishment and stability of the menstrual cycle depend on:

A. The release of prolactin by the anterior pituitary lobe
B. The periodic release of gonadoliberin
C. Different duration of the follicular phase
D. The content of progesterone synthesized by the corpus luteum
E. The content of estrogens secreted by the ovaries.

3. Synthesis and secretion of which of the listed substances controls gonadoliberin?

A. FSH and LH
B. Dopamine
C. V. Prolactin
D. Norepinephrine
E. Tyroliberin.

4. Which of the above is the basis for the occurrence of dysmenorrhea?

A. A. Isolation of prostaglandins
B. B. A drop in progesterone levels
C. B. Ovulatory disorders
D. G. The state of the secreting endometrium
E. D. Impaired function of the corpus luteum.

5. Which of the listed women is most characteristic of dysmenorrhea?

A. A teenager
B. A woman taking oral contraceptives
C. a 48-year-old woman with an irregular menstrual cycle
D. d. An athlete who often participates in marathon races and has very rare menstruation
E. d. a 35-year-old woman with a regular menstrual cycle.

6. All of the following methods can be used for endometrial examination, EXCEPT:

A. Laparoscopy
B. Endometrial biopsy
C. Hysteroscopy
D. Bacterial seeding of the contents of the uterine cavity
E. Hysterography.

7. The time of ovulation is best determined on the basis of:

A. Peak estrogen levels
B. Preovulatory increase in progesterone levels
C. Release of FSH
D. The beginning of the release of LH.

8. What is the cause of the menopausal heat wave?

A. Release of FSH
B. Release of LH
C. Sharp drop in estrogen levels
D. A sharp drop in progesterone levels
E. None of the above.

9. The physiological characteristics of perimenopause include all of the following, EXCEPT:

A. Reduction in the number of follicles in the ovary
B. Reduction in the duration of the menstrual cycle
C. Reduction in the concentration of estrogen
D. Reduction of FSH secretion
E. Reduction of follicle sensitivity to FSH.

The practical part
Bimanual vaginal examination

1. Put on a glove. Insert your fingers into the vagina, exerting the main pressure on the back wall of the vagina. The thumb should be withdrawn, and the ring finger and little finger should be bent. In this position, the fingers do not exert noticeable pressure on the perineum, which allows a woman to avoid unpleasant sensations, and also makes it possible to correctly position the examining fingers. Pay attention to the presence of nodes and soreness of the vaginal walls, including in the places of projection of the urethra and bladder on the anterior wall.

2. Palpate the cervix, paying attention to its position, shape, consistency, surface character, mobility and soreness. Normally, cervical palpation is painless. Palpate the vaginal arches.

3. Palpate the uterus. Put your other hand on your stomach in the middle between the navel and the symphysis. With the hand in the vagina, lift the cervix and the body of the uterus, with the other hand push in and down, trying to grab the uterus between your hands. Pay attention to its size, shape, consistency, mobility, as well as the presence of soreness or tumors. If you cannot palpate the uterus in these ways, then perhaps it is displaced posteriorly. In this case, for palpation, you need to put your fingers in the posterior arch of the vagina.

4. Palpate both ovaries alternately. Put your left hand on the right lower quadrant of the abdomen, and with the other hand find the right lateral arch of the vagina. Pressing on the stomach with the left hand and releasing the hand, try to bring the ovaries closer to the right hand. Palpate the right ovary and adjacent structures (when they are enlarged). Lightly palpate the ovary with two fingers and, if possible, determine its size, shape, consistency, mobility and soreness. Also examine the left ovary. Normally, ovarian palpation is somewhat painful.

5. When palpating the uterus in the retroversion position, rectal-vaginal examination is especially valuable. Lubricate the gloves. Insert the index finger into the vagina, the middle finger into the rectum. Ask the woman to tense up so that the anal sphincter relaxes. The study is similar to the vaginal one, but at the same time it is possible to palpate part of the uterine wall behind the cervix.

Security questions

1. Clinical forms of premenstrual syndrome.
2. Severity of premenstrual syndrome.
3. Treatment of premenstrual syndrome.
4. Climacteric syndrome, severity.
5. Treatment of menopausal syndrome.
6. Post-castration syndrome, severity.
7. Principles of treatment of post-castration syndrome.
8. Criteria for evaluating the effectiveness of treatment of neuroendocrine syndromes.
9. Differential diagnosis of neuroendocrine syndromes.
10. Prevention of neuroendocrine syndromes.

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10. Search on the Internet for data on premenstrual, post-castration and menopausal syndromes on the sites – www.rh..org., www.med-site/narod.RU/index.htm .