

ЛД-21 ИН

Federal State Budgetary Educational Institution
higher education "North Ossetian State Medical Academy"
Ministry of Health of the Russian Federation
(FGBOU VO SOGMA MRussian Health Ministry)

DEPARTMENT OF INTERNAL DISEASES №2

HYPERPROLACTINEMIA

METHODOLOGICAL MATERIALS

main professional educational program of higher education - specialty program in the
specialty 31.05.01 General Medicine

Vladikavkaz

Methodical materials " HYPERPROLACTINEMIA" are intended for teaching 5th-year students (9th semester) of the medical faculty of the Federal State Budgetary Educational Institution of Higher Education SOGMA of the Ministry of Health of the Russian Federation in the discipline" Endocrinology"

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Hyperprolactinemia is a condition characterized by persistent excess levels of prolactin (PRL) in the blood serum, accompanied by various pathological changes such as impaired sexual function, infertility, obesity, metabolic syndrome, osteoporosis, etc. Hyperprolactinemia is an important interdisciplinary medical problem, which indicates the need to get acquainted with it not only for obstetricians-gynecologists, endocrinologists, but also doctors of other specialties (andrologist, urologist, etc.).

Hyperprolactinemia syndrome is a symptom complex that develops against the background of hyperprolactinemia and is accompanied by menstrual and reproductive disorders in women. The syndrome includes hyperprolactinemic hypogonadism as an independent neuroendocrine disease (prolactinomas, an idiopathic form of hypogonadism), as well as secondary (symptomatic) forms of hyperprolactinemia that develop as a result of a number of other endocrine or somatic diseases and conditions.

Until the 70s of the last century, it was not proven that prolactin is synthesized in the human body. In animals, this hormone of the anterior pituitary gland was isolated by Riddel and Bates in 1933. But it was not until 1953 that Argonz and Castilo suggested that a similar substance, which controls lactation, is also synthesized in the human body. And in the early 70s of the twentieth century, three epoch-making events took place, which began the development of neuroendocrinology. In 1970, Frantz and Kleinberg developed the first method for the determination of prolactin (RIA), in 1972 Hwang and Guyda isolated prolactin in humans, and in 1974 Vesina and Sutton proposed using computed tomography to determine the presence of pituitary microadenomas. In the USSR, the history of the study of hyperprolactinemia began in 1974.

Прошло несколько лет, и были определены те основные функции, которые пролактин выполняет в нашем организме. Оказалось, что сфера его влияния значительно шире, чем регуляция лактации и даже репродуктивной функции. Так, пролактин принимает участие в регуляции поведенческих реакций, жирового и углеводного обмена, метаболизма костной ткани, иммунной системы. В свое время даже высказывались предложения переименовать пролактин и назвать его версатилином – «вездесущим и всемогущим гормоном».

Prl is a polypeptide hormone containing 198 amino acid residues with a molecular weight of 23 kDa; secreted by acidophilic cells (prolactotrophs) of the anterior pituitary gland, which make up 11-29% of the total cellular composition of the adenohypophysis and are concentrated mainly in its posterolateral region; has a high homology in the sequence of amino acids with molecules of growth hormone and human placental lactogen, which significantly hampered and delayed until 1979. its isolation and identification. The gene responsible for PRL synthesis is localized on chromosome 6. PRL receptors are found in the mammary glands, heart, lungs, liver, thymus, spleen, pancreas, adrenal glands, kidneys, etc. The PRL receptor - transmembrane, belongs to the family of cytokine receptors. Genes responsible for the synthesis of PRL and STH receptors

The secretion of PRL in the fetus begins at the 5-7th week of embryonic development. From the 20th week of pregnancy, its content progressively increases, reaching a peak at the time of delivery (up to 5000-6000 mU / L or 235-285 ng / ml). Then the concentration of PRL in the blood serum decreases and by the 3rd month of life reaches the level of 100-250 mU / L or 4.7-11.8 ng / ml.

During puberty in girls, under the influence of an increasing level of estrogen, the content of PRL approximately doubles and remains so throughout the entire reproductive period of a woman's life. In postmenopausal women, the level of PRL decreases.

During pregnancy and within 4-6 weeks after childbirth, nursing mothers have a significant increase in the concentration of PRL in the blood up to 200-320 ng / ml. In the next 4-12 weeks of the postpartum period, the basal secretion of prolactin decreases to normal values, although a slight rise in PRL secretion is observed with each breastfeeding (mechanical irritation of the nipple).

In the early 90s of the last century, it was proved that a quarter of the prolactin present in the blood is of extra-pituitary origin.

It was found that prolactin is secreted by the higher parts of the brain, mammary gland, myometrium and decidual tissue, T-lymphocytes. Due to the fact that the cells of the immune system not only produce PRL, but also possess its receptors, it is assumed that PRL can act as an immunomodulator.

In humans, PRL secretion has a pulsating character: distinct changes in PRL secretion were revealed during the day, which are not controlled by the circadian rhythm: a constant increase in PRL is noted during sleep, regardless of whether it occurs during the day or at night. An increase in PRL is noted after 60-90 minutes after falling asleep and is not associated with a specific stage of sleep. After awakening, the concentration of PRL in plasma decreases sharply, reaching the lowest values in the late morning hours, with a tendency to increase in the afternoon. However, these fluctuations in BPD during the day in non-stress states are always within normal range. The half-life of PRL in the blood is 20-30 minutes.

The secretion of PRL is under complex neuroendocrine control; various factors are involved in it, including neurotransmitters, hormones of the peripheral endocrine glands. But above all, the secretion of PRL by the pituitary gland is under direct hypothalamic control. The factors involved in the regulation of PRL secretion can be conditionally divided into two groups: PRL-inhibiting and PRL-stimulating.

PRL-inhibiting factors include: dopamine (DA), somatostatin, gamma-aminobutyric acid, gastrin, gastrin-releasing peptide, histidyl-proline-diketopiperazine, gonadotropin-binding protein, gonadotropin-releasing hormone (GnRH).

PRL-stimulating factors include: thyrotropin-releasing hormone, neurotensin, melanocyte-stimulating hormone, oxytocin, serotonin, histamine, GnRH, vasointestinal peptide, opiates (enkephalin, β -endorphin, methenkephalin, amino acids 27, acetylcholine -isoleucine and substance P, angiotensin II, insulin, estrogens, androgens, oral contraceptives.

Thyroid stimulating hormone (TSH) and thyroid hormones have both stimulating and inhibitory effects on PRL secretion.

The hypothalamic-pituitary system has both an inhibitory and a stimulating effect on the secretion of PRL. PRL is the only hormone of the anterior pituitary gland that is under the inhibitory influence of the hypothalamus. This inhibitory effect is due to the fact that, dopamine, which is produced in the hypothalamic tuberoinfundibular dopaminergic tract, whose neurons are located in the region of the arcuate and periventricular nuclei of the mediobasal region of the hypothalamus and enters the pituitary gland through the portal circulatory hypothalamic-pituitary tract, which inhibits the secretion of dopamines on the lactothoracic receptors by stimulating lactotal receptors. There are several types of dopamine receptors, the main ones being D1 and D2. Type D1 receptors stimulate adenylate cyclase, and type D2 receptors inhibit it. Dopamine and its agonists stimulate D2 receptors, which leads to inhibition of adenylate cyclase, a decrease in intracellular cAMP, and a decrease in the release and secretion of PRL. On the other hand, PRL is able to activate dopaminergic neurons, thereby providing hypothalamic control with its own products (short loop of the feedback mechanism). Control is carried out through the activation of dopaminergic nerve endings of the median eminence by increased PRL, which entails an increase in dopamine concentration, and this, in turn, leads to a decrease in PRL.

PRL secretion is inhibited by dopaminergic agonists and serotonin antagonists. Water load reduces the level of PRL in the blood by 50% or more.

Currently, different isoforms of circulating PRL are known:

1. Low molecular weight PRL (molecular weight (Mr) 16 kDa) is a product of hydrolysis of a monomer with Mr 23 kDa and represents the terminal fragments of PRL of different composition. It is assumed that this form of the hormone is actively involved in paracrine and autocrine hormonal interactions, but the features of the biological action of this form of the hormone at the level of the central nervous system are still unknown. Participation in human reproductive function has not been proven. It is believed that this isomer participates in the growth and development of mammary glands, the processes of angiogenesis, increases more than 30 times in the 3rd trimester of pregnancy and childbirth, 10 times - during breastfeeding.
2. "Small" PRL (MR about 23 kDa), a monomeric form of the hormone with high receptor binding and biological activity, the main role is the regulation of reproductive processes and lactation.
3. The glycosylated form of PRL (Mr 25 kDa) differs from the "small" form of PRL by an additional oligosaccharide chain and, accordingly, by a slightly higher molecular weight. It is believed that it is this form of the hormone that has the greatest biological activity and is the main one in pituitary adenomas.
4. "Big" PRL, or big-prolactin (MR about 50 kDa), possibly consisting of dimeric and trimeric forms, its effect on the human body is not clearly defined.
5. "Big-big" PRL, or big-big-prolactin (macroPRL) (MR about 100 kDa), which is either a tetramer of "small" PRL or "small" PRL associated with IgG.

The main biological effects of PRL are associated with the activity of monomeric low molecular weight isoforms (16 kDa, 23 kDa, 25 kDa); high molecular weight isoforms have a lower affinity for receptors and, therefore, have little biological activity.

BPD affects almost all organs and tissues of the body, i.e. is a polyfunctional hormone. It affects the reproductive system, providing reproduction and lactation, water-electrolyte metabolism, has an anabolic effect on morphogenesis and growth, metabolic effect on metabolism, psychotropic effect on behavioral responses, as well as immune effect, affecting immunoregulation [7]. One of the main properties of PRL is its ability to influence breast development and lactation. Together with ovarian estrogens, it promotes the growth of the mammary glands, stimulates the formation of milk in them, and enhances the synthesis of milk proteins. Prolactin is also a luteotropic hormone, as it supports the function of the corpus luteum and the formation of progesterone by it.

Extra-pituitary secretion of PRL

Modern immunohistochemical methods have made it possible to detect the presence of PRL in malignant tumors, intestinal mucosa, endometrium, decidua, granulosa cells, proximal renal tubules, adrenal glands. The data obtained indicate that PRL is involved in all vital functions of the body.

Decidual endometrial cells produce PRL, this process is activated after implantation of a fertilized egg, reaching a peak by 20-26 weeks of gestation, and decreases before childbirth. All molecular forms of PRL are found in the amniotic fluid; the decidual tissue is the source of its synthesis. Decidual PRL prevents blastocyst rejection during implantation, inhibits the contractile function of the uterus, promotes the development of the immune system and surfactant in the fetus, and participates in osmoregulation.

The presence of PRL was detected in the cerebrospinal fluid, and even after hypophysectomy, which indicates the possibility of PRL secretion by brain neurons, it ensures the constancy of the cerebrospinal fluid, effects on astrocytes, regulation of sleep and rest cycles, and modification of eating behavior. It was revealed that PRL is produced by the skin; fibroblasts of the connective tissue are the source of local synthesis.

Almost all immunocompetent cells express the PRL receptor. Lymphocytes and thymocytes synthesize and secrete PRL. It has been determined that autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis, diffuse toxic goiter, multiple sclerosis are accompanied by hyperprolactinemia. In acute myeloid leukemia, an increase in the level of PRL in the blood was also revealed.

The physiological significance of ectopic PRL production is not fully understood. It is assumed that extra-pituitary PRL can act as a cytokine and provide vital functions for the organism. In addition, the synthesis of extra-pituitary PRL can partially compensate for the lack of its production by the pituitary gland.

Epidemiology

According to various authors, the prevalence of pathological hyperprolactinemia ranges from 10 to 30 cases per 100 thousand people, occurs in 5% of women of reproductive age. Microadenomas of the pituitary gland are found in 1.5-26.7% of studies of intravital biopsies. Hyperprolactinemia is diagnosed in 17% of women with polycystic ovary syndrome, in 14% of cases - in patients with secondary amenorrhea.

Causes of hyperprolactinemia

In 60% of cases, hyperprolactinemia outside lactation is caused by lactotrophic adenomas (prolactinomas), which account for about 40% of all pituitary adenomas. Based on tumor size, prolactinomas are classified into microprolactinomas (up to 10 mm) and macroprolactinomas (over 10 mm).

On autopsy, on average, 12% of cases reveal clinically asymptomatic pituitary adenomas. Clinically asymptomatic prolactinomas prevail in the population, with prevalence ranging from 6-10 cases per 100,000 people to about 50 cases per 100,000 people. In an analysis of 1607 patients with hyperprolactinemia receiving medication, the mean prevalence of asymptomatic prolactinomas was approximately 10 cases per 100,000 in men and 30 cases per 100,000 in women, with a peak prevalence in the latter aged 25-34 years. The prevalence of hyperprolactinemia ever treated was an average of 20 cases per 100,000 among male patients and approximately 90 cases per 100,000 among female patients. In women aged 25-34 years, the annual incidence of hyperprolactinemia is reported to be amounted to 23.9 cases per 100,000 people per year. Prolactinoma rarely manifests in childhood and adolescence. Menstrual irregularities and galactorrhea can be observed in girls, while in boys, delayed sexual development and hypogonadism are more common. Treatment is the same as for adult patients.

In rare cases, prolactinomas can be one of the manifestations of a hereditary disease, the so-called type 1 multiple endocrine neoplasia syndrome, or be diagnosed as part of a family of isolated prolactinomas. Hyperprolactinemia can also develop as a result of disorders of the hypothalamic-pituitary dopaminergic relationship under the influence of pharmacological drugs or other pathological conditions. In some cases idiopathic hyperprolactinemia is observed.

The main reasons contributing to the development of hyperprolactinemia:

Physiological conditions that can cause an increase in prolactin levels include pregnancy, lactation, stress, exercise, sleep, and some drugs. In patients with renal failure, hyperprolactinemia may be detected due to a decrease in prolactin clearance and changes in the central regulation of prolactin. In particular in the direction of increasing the production of the hormone. Dialysis does not affect serum prolactin levels, but serum prolactin levels return to normal after kidney transplantation. Hyperprolactinemia contributes to the development of symptoms of hypogonadism

that accompanies kidney disease, and menstruation may return after bromocriptine therapy. Some patients with primary hypothyroidism also develop hyperprolactinemia, since long-term or inadequate therapy for primary hypothyroidism can cause hyperplasia of pituitary cells, which, in turn, mimics a tumor. Hyperprolactinemia and enlargement of the pituitary gland due to insufficient thyroid function can be reversible during therapy with L-thyroxine, which will weaken the effect of TSH. Since the secretion of prolactin is inhibited by dopamine of the hypothalamus, destruction or compression of the pituitary pedicle by a hormonally inactive pituitary tumor or other paracellular formations will lead to hyperprolactinemia.

Etiology of hyperprolactinemia

- • physiological conditions (coitus, physical activity, lactation, pregnancy, sleep, stress); • pathological conditions (disorders of the hypothalamic-pituitary system, hypothyroidism, granulomatous and infiltrative processes, radiation, Rathke's pocket cyst, damage to the pituitary gland as a result of trauma or surgery,); • tumors (craniopharyngioma, germinoma, metastatic lesion, meningioma, growth of a tumor located above the Turkish saddle); • damage to the pituitary gland (acromegaly, lymphocytic hypophysitis, plurigormonal adenoma, prolactinoma, trauma, surgery); • systemic disorders (chest trauma, shingles, chronic renal failure, liver cirrhosis, epileptic seizure, polycystic ovary syndrome, false pregnancy syndrome); • The use of pharmacological drugs (anesthetics, anticonvulsants, antidepressants, antihistamines, antihypertensive drugs, acetylcholine agonists, narcotic drugs, stimulants of the release of catecholamines, dopamine receptor blockers, inhibitors of dopamine synthesis, neuropeptides, neuroleptics, opiates).

In patients with large hormonally inactive pituitary tumors, craniopharyngiomas, or granulomatous infiltration of the hypothalamus, hyperprolactinemia may be caused by compression of the pituitary pedicle or dopaminergic neuronal damage. According to the results of a study of 226 patients with confirmed hormonally inactive macroadenomas of the pituitary gland, the prolactin level above 94 nm / l is a reliable difference between prolactinoma and hormonally inactive pituitary adenoma.

Classification

Classification of hyperprolactinemia syndrome:

- Hyperprolactinemic hypogonadism:
- prolactinomas: A) microadenomas; B) macroadenomas;
- idiopathic hyperprolactinemia.

- Hyperprolactinemia in combination with other hypothalamic-pituitary diseases:
- hormone-active pituitary adenomas;
- hormone-inactive tumors of the sellar and parasellar regions;
- syndrome of "empty" Turkish saddle;
- systemic diseases;
- pathology of cerebral vessels;
- radiation, surgical and other traumatic effects;
- lymphocytic hypophysitis.
- Symptomatic hyperprolactinemia:
- damage to the peripheral endocrine glands;
- drug-induced hyperprolactinemia;
- neuro-reflex hyperprolactinemia;
- renal, liver failure;
- hereditary diseases;
- alcoholic hyperprolactinemia;
- psychogenic hyperprolactinemia;
- hyperprolactinemia of professional athletes.
- Extra-pituitary prolactin production.
- Asymptomatic hyperprolactinemia.
- Mixed forms.

Infertility and hypogonadism due to hyperprolactinemia.

In the structure of endocrine infertility, hyperprolactinemia occupies a leading place, accounting for 40%. According to the WHO recommendations, the first study that is carried out for women from the surveyed couples is to determine the level of PRL in the blood (after excluding the male factor of infertility).

Hyperprolactinemia inhibits the secretion of gonadotropins, reduces their basal level, which leads to a decrease in the secretion of sex hormones. In this situation, folliculogenesis is suppressed, the number of granulosa cells in the follicles decreases, FSH reception decreases, and the production of 17β -estradiol is suppressed. Hyperprolactinemia blocks LH receptors in the ovaries, causes premature regression of the corpus luteum and suppression of GnRH release, and reduces progesterone synthesis. In other words, hyperprolactinemia causes a decrease in the secretion of sex hormones, which is why this condition is called hyperprolactinemic hypogonadism.

Hyperprolactinemic hypogonadism is indicated by a combination of clinical signs, such as amenorrhea with galactorrhea, amenorrhea with estrogen deficiency and hyperplasia of the mammary glands, caused by the cessation of menstruation in women of childbearing age who have a normal menstrual cycle without loss of ovarian function (no "hot flashes"), amenorrhea with uterine hypoplasia and estrogen deficiency, an extended menstrual cycle with good development of the mammary glands and uterine hypoplasia, the appearance of galactorrhea after the

use of progestins, or the absence of a menstrual-like reaction to progestins (hyperinhibition syndrome).

Hyperprolactinemia and pregnancy

During pregnancy, the PRL level rises significantly - up to 200-400 ng / ml, ie. 10-20 times. In this regard, there is a certain risk of a symptomatic increase in the content of PRL during pregnancy. Studies carried out in recent years have shown that it is low for microprolactin - 2.6-4.5% and high for macroprolactin - 15-35%.

Pregnancy in patients with hyperprolactinemia proceeds with characteristic complications and has its own characteristics. In the first trimester, there is a high threat of abortion (48.4%, in healthy 15%), spontaneous abortion (16.1%). Non-developing pregnancies account for 80% of the total number of early terminated pregnancies. In pregnant patients, the termination of the development of the embryo is noted at 6-7 weeks.

In the second trimester of pregnancy, the frequency of the threat of termination at various times also increases (40.3%). The high frequency of spontaneous abortion at various times is explained by a decrease in progesterone secretion in hyperprolactinemia.

In the third trimester, there is a high frequency of edema (45%), premature birth (11.8%), and placental insufficiency. According to ultrasound, 47% of patients with hyperprolactinemia have signs of premature maturation of the placenta, hemodynamic disturbances in the aorta and middle cerebral artery of the fetus. Signs of chronic fetal hypoxia are detected according to cardiotocography in 39% of cases.

The course of the birth act has the following features: untimely rupture of amniotic fluid (47.4%), weakness of labor (36.8%), acute fetal hypoxia (7.9%). Hyperprolactinemia is not an independent indication for cesarean section, therefore, it is optimal to give birth to this contingent of pregnant women through the vaginal birth canal. However, the high incidence of obstetric complications leads to operative delivery in 33.3% of cases.

Analysis of perinatal outcomes showed a high incidence of newborn asphyxia (47%) and an insignificant incidence of fetal growth retardation syndrome (7.8%).

Hyperprolactinemia and lactation

During pregnancy, lactogenesis is minimal due to the high concentrations of estrogen and progesterone that block the PRL receptor. After childbirth, against the background of a decrease in the level of these hormones, the number of prolactin receptors increases and lactation increases. During lactation, the content of PRL increases slightly, and by 3-4 weeks of the postpartum period decreases to the upper limits of the norm. During sucking, PRL is periodically ejected, reaching a maximum by the 30th minute after the start of sucking. By the 70-80th day after childbirth, the act of sucking no longer causes a significant increase in the level of PRL. The nature of lactation depends not so much on the duration of sucking, but on its frequency.

It is known that the process of breastfeeding stimulates the secretion of PRL, and its overproduction may be a risk factor for prolactinoma growth. However, no convincing evidence of the negative effect of natural feeding on the course of hyperprolactinemia, including the size of prolactinoma, has been found. The literature data confirm that a comprehensive computer-X-ray examination of patients with hyperprolactinemia, with the presence of macroprolactin, did not reveal a negative effect of natural feeding on the dynamics of the disease. Progression of prolactinoma according to MRI data was revealed in none of the patients during pregnancy and after childbirth. Consequently, in puerperas with prolactinomas, it is possible to preserve lactation. However, for patients with hyperprolactinemia, it is advisable to limit the period of feeding the child to 6-12 months, and in some cases refuse it. The question of breastfeeding in patients with macroprolactinemia should be decided individually in each case.

After childbirth, in 1/3 of patients with hyperprolactinemia, the level of PRL in the blood serum normalizes, and a spontaneous remission of the disease is observed. Such patients do not need to resume treatment. Cancellation of therapy is also possible in patients with microprolactinomas. However, all these patients require further dynamic follow-up for 5 years.

Hyperprolactinemia and metabolic disorders

Hyperprolactinemia, manifested primarily by disorders of the reproductive system, is often accompanied by metabolic changes, including overweight (BMI), obesity, and metabolic syndrome. BMI and obesity are detected in 65% of patients with hyperprolactinemia. BMI is observed in a third of women, regardless of the form of the disease. Obesity II-III degree is more common with prolactinomas than with idiopathic hyperprolactinemia. According to domestic scientists, obesity is observed in 40-60% of patients with hyperprolactinemia, while the prevalence of obesity in macroprolactinomas is higher than in the population.

Hyperprolactinemia also affects the state of carbohydrate metabolism, contributing to impaired glucose metabolism, causing insulin resistance. Compared to controls, patients with hyperprolactinemia showed a higher HOMA index, they have a higher level of both basal and stimulated insulin. This may be due to the fact that prolactin inhibits the production of adiponectin, a specific protein of adipose tissue that positively corrects with insulin sensitivity.

Hyperprolactinemia is often accompanied by insulin resistance, hyperandrogenism, arterial hypertension, dyslipidemia, impaired endothelial function, activation of inflammatory markers (C-reactive protein, IL-6, TNF, etc.). The metabolic effect of prolactin explains the increased frequency of metabolic syndrome in patients with hyperprolactinemia. Obesity as the main component of the metabolic syndrome indicates the participation of prolactin in the regulation of body weight and energy metabolism.

Physiological hyperprolactinemia during pregnancy and lactation is the best way to reveal the effect of prolactin on these processes.

Prolactin is a peptide orexigenic hormone that has receptors in the central nervous system associated with the regulation of appetite. The effect of prolactin on an increase in appetite is due to a change in the content of neuropeptide Y and agoutin-like protein in the central nervous system. Hyperphagia induced by prolactin in early pregnancy is caused by sex steroids, since prolactin increases the secretion of progesterone, which gives orexigenic effect, and inhibits the cyclic production of estradiol. In turn, estradiol reduces appetite due to the activation of neurons in arcuate nuclei and increases energy consumption. Hyperphagia, characteristic of later stages of pregnancy, is due to leptin resistance, which is a physiological mechanism that provides an increase in appetite and thereby the supply of additional energy.

After childbirth, with lactational hyperphagia, prolactin affects the energy-intensive processes of lactogenesis. These processes cause a decrease in the energy balance, which leads to an increase in the appetite of nursing mothers and thus to an increase in body weight.

Prolactin is involved in adipogenesis. Prolactin blocks the secretion of adiponectin, the concentration of which is sharply reduced during pregnancy and lactation. In adipose tissue, under the influence of prolactin, lipogenesis is suppressed. Prolactin is synthesized in adipocytes, but the contribution of adipocytic prolactin to total concentration is not clear enough.

Dopamine is also involved in hyperphagia. It is clear that in morbid obesity, the number of D2 receptors in the striatal region is inversely proportional to BMI. It was confirmed that in obesity, there is a clear decrease in dopaminergic activity, and clinically there is an increase in appetite, overeating as a compensatory response that overcomes dopamine deficiency. By interacting with D2 receptors, dopamine inhibits the synthesis of prolactin by adipocytes.

Thus, in hyperprolactinemia, an increase in body weight may be due to an increase in appetite, a change in hormone content, activation of adipogenesis, inhibition of lipogenesis, an increase in adiponectin secretion, leptin resistance, a decrease in energy consumption due to a violation of the transdifferentiation of white adipocytes into brown ones, a decrease in dopaminergic activity.

Obesity as one of the components of the metabolic syndrome does not contribute to a high increase in the development of cardiovascular pathology and overall mortality. It was revealed that prolactin is produced not only by adipocytes, but also by macrophages of atherosclerotic plaques, which may indicate a connection with diabetes mellitus and atherosclerosis.

Studies involving 4000 patients followed for 10 years have shown that the upper level of prolactin, even within the reference values, is associated with an increased risk of all-cause mortality due to cardiovascular diseases. In this regard, the long-term consequences of the metabolic effects of prolactin should be taken into account. , timely diagnose and treat this pathology, which will help reduce the risk of cardiovascular disorders

Diagnostics

Complaints and anamnesis. Complaints about: · violation of menses; · weight gain; · headaches; · in men, gynecomastia; · lactorrhoea. Anamnesis: · to find out the features of menstrual dysfunction, the nature of the violation, the age at which it arose, the relationship of the disease with the onset of sexual activity, pregnancy, abortion, taking combined estrogen-progestin drugs, cyclic hormone therapy; impaired reproductive functions; presence of headaches that do not stop when taking analgesics; sleep disturbances, irritability, weakness, fatigue; decreased libido; changes in body weight, especially after the onset sexual activity; · discharge from the mammary glands; · visual disturbances. Physical examination:

The main clinical manifestations of hyperprolactinemia:

Violations reproductive function: late menarche; violation of menstrual function in women - primary or secondary amenorrhoea, opsomenorrhoea, oligomenorrhoea, anovulation, shortening of the luteal phase; hypoplasia uterus, polycystic veins; infertility, both in women and in men; galactorrhoea in women and in men (20%). The severity is assessed by the following scale: (+) - single drops with strong pressure (++) - abundant drops with strong pressure (+++) - spontaneous milk release · decreased libido in women and men; · decreased potency in men; · gynecomastia in men; delayed sexual development in girls and boys. Neurological symptoms (in the presence of a pituitary adenoma): headaches, frequent, less often permanent; bitemporal hemianopsia; paralysis of III, IV, V, VI paracranial nerves; nasal liquorrhea. Psycho-emotional disorders:

Taking an anamnesis for hyperprolactinemia implies a thorough questioning about current or previous drug therapy, concomitant endocrine and systemic diseases, chronic pathology of the liver, kidneys, reproductive system organs, head and neck trauma or radiation, surgical interventions in the hypothalamic-pituitary region.

Physical examination.

A general examination involves an assessment of the general physical condition, height and body weight, secondary sexual characteristics, traces of intravenous injections. In patients with hyperprolactinemia, an assessment of the neurological status (to exclude visual field disturbances), examination of the thyroid gland and a thorough examination of the mammary (mammary) glands are also necessary. Chest injuries and shingles should also be ruled out. Examination of the mammary gland in order to detect galactorrhoea consists in expressing it with movements from the edges of the areola to the center of the nipple. The appearance of milk indicates galactorrhoea.

Laboratory diagnostics.

Laboratory and instrumental examination includes 4 main stages:

- Confirmation of hyperprolactinemia (HP);
- Exclusion of symptomatic forms of the disease: determination of the functional

state of the thyroid gland, exclusion of polycystic ovary syndrome (PCOS), hepatic and renal failure, neuro-reflex and drug influences, etc., physiological HP (pregnancy, breastfeeding);

- Visualization of the hypothalamic-pituitary region;
- Clarification of the state of various organs and systems (carbohydrate and fat metabolism, bone tissue, etc.).

Determination of PRL in blood serum.

The main diagnostic criterion for hyperprolactinemia is the determination of the level of prolactin in the blood serum. The difficulty in interpreting the indicators of the basal prolactin level is due not only to a transient increase in the hormone during stress or excessive physical exertion, but also to the significant variability of indicators in the same patient, subject to all recommendations for blood collection.

Given the circadian rhythm of BPD production, blood sampling should be carried out from 9 to 11 am.

To exclude spontaneous or stress-related fluctuations in the PRL level, it is advisable to determine PRL three times in separate or combined portions of blood, especially at its borderline levels.

In cases of a sharp increase in the level of the hormone, it is advisable to carry out its determination with dilution.

In women with preserved menses, prolactin is investigated 5-7 days from the beginning of the menstrual cycle.

It is recommended to conduct at least two laboratory tests of the level of prolactin. Foreign recommendations indicate that a single detection of an increased level of serum prolactin is sufficient to make a diagnosis, provided that the sample was obtained from a patient who does not experience excessive stress during venipuncture. Repeated measurement of prolactin levels using samples with thyroliberin, levodopa, domperidone.

The concentration of prolactin is expressed in ng / ml or in $\mu\text{U} / \text{ml}$ (1 ng / ml corresponds to 30.3 $\mu\text{U} / \text{ml}$), or in mIU / ml (1 mIU / ml corresponds to 21 ng / ml).

The PRL level in blood serum in healthy women of reproductive age does not exceed 20 ng / ml (600 $\mu\text{U} / \text{ml}$), in men - 15 ng / ml (450 $\mu\text{U} / \text{ml}$).

As a rule, microadenomas are associated with a level of more than 5000 mU / L, macroadenomas - more than 10000 mU / L, while a prolactin level of less than 2000 mU / L is more characteristic of non-tumor hyperprolactinemia. However, given the significant variations in the prolactin level, it is difficult to judge the size of the tumor by the degree of its increase. If there is a discrepancy between the large size of the pituitary adenoma and a moderate increase in the level of prolactin, it is recommended to consistently dilute the blood serum to exclude false results.

The contradiction between the significant size of the tumor and a moderate increase in the level of prolactin may be due to compression of the pituitary pedicle by the volumetric formation of the sellar region or imperfection of laboratory diagnostics - "HOOK" - effect. "HOOK" - effect is an artifact in the method of

determining the level of prolactin and some other peptide hormones, in which the determined level of the hormone may be slightly increased or even normal at very high true values.

In patients with asymptomatic hyperprolactinemia, it is recommended to exclude the phenomenon of macroprolactinemia.

Although 85% of circulating prolactin is monomers (23.5 kDa), serum also contains covalently linked dimers, “big prolactin,” and large polymeric forms, “big-big prolactin”. The term macroprolactinemia means a situation in which large polymeric forms predominate in the circulating blood. Anti-prolactin antibodies can also be associated with macroprolactinemia. Macroprolactin is a less active form, and therefore macroprolactinemia should be suspected when the typical symptoms of hyperprolactinemia are absent. One of the methods for detecting macroprolactin in serum is precipitation with polyethylene glycol. Retrospective studies of patients with hyperprolactinemia found 40% of cases of macroprolactinemia. In such cases, among the symptoms are galactorrhea (20%), oligo- and amenorrhea (45%) and pituitary adenomas (20%).

Additionally, research is carried out:

Thyroid hormones - St. T4 and TSH

· LH, FSH, testosterone, estradiol.

Instrumental diagnostics.

The main method for detecting or excluding tumor formations in the hypothalamic-pituitary region is MRI of the pituitary gland with contrast enhancement. It is necessary to resort to this study after excluding secondary causes of hyperprolactinemia or with a primary suspicion of an existing tumor (concomitant headache, visual field disturbances). For better visualization, it is recommended to conduct a study in the T1 and T2-weighted images with the use of contrast enhancement.

If it is impossible to conduct an MRI, CT is used;

- In case of detection of a macroadenoma, perimetry is necessary;

- Ultrasound of the pelvic organs in women, the prostate gland in men;

- Ultrasound of the mammary glands - with signs of mastopathy.

Indications for consultation with specialists:

- Consultation with a neurosurgeon - to confirm the presence of an adenoma and determine the treatment tactics;
- Ophthalmologist consultation - for perimetry and ophthalmoscopy;
- Consultation of a gynecologist - to exclude PCOS.

Differential diagnosis

Given the variety of etiological factors leading to true hyperprolactinemia, it is necessary to conduct a mandatory examination of patients with this pathology

(history, examination of organs and systems involved in the regulation and metabolism of PRL, laboratory studies).

For differential diagnostics, the following is carried out:

- hormonal screening: determination of the level of TSH, free thyroxine, antibodies to thyroglobulin, FSH, LH, estriol, testosterone, cortisol, dehydroandrosterone / dehydroandrosterone / sulfate, which allows detecting thyroid pathology and other hormonal disorders;
- X-ray studies - MRI, CT of the brain to confirm or exclude tumor (organic) diseases, as well as to determine the extent of the lesion; When macroprolactinoma is detected, it is also necessary to determine ACTH to confirm or exclude adrenal insufficiency, insulin-like growth factor type 1 in connection with an increase in the level of PRL in somatotropinomas
- examination of the fundus and visual fields to clarify the state of the optic-chiasmal area.

Comparison of the clinical picture of the disease, the content of PRL, data of X-ray and ophthalmic research methods allows to differentiate functional hyperprolactinemia from organic [.

In primary hypothyroidism, hyperprolactinemia develops in response to a decrease in the level of thyroid hormones and an increase in the secretion of thyroliberin, which stimulates the secretion of two hormones - PRL and TSH.

To exclude PCOS as a possible cause of infertility, in addition to determining hormones, an ultrasound of the pelvic organs should be performed, as well as the determination of C-peptide and insulin to exclude insulin resistance and hyperinsulinemia.

In cases of a burdened family history, a combination of prolactinoma with other endocrine diseases or an aggressive course of the disease, it is recommended to perform a genetic study to clarify the diagnosis, determine the tactics of patient management and prognosis. As a rule, pituitary tumors, including prolactinomas, are sporadic. However, some of them are included in a number of hereditary syndromes, such as MEN1 (MEN1 gene mutation), Carney complex (PRKAR1A gene mutation), and familial isolated pituitary adenomas, the development of which associated with mutations in the AIP suppressor gene.

In one third of patients with kidney disease, hyperprolactinemia develops due to a decrease in excretion and an increase in hormone production.

Hyperprolactinemia is observed when taking medications: neuroleptics, antidepressants, anticonvulsants, opiates, anesthetics, antihypertensive drugs, combined oral contraceptives, etc. Idiopathic hyperprolactinemia is evidenced by the exclusion of possible reasons for the functional increase in prolactin against the background of the normal structure of the hypothalamic-pituitary region according to MRI data. Approximately 10% of such patients are diagnosed with microadenoma after a while, and in 30% spontaneous remission is observed. The level of prolactin has a certain value in carrying out a differential analysis, however, there are no clear criteria for a particular nosology. A significant increase in the level of prolactin more than 5000 mU / L (250 mg / L), indicating in favor of

prolactinoma, can also be observed during treatment with metoclopramide, risperidone, phenothiazine. If you suspect the development of pharmacological hyperprolactinemia, it is recommended to re-determine the level of prolactin 72 hours after discontinuation of the drug, if this does not pose a risk to the patient.

The mechanism of hyperprolactinemia with the use of drugs lies in their anti-dopamine action. The level of prolactin with oral administration of drugs increases gradually and to normalize it, a 3-day break in therapy is enough. Despite the fact that drug hyperprolactinemia is often asymptomatic, women may experience galactorrhea, amenorrhea, and men - decreased libido and erectile dysfunction.

Verapamil causes hyperprolactinemia in 8.5% of cases, presumably due to dopamine blockade. Opiates and cocaine, acting through μ -receptors, cause mild hyperprolactinemia. The role of estrogens in the development of this pathology remains controversial. Among women taking oral contraceptives with high doses of estrogen, 12-30% had an increase in serum prolactin. It should be noted that for a number of drugs it is difficult to accurately determine the period of complete elimination of the drug and the normalization of prolactin levels, especially for depot forms. In any case, the abolition of psychotropic drugs should be carried out by a psychiatrist after assessing the possibility of use alternative treatment.

Differential diagnosis and justification for additional research:

Diagnosis	Rationale for differential diagnosis	Surveys	Diagnosis exclusion criteria
Primary hypothyroidism	In primary hypothyroidism, an increase in the level of PRL in the blood serum is possible	Determination of TSH, svT4	Primary hypothyroidism
Other (except prolactinoma) pathological conditions of the brain: brain surgery, craniopharyngioma, meningioma, hypophysitis, brain trauma, etc.	Moderate increase in serum PRL	MRI of the pituitary gland with contrast enhancement	Lack of visual signs of prolactinoma
Systemic disorders: chest trauma, herpeszoster, CKD,	Moderate increase in serum PRL	Study of the history of life and disease, as	Identification of the listed conditions

liver cirrhosis, head irradiation, epilepsy, PCOS, false pregnancy syndrome		well as data from a previous examination, taking into account the underlying disease	
The use of pharmacological drugs: anesthetics, anticonvulsants, antidepressants, etc.	Moderate increase in serum PRL	Study of the history of life and disease, as well as data from a previous examination, taking into account the underlying disease	Revealing the facts of taking medications

Treatment

Drug treatment:

The choice of treatment depends on the cause of the syndrome. The main method of HP treatment is medication, which, in the presence of prolactinoma, competes with surgical, radiation and combined therapies.

Drug treatment is dopamine agonists. With a different genesis of an increase in PRL, pathogenetic therapy of the underlying disease is carried out.

With the phenomenon of macroprolactinemia, treatment is not required.

Conservative treatment.

Treatment goals:

- normalization of prolactin levels;
- reduction in the size of the tumor;
- elimination of symptoms of hyperprolactinemic hypogonadism and restoration of fertility;
- prevention of recurrence or resumption of tumor growth.

Patients with symptomatic hyperprolactinemia, micro- or macroprolactinomas require treatment to prevent tumor growth and minimization of the consequences.

- Conservative therapy (use of dopamine agonists) is recommended as the treatment of choice in patients with hyperprolactinemia tumor genesis.

Comments. The priority of drug treatment with prolactin over surgery and radiation therapy has been repeatedly shown in a large number of studies. Dopamine agonist therapy in hyperprolactinemia syndrome is the most appropriate from the point of view of the pathogenesis of the disease. When using dopamine agonists, the synthesis and secretion of prolactin decreases, and the size of the adenoma decreases.

Currently on the territory of the Russian Federation the following dopamine agonists are registered:

- Cabergoline is an ergoline selective dopamine D2 receptor agonist. The long half-life allows the drug to be used 1-2 times a week. The initial dosage is 0.25-0.5 mg per week, followed by increasing the dose until the prolactin level normalizes. As a rule, the average dose is 1 mg per week, although in cases of resistant prolactinomas it can be 3-4.5 mg per week. Cabergoline is recommended as a first-line drug, as it is most effective in normalizing prolactin levels and reducing tumor size.

- Bromocriptine* is an ergoline dopamine receptor agonist. Bromocriptine drugs were the first to be used to treat hyperprolactinemia more than 30 years ago. Unlike cabergoline, bromocriptine is a non-selective agonist of dopamine receptors in the brain, which leads to more side effects. The initial dosage is 0.625-1.25 mg per day, therapeutic the range is 2.5-7.5 mg per day.

- Quinagolide - is a non-ergoline selective dopamine receptor agonist. The initial dose is 25 mcg per day with a gradual increase every 3-5 days by 25 mcg. Average daily dose about 75 mcg, maximum 300 mcg.

In placebo-controlled studies, treatment with cabergoline (0.125-1.0 mg 2 times a week) for 12-24 months in patients with prolactin-secreting microadenomas achieved normalization of prolactin levels in 95% of cases. When using cabergoline, the menstrual cycle was restored in 82% of women with amenorrhea. In a prospective study of 26 untreated patients with macroprolactinomas, normoprolactinemia was achieved within 6 months in 81% of patients receiving 0.25-2.0 mg cabergoline per week, and 92% experienced significant tumor regression. In a retrospective study of 455 patients, the use of cabergoline was able to normalize prolactin levels in 92% of cases of idiopathic hyperprolactinemia or microadenoma and in 77% of 181 patients with macroadenoma.

Based on experience, in 90% of men with latent macroadenomas or microadenomas, prolactin levels return to normal after treatment with bromocriptine, cabergoline and other dopamine agonists. Men who received cabergoline treatment for 6 months (0.5-1 mg twice a week) recovered spontaneous nocturnal erection, as well as sperm count and sperm motility. The use of prolonged dopaminomimetics (cabergoline) allows you to obtain the maximum therapeutic effect. The most preferred drug for the treatment of prolactin, including giant tumors (size 40 mm), is cabergoline.

It remains unclear why cabergoline is more effective than bromocriptine, but this can be explained by the greater affinity of cabergoline for dopamine receptors, moreover, the rarer occurrence of adverse effects with cabergoline treatment increases patient compliance. In clinical trials, there is no reliable data comparing different dopamine agonists with respect to mass effect reduction. However, results from various studies find that bromocriptine promotes a reduction in pituitary tumor size by about 50% in two-thirds of patients, compared with a 90% reduction in pituitary tumors using cabergoline.

- Some patients with microadenomas and asymptomatic disease are not advised to prescribe drug therapy due to the low likelihood of tumor growth. **Comments.** This approach is relevant among patients of premenopausal age, provided that the menstrual cycle is preserved and the complete absence or I degree of galactorrhea, as well as women in peri and postmenopausal women, when an increased level of prolactin does not contribute to the development of hypogonadism.

- Reducing the dose of the drug used or canceling it is recommended not earlier than after 2 years of continuous treatment, provided that prolactin levels are normalized for a long time and the tumor is significantly reduced or absent according to the MRI of the brain.

Treatment effectiveness indicators:

- Normalization of PRL level in blood serum;
 - Achievement of regression / stabilization of adenoma growth;
- Elimination of manifestations of hyperprolactic hypogonadism, restoration of fertility.

Comments. The approach to monitoring the effectiveness of treatment is more individual for each patient due to differences in tumor size, growth rate and response to treatment. The likelihood of radicalism of drug therapy increases in patients with idiopathic hyperprolactinemia or in the presence of pituitary microadenoma, who have been receiving dopamine agonist therapy continuously for at least 2 years. Despite the possibility of canceling therapy with positive dynamics, this issue must be approached individually. It is undesirable to cancel dopamine agonists for prolactinomas bordering on the visual cross or cavernous sinus.

The main criteria for discontinuation of drug therapy are: • duration of treatment is more than 2 years; • normalization of prolactin levels; • absence of adenoma according to MRI; • a significant decrease in the size of the tumor (more than 50% of the original size or a decrease in the size of the macroadenoma less than 10 mm); • pregnancy; • postmenopause; • the possibility of further medical supervision.

The risk of recurrence after withdrawal ranges from 26% to 69%, and all studies show that prolactin levels and tumor size are predictors of recurrence. Relapse most often occurs within a year of withdrawal, and in one study, the risk of relapse was 18% per millimeter of tumor mass. There is a cancellation of therapy

with no data on tumor growth, but up to 28% of such patients subsequently develop hypogonadism, so the proposal needs a long-term monitoring and treating these patients.

After the abolition of dopamine agonists, dynamic control of prolactin levels is performed once every 3 months for 1 year, then annually for at least 5 years, MRI of the brain is indicated if there are signs of tumor growth.

Surgery.

Performing transsphenoidal adenomectomies is recommended only in specialized hospitals with highly qualified surgical personnel. Relapse after surgical treatment is less common in microprolactinomas, with macroprolactinomas it reaches 80%. The duration of the relapse-free period is individual, in most cases it does not reach 3 years.

Indications for surgical treatment of PRL - secreting pituitary adenomas:

Absolute intolerance to dopamine agonists

- Continued tumor growth while taking adequate doses of dopamine agonists;
 - Apoplexy of the pituitary gland;
 - Liquorrhea while taking dopamine agonists;
 - Macroadenoma in patients with mental illness in the presence of contraindications to the appointment of dopamine agonists.
 - Lack of normalization of the PRL level despite the use of drugs;
- Tumors invading the sphenoidal sinus or accompanied by liquorrhea;
- Adenomas with significant suprasellar extension and signs of compression of the optic chiasm.

Further management:

- Dynamic study of the level of PRL in the blood serum: the first study 10-15 days after the operation, then monthly. After reaching normoprolactinemia, PRL is determined once every 6 months. MRI of the pituitary gland with contrast enhancement is performed once a year.
- If, 10-15 days after the operation, the reduction or normalization of the level of PRL does not occur, one can think about incomplete removal of the adenoma and expect a relapse of the PRL-secreting adenoma in the future. In these cases, the appointment of dopamine agonists (see above) is indicated for at least 2 years, and possibly for life. Spontaneous remissions of the disease are possible.
- In case of intolerance to the latter or resistance to them, as well as with aggressive prolactinomas and carcinomas, radiation therapy is prescribed.

In case of damage during surgery to adjacent structures and the development of clinical signs of panhypopituitarism, an examination is carried out to exclude a deficiency of other pituitary hormones and the appointment, if necessary, of lifelong hormone replacement therapy.

Microadenomas are less likely to relapse than macroadenomas.

Treatment effectiveness indicators:

- Normalization of PRL level in blood serum;
- Achievement of regression / stabilization of adenoma growth;

· Elimination of manifestations of hyperprolactic hypogonadism, restoration of fertility.

Other treatment.

Radiation therapy for patients with prolactinomas is recommended only if it is necessary to influence the residual tumor tissue when it is impossible to perform radical surgery or intolerance / resistance to treatment with dopamine agonists when aggressive prolactins or prolactocarcinomas.

Comments. Radiation therapy, like surgical treatment, is not the treatment of choice for tumor hyperprolactinemia. A number of authors point out the advisability of temporarily discontinuing dopamine agonists before radiotherapy to improve the results. • In patients with hyperprolactinemic hypogonadism, decreased bone mineral density, it is recommended to consider prescribing estrogen or testosterone preparations. • In patients with refractory or partially refractory prolactinomas, it is recommended that the dose of dopamine agonists be increased to the maximum tolerated dose before considering surgery. If bromocriptine is intolerant, it is recommended to replace it with cabergoline or another dopamine agonist. **Comments.** Tumor resistance to treatment is observed while maintaining an increased level of bioactive prolactin against the background of the maximum tolerated doses of dopamine agonists and the absence of tumor shrinkage by less than 50% of the original size. Complete resistance is manifested by the absence of any significant effect from the appointment of dopamine agonists, partial resistance is observed with a decrease in prolactin secretion without normalizing its level. Typically resistant tumors more common in men.

• For patients receiving high initial doses of dopamine agonists (more than 2 mg per week) or standard doses for more than 5 years of therapy, echocardiography is recommended to exclude pathology of the valve apparatus. **Comments.** A significant number of studies have been published proving the safety of using standard doses of cabergoline. • Temozolomide is the drug of choice for the treatment of prolactocarcinomas. **Comments.** Malignant prolactinoma is characterized by metastatic spread in the central nervous system and beyond, it is quite rare, in total about 50 cases are described in the literature. Currently, there are no reliable pathological markers that make it possible to assess the malignant potential of a tumor, however, the aggressiveness of the mass may be evidenced by such factors as the presence of multiple mitoses, nuclear atypia, a positive reaction to the immunomarkers p53, Ki-67. The mortality rate of patients with prolactocarcinomas after the detection of metastases is more than 40% during the first year. In most cases, these patients undergo all the treatments without corresponding improvement. Chemotherapy, including drugs such as procarbazine, vincristine, cisplatin, and etoposide, is ineffective. Several cases of the positive effects of temozolomide have been described. In most cases, these patients undergo all the treatments without corresponding improvement. Chemotherapy, including drugs such as procarbazine, vincristine, cisplatin, and etoposide, is ineffective. Several cases of the positive effects of temozolomide have been described. In most

cases, these patients undergo all the treatments without corresponding improvement. Chemotherapy, including drugs such as procarbazine, vincristine, cisplatin, and etoposide, is ineffective. Several cases of the positive effects of temozolomide have been described.

Planning pregnancy in patients with hyperprolactinemia

In patients with hyperprolactinemia of childbearing age, receiving therapy with dopamine agonists and wishing to exercise childbearing function, pregnancy planning should be carried out.

When pre-gravid preparation for pregnancy, all women planning a pregnancy should undergo imaging of the pituitary gland (MRI or CT), as well as an assessment of the visual fields. When treating with dopamine agonists, contraception with barrier agents is recommended, since with normalization of the level of PRL, fertility is quickly restored.

In patients with micro- and macroprolactinomas resistant to dopamine agonists or with intolerance to this treatment, it is advisable to consider surgical treatment before pregnancy. The growth of macroprolactin during pregnancy occurs in 31% of cases, and after pre-gestational surgical treatment is reduced to 2.8-4.3%. Optimal for conception is a stable normalization of the PRL level in the blood and a decrease in the size of the tumor (less than 10 mm). In this situation, contraception is canceled and pregnancy planning is carried out. If menstrual irregularities are detected in such patients or hypogonadism is noted at the stage of pre-gravid preparation, this pathology is treated.

Pregnancy and hyperprolactinemia.

- The most favorable background for conception is a complete normalization of prolactin levels and a decrease in tumor size less than 10 mm. Comments. After the appointment of therapy with dopamine agonists, it is advisable for patients of reproductive age to use barrier contraception, since in the case of tumor sensitivity to the action of drugs, ovulation and fertility are restored soon after the prolactin level is normalized.
- In the management of patients of reproductive age with micro- or macroadenomas resistant to treatment with dopamine agonists or in cases of drug intolerance, it is recommended to consider surgical treatment before conception. Comments. Of course, in such cases, given the likelihood of the development of postoperative hypopituitarism, the risk and potential benefits of surgery must be carefully assessed. The growth of macroprolactin during pregnancy is observed in 31% of cases, while after pregestational surgery or radiation treatment, this indicator decreases to 2.8-4.3%, which is comparable to the risk for microprolactin.
- When confirming the fact of pregnancy, it is recommended withdrawal of dopamine agonist therapy.
- In patients with macroprolactinomas who become pregnant while taking dopamine agonists, it is recommended to consider the possibility of further use of drug therapy, especially when the tumor is close to the chiasm or cavernous sinuses.

Comments. Since bromocriptine crosses the placenta, it is better to exclude drug effects on the fetus in the first 4 weeks after conception - a critical period of early organogenesis. In more than 6,000 pregnancies that occurred and were reported in women taking bromocriptine for hyperprolactinemia, there was no increase in the incidence of congenital malformations or abortions. Long-term observations of a sample of children under 9 years of age who were exposed to the drug in the prenatal period also showed no harmful effects. The use of cabergoline appears to be safe in the treatment of infertility in women with hyperprolactinemia, but there are much fewer publications regarding the experience with this drug. In a prospective study of 85 women, 80 of whom became pregnant while taking cabergoline, the drug was canceled by 5 weeks of gestation, all children were born healthy in the absence of tumor enlargement in their mothers. Consequently, the prevailing data on the absence of harm to the fetus when using bromocriptine or cabergoline in early pregnancy. On the other hand, quinagolide has a less safe profile with relatively few reported pregnancies and should not be given to women planning a pregnancy.

Management of patients with prolactinomas during pregnancy.

- In pregnant women with prolactinomas, it is not recommended to measure prolactin levels.

Comments. During pregnancy, the serum prolactin level increases tenfold, reaching values from 150 to 300 $\mu\text{g} / \text{l}$, depending on the gestational age. Moreover, the pituitary gland increases in volume by more than 2 times, primarily due to the increase in the number of lactotrophs under the influence of estrogens. When dopamine agonist therapy is discontinued early in pregnancy, serum prolactin levels rise and subsequent increases in prolactin levels do not accurately reflect tumor growth and activity. Moreover, serum prolactin levels may not increase throughout pregnancy in patients with prolactinomas. Pregnancy may improve the course of prenatal hyperprolactinemia because postpartum serum prolactin levels are often lower than pre-conception levels; in some patients, hyperprolactinemia may resolve completely after pregnancy.

For the purpose of dynamic control, pregnant women with prolactinomas are shown observation of an obstetrician-gynecologist, endocrinologist and ophthalmologist. Patients with microadenomas are shown a clinical examination, which includes the collection of complaints and an examination once a trimester. For women with macroadenomas, consultations should be carried out at least once a month with a mandatory examination by an ophthalmologist and perimetry once every 2-3 months. • Routine MRI of the Turkish saddle for pregnant patients with microadenomas or macroadenomas if there is no clinical evidence for tumor growth, for example, narrowing of the visual fields is inappropriate.

Comment. It is speculated that macroprolactinomas can grow during pregnancy. In the case of microadenomas, growth is less likely. Dopamine agonist therapy is discontinued in patients upon diagnosis of pregnancy; as a result, the reduction in

tumor size induced by these drugs may be canceled out. The high estrogen levels associated with pregnancy stimulate lactotroph hyperplasia in the healthy pituitary gland, and this physiological growth of the pituitary gland can cause the tumor to spread beyond the sella turcica. Ultimately, high estrogen levels can directly stimulate prolactinoma growth.

Basically, an increase in micro- and macroprolactin, localized in the sella turcica, is not accompanied by symptoms of tumor growth during pregnancy. In a review of studies including 457 pregnant women with microadenomas, 2.6% of cases developed symptoms of tumor growth. In studies of tumor growth using imaging research methods, the risk of tumor growth was observed slightly more often (4.5-5%). Because the risk of developing symptoms of tumor growth is quite low, pregnant patients with microadenomas may undergo clinical studies for adenomas every trimester. On the other hand, the risk of developing symptoms of tumor growth in pregnant women with macroadenomas is significantly higher. In patients who have undergone surgery or radiation therapy for a pituitary adenoma before pregnancy, the risk of developing symptoms of tumor growth was 2.8%, a small difference in the case of risk for microadenoma. However, in patients with macroadenomas without surgery or radiation therapy before pregnancy, the risk of developing symptoms of tumor growth was 31%. The onset or worsening of headache, or changes in vision, or both of these symptoms are the basis for the study of visual fields and imaging of the pituitary gland using MRI without contrast.

- Women with macroprolactinomas without pituitary adenoma volume reduction with a history of dopamine agonist therapy or with bromocriptine and cabergoline intolerance are advised to consider the benefits of surgery before pregnancy.

Comments. Some endocrinologists may recommend surgical treatment to all women with macroprolactinomas before pregnancy, although this can cause hypopituitarism, which may lead to the need for assisted reproductive technologies for pregnancy (for example, induction of ovulation with gonadotropins), as well as the need for

lifelong hormone replacement therapy.

- If tumor growth or symptom progression is detected, it is recommended to resume therapy with dopamine agonists (bromocriptine, cabergoline) during pregnancy.

Comment. If the pituitary adenoma during pregnancy reaches a size at which it can induce a mass effect, treatment options include reinstatement of dopamine agonists or surgery for the adenoma. There are no controlled studies on this and there are few case studies to assess the potential risk of each approach. Continuation of bromocriptine therapy throughout pregnancy was reported in approximately 100 patients. This treatment is not harmful, however, one case of undescended testicle and one case of clubfoot has been reported. Bromocriptine is the drug of choice among dopamine agonists when taken in divided doses due to the large amount of published experience. In patients with bromocriptine intolerance, cabergoline may

be used. If the resumption of dopamine agonist therapy does not reduce the tumor size and improve the clinical picture, surgery may be initiated. There are currently no published data assessing the comparative risks of dopamine agonist therapy and surgery during pregnancy; however, some endocrinologists favor dopamine agonist therapy in these settings. If the gestational period is approaching the time of birth, it may be advisable to induce labor before some endocrinologists prefer dopamine agonist therapy in these settings. If the gestational period is approaching the time of birth, it may be advisable to induce labor before some endocrinologists prefer dopamine agonist therapy in these settings. If the gestational period is approaching the time of birth, it may be advisable to induce labor before neurosurgical treatment.

- Performing transsphenoidal adenomectomy in the absence of response to drug treatment and progressive loss of vision is recommended in the second trimester of pregnancy.

Comments.In the case of tumor growth during gestation, surgical treatment can also serve as an alternative to medication. • In patients with hyperprolactinemia, it is recommended to limit the period of breastfeeding to 6-12 months.

Comments.There are no data in the literature indicating the progression of adenomas during breastfeeding. Comprehensive clinical and radiological examination of patients with hyperprolactinemia after childbirth and lactation did not reveal any negative dynamics of the disease. Management of postmenopausal prolactinoma patients. • In postmenopausal patients with microprolactinomas, it is recommended to consider the possibility of discontinuation of therapy with further dynamic control within 5 years.

Infertility treatment for hyperprolactinemia

The use of pathogenetic therapy - the dopamine agonist cabergoline in hyperprolactinemia effectively restores fertility: in 72% of patients treated with this drug within 24 weeks, ovulation is restored and pregnancy occurs, and in 90% - with therapy up to 40 weeks. In patients with functional hyperprolactinemia, pregnancy is possible during treatment with dopamine agonists in any cycle of taking the drug. In prolactinomas, the duration of therapy with dopamine agonists is 2 years. In patients with prolactinomas, the increase in the duration of treatment is due to the achievement of the maximum tumor shrinkage before the onset of pregnancy. The effectiveness of treatment in relation to the onset of pregnancy is lower in women with hyperprolactinemia lasting more than 10 years. With the normalization of the PRL content in the blood, but the absence of ovulation is the induction of ovulation - clomiphene 50-100 mg from the 5th to the 9th day of the menstrual cycle. In the absence of ovulation, an ovulatory dose of human chorionic gonadotropin is additionally prescribed - 7500-10,000 units. in the presence of a dominant follicle 18-20 mm. Given the decrease in progesterone levels in hyperprolactinemia, it is advisable to prescribe gestagens in phase II of the cycle

(duphaston 20 mg / day or morning 200 mg / day from the 16th to the 25th day of the menstrual cycle).

In the absence of pregnancy, operative laparoscopy (PCOS, endometriosis) is indicated.

The effectiveness of infertility treatment in hyperprolactinemia is determined by the level of gonadotropins. The maximum effect of infertility treatment was obtained with a low level of gonadotropins - 80.6%; in patients with a high level of gonadotropins, reproductive function is not restored.

Treatment of hypogonadism in hyperprolactinemia

The mainstay of treatment for hyperprolactinemic hypogonadism is dopamine agonists. If the normalization of the PRL level is not accompanied by the restoration of the menstrual cycle, which is more often the case with macroprolactinomas, it is advisable to prescribe female sex hormones. When prescribing sex steroids, the adequacy of the dosage of estrogens should be observed, with a preserved uterus, a combination with gestagens, mandatory monitoring of the patient's condition during treatment.

Before the treatment with sex hormones and with further observation of the therapy, an examination is carried out, which includes:

- determination of the state of the mammary glands once a year;
- Ultrasound of the pelvic organs with the determination of the thickness of the endometrium 2 times a year;
- cytological examination of a smear from the cervix once a year;
- biochemical blood test with determination of lipid spectrum, transaminases 2 times a year;
- osteodensitometry once a year.

Before 45-52 years, it is recommended to prescribe drugs containing 2 mg of estradiol, after 50-52 years - 1 mg of estradiol. In patients over 45 years of age, sex steroids with a low content of estrogen are advisable to prescribe in a continuous mode that does not give bleeding. It is advisable to discontinue treatment with sex steroids before the age of 55.

Management of drug-induced hyperprolactinemia.

In patients with symptoms suspected of drug-induced hyperprolactinemia, it is suggested to cancel drug therapy for 3 days or replace the drug with an alternative drug under the control of serum prolactin. Discontinuation of the antipsychotic drug or its replacement should be accompanied by the consultation of the attending physician. If the drug cannot be discontinued and the detection of hyperprolactinemia does not coincide with the initiation of therapy, pituitary

imaging (MRI) is recommended to differentiate drug-induced hyperprolactinemia and symptomatic hyperprolactinemia due to hypothalamic or hypothalamic tumors.

Comment. The most common cause of non-neoplastic hyperprolactinemia is medication, especially antipsychotics / antipsychotics. Among patients receiving typical antipsychotics (phenothiazine or butyrophenone), 40 to 90% have hyperprolactinemia, as do 50-100% of patients on risperidone. Prolactin levels rise more slowly with oral administration of the drug, and it usually takes 3 days to return to normal levels after stopping the drug. In some patients, drug-induced hyperprolactinemia remains asymptomatic, while galactorrhea and amenorrhea may develop in women, and decreased libido and erectile dysfunction in men. There is also evidence of an increased risk of bone loss in women with antipsychotic-induced hyperprolactinemia.

Drug-induced hyperprolactinemia is usually associated with prolactin levels in the 25 to 100 $\mu\text{g} / \text{L}$ range, but metoclopramide, risperidone, and phenothiazine can lead to prolactin levels in excess of 200 $\mu\text{g} / \text{L}$. The mechanism lies in the antagonism of these drugs in relation to dopamine. Variants of the D2 receptor gene in patients taking these antagonists may enhance the hyperprolactinemic effect.

Verapamil is the cause of hyperprolactinemia in 8.5% of patients, presumably due to blockage of hypothalamic dopamine. Opiates and cocaine act through μ receptors and cause mild hyperprolactinemia.

The role of estrogen among the causes of hyperprolactinemia is controversial: in some women (12 to 30%) taking high-dose estrogen-containing oral contraceptives, serum prolactin levels may slightly increase, but therapy in this case is most often not required.

In the case of drug-induced hyperprolactinemia, the attending physician and the patient should jointly decide on the priority treatment program by assessing the available ones. Such an assessment should include the possibility of using alternative drugs (antipsychotics with low antagonism to dopamine or aripiprazole, an atypical antipsychotic with both antagonistic and agonistic effects on dopamine, the use of which can reduce prolactin levels and reduce the effects caused by hyperprolactinemia), their advantages and disadvantages, and the possibility of development against the background of receiving undesirable effects due to constant hyperprolactinemia.

Patients with asymptomatic drug-induced hyperprolactinemia do not need treatment. If the medication cannot be stopped or the drug cannot be changed and the patient has symptoms of hypogonadism or decreased bone mass, estrogen or testosterone therapy should be considered.

As a first step towards the treatment of drug-induced hyperprolactinemia, it is proposed to discontinue the drug, if possible, or replace it with an alternative that is

unable to cause hyperprolactinemia. If it is impossible to cancel or replace the medication, it is proposed to add dopamine agonists to the therapy, but with caution, in agreement with the attending physician and under his supervision. The feasibility of treating a patient with antipsychotic-induced hyperprolactinemia with dopamine agonists remains controversial. Some studies suggest that dopamine agonist therapy will help normalize prolactin levels in only 75% of these patients, but will lead to an exacerbation of psychosis.

It is recommended to take into account, first of all, the possibility of the development of adverse consequences of therapy with dopamine agonists in the case of antipsychotic-induced hyperprolactinemia, including exacerbation of psychosis, secondly, the advantages that therapy with dopamine agonists can give in this case, and the adverse consequences of the hyperprolactinemia itself, which developed as a result of taking medications that can not be canceled or replaced.

Resistant and malignant prolactinoma

For symptomatic patients who do not achieve normal prolactin levels or do not significantly decrease tumor size on standard doses of a dopamine agonist (resistant prolactinomas), it is recommended to increase doses to the maximum tolerated before deciding on surgical treatment.

Comment. The response to dopamine agonists varies. Most prolactinoma patients treated with standard doses of dopamine agonists respond by normalizing prolactin levels and reducing tumor size. However, some patients do not respond well. The phenomenon of dopamine agonist resistance includes the failure to achieve normal prolactin levels at the maximum tolerated doses of the dopamine agonist and the failure to achieve a 50% reduction in tumor size. Failure to restore fertility in patients receiving a standard dose of a dopamine agonist may also be considered a resistance to therapy. Some patients may have an inappropriate response, such as shrinking tumor size without normalizing prolactin levels, and vice versa, others may have partial resistance and will require large doses of dopamine agonists to be effective. Dopamine agonist resistance differs from intolerance, where the occurrence of side effects precludes their use.

The reasons for resistance to dopamine agonists are not fully understood, there are various mechanisms underlying them. There is a decrease in the number of D2 receptors, the expression of which occurs on resistant prolactinomas, but this is not always found. Binding to the D2 receptor occurs normally; no mutations have been found in prolactinomas. The ratio of D2 receptor isoforms may vary, and molecular damage to the receptor may occur.

Microadenomas are less resistant to dopamine agonists than macroadenomas. 10% of patients with microadenomas and 18% of patients with macroadenomas do not respond to normal prolactin levels to cabergoline. Moreover, men are more likely to be resistant to dopamine agonists than women.

Increasing the dose of cabergoline by more than 11 mg per week is necessary for some patients to overcome resistance. However, long-term therapy with high doses of cabergoline can be dangerous due to the potential risk of developing cardiac valve regurgitation. Patients with Parkinson's disease who receive an average of 3 mg cabergoline daily are at risk of developing valve regurgitation. In contrast, 6 of 7 studies analyzing heart valves in 500 patients with prolactinomas on standard doses of cabergoline showed no evidence of clinically significant valvular lesions. According to one study, 57% of cases showed tricuspid valve regurgitation in patients treated with cabergoline, but there was also significant tricuspid valve regurgitation in the control group.

Dose escalation should be incremental and dependent on prolactin levels. In patients requiring long-term use of very high doses, echocardiography is necessary to assess valvular changes. The exact dosages and duration of their use, which require monitoring in the form of echocardiography, are currently determined, and patients receiving conventional doses of cabergoline (1-2 mg per week) are likely to not require regular echocardiography.

- Patients with bromocriptine resistance are advised to switch to cabergoline.

Comment. Cabergoline is recommended as a first-line therapy for patients with prolactinoma, but approximately 10% of patients are resistant to this drug. On the other hand, about 25% are resistant to bromocriptine, and 80% of these patients can achieve normoprolactinemia with cabergoline. Clinical studies have not provided accurate comparisons of the mass-reducing effect of different dopamine agonists. However, results from various studies indicate that bromocriptine promotes tumor shrinkage by about 50% in two-thirds of patients, while cabergoline leads to tumor shrinkage in more than 90% of cases.

- There are no controlled studies regarding the results of surgical treatment of tumors that are resistant to drug therapy. However, 7 to 50% of prolactin-secreting tumors recur after resection. Side effects of surgical treatment include hypopituitarism, diabetes insipidus, liquorrhea, and local infections.

Radiation therapy should be used in cases of resistant or malignant prolactinomas. Normalization of prolactin levels occurs in about 1/3 of patients after radiation therapy. Also, with the help of radiation therapy, tumor growth can be controlled, it can be used in patients over 20 years of age to achieve maximum

effect and may not lead to normalization of prolactin levels. Radiation therapy is associated with side effects such as hypopituitarism and, less commonly, cranial nerve damage and secondary tumor formation.

- In patients with malignant prolactin, temozolomide therapy is suggested.

Comment. Malignancy of prolactinoma is defined as metastasis within or outside the central nervous system. Malignant prolactinomas are rare, with about 50 cases reported. It is histologically impossible to differentiate between carcinoma and adenoma. Currently, there are no markers that could serve as predictors of prolactinoma malignancy. Most often, patients with invasive prolactinoma have already undergone drug therapy, surgical treatment and / or radiation therapy, often years earlier there was already a progression, in fact, metastases. Very rarely, prolactinoma is malignant from the very beginning.

The treatment of malignant tumors is a complex process; the survival rate is usually about 1 year. Surgical intervention may be necessary to reduce the severity of the compression effect. Chemotherapy including procarbazine, vincristine, cisplatin, and etoposide can be used, but with little effect. Several reports suggest the use of temozolomide, an alkylating agent, with sufficient efficacy. Temozolomide therapy reduces prolactin levels and stops tumor growth if the tumor does not express methylguanine-DNA methyltransferase in samples, but the value of this test as a predictor of the outcome of temozolomide therapy is low.

Rehabilitation and outpatient treatment

Specific rehabilitation measures for patients with hyperprolactinemia has not been developed. The approach to monitoring the effectiveness of treatment is more individual for each patient due to differences in tumor size, growth rate and response to treatment. Monitoring of patients taking dopamine agonists includes:

- Periodic measurement of prolactin levels, initially 1 month after the start of treatment to correct therapy

for faster achievement of normal prolactin levels and regression of hypogonadism;;

- MRI examination of the brain after 1 year (or 3 months in patients with macroprolactinoma with an increased level of prolactin while taking antidopaminergic drugs or with the addition of new symptoms (galactorrhea, visual field disorders, headaches,

hormonal disorders);

- Consultation with an ophthalmologist to check the visual fields in patients with macroprolactinomas when signs of optic chiasm compression appear;
- Monitoring of concomitant diseases, if necessary: secondary osteoporosis, galactorrhea against the background of normalization of prolactin levels, impaired secretion of other pituitary hormones in the case of macroadenomas with the development of hypopituitarism.

After adenomectomy, it is necessary to dynamically monitor the prolactin level at least 1 time every 3 months for 1 year, then annually for at least 5 years.

Prevention and dispensary observation.

No specific preventive measures have been developed for patients with hyperprolactinemia.

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