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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

FEATURES OF PATHOLOGY OF THE REPRODUCTIVE SYSTEM IN WOMEN WITH HYPERPROLACTINEMIA, DIAGNOSTICS AND EFFECTIVENESS OF MODERN CORRECTION METHODS

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GENERAL REVIEW OF THE WORK

Relevance of the topic. Hyperprolactinemia (HP) is a neuroendocrine syndrome characterized by increased secretion of prolactin (Prl). The frequency of hyperprolactinemia in the population is up to 1%. The incidence of hyperprolactinemia in women in the active reproductive period is 5-14%, and in infertile women it is 30-40 %.[1;2]

Prl is a polypeptide hormone consisting of 199 amino acids, has a molecular mass of 23.5 kDa and is chemically similar to placental lactogen and growth hormone. Discharge period of prolactin in the blood is 20-30 minutesr.[3]

According to the clinical recommendations of the International Society of Endocrinologists, the causes of HP include the following nosological units: physiological, hypothalamic-pituitary damage, tumors, pathologies of the pituitary gland, systemic disorders, drug causes.[4]

According to the literature, HP can cause hypogonadism. Symptoms of this syndrome include oligomenorrhea, infertility, galactorrhea, and general illness. Symptoms of chronic HP include sexual dysfunction, including decreased libido, absent of orgasm, impotence, reproductive dysfunction, including anovulation, irregular menstruation, infertility, decreased estrogen and testosterone levels, breast pathology, and other diseases. In these women, high-frequency pathologies of the mammary glands: galactorrhea, enlargement and

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[1] Smolarczyk R., Teliga-Czajkowska J., Romejko-Wolniewicz E., Czajkowski K. How to deal with hyperprolactinaemia? // Am. J. Archives of Perinatal Medicine., 2014, vol.20, №2, p.96-98.

[2] Thirunavakkarasu K., Dutta P., Sridhar S. Macroprolactinemia in hyperprolactinemic infertile women // Am. J. Endocrine, 2013, №44, p.750-755

[3] Татарчук Т.Ф., Ефименко О.А. Роль гиперпролактинемии в становлении и реализации репродуктивной функции // Международный эндокринологический журнал, 2010, №3, в.27, с.25-28.

[4] Melmed S., Casanueva F.F., Hoffman A.R. Diagnosis and Treatment of Hyperprolactiemia: An Endocrine Society Clinical Practice Guidelines // JCEM., 2011, vol.96, №2, p.273-288

dysplasia of the mammary glands are noted. Other diseases and pathological conditions include demineralization of bones, osteoporosis, cardiovascular disease, depression. It was found that there is no correlation between Prl levels and clinical symptoms.[1]

Another clinical sign is galactorrhea, the incidence of this symptom in women with HP is 33%. It has been established that galactorrhea can also be found at normal Prl levels and no correlation is observed between galactorrhea and Prl levels.[5;6;7;]

It should be noted that one of the causes of HP is the using of antipsychotic drugs. Against the background of taking these drugs, an increase in Prl levels is noted as a result of hypothalamic dopamine blockade. These patients have irregular menstruation, gynecomastia in men, osteoporosis, infertility, sexual disorders in both genders, Hyperprolactinemia is often asymptomatic. HP can be observed against the background of taking haloperidol, metoclopramide, risperidone, olanzapine, clozapine, aripiprazole, gitiapine, domperidone, veropamil.[8;9]

Several dopamine agonists are currently used to treat HP, including bromocriptine, pergolid, and cabergoline in the United States, and guinogolide in the United Kingdom.

It is advisable to prescribe dopamine agonists and oral contraceptives in asymptomatic microprolactinomas. In macropro-

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[5] Moswad N.S., Caplin A. Diagnosis, management, and long-term outcomes of rectovaginal endometriosis // Int.J.Womens Health., 2013, №5, p.753-763.

[6] Pereira-Lima J.F., Leães C.G., Freitas Neto F.M., Barbosa M.V., da Silva A.L.M. Hyperprolactinemia and body weight: prevalence of obesity and overweight in patients with hyperprolactinemia // Res.J.Endocrinol.Metab., 2013, №1, p.2-6.

[7] Shibli-Rahhal A., Schlechte J. Hyperprolactinemia and infertility // Endocrinol Metab Clin North Am, 2011, vol.40, №4, p.837-846.

[8] Miyamoto B.E., Galeki M., Francois D. Guidelines for Antipsychotic-Induced Hyperprolactinemia // Am. J. Psychiatr Ann., 2015, vol.45, №5, p.266-272.

[9] Witchel S.F., Oberfield S., Rosenfield R.L., Codner E., Bonny A. The diagnosis of polycystic ovary syndrome during adolescence // Am. J. Hormone research in pediatrics, 2015, vol.83, №6, p.376-389.

lactinoma, surgery is recommended, and in malignant prolactinomas, radiation and chemotherapy are recommended.

Despite numerous scientific studies, there are no indicators of the incidence of hyperprolactinemia, reproductive and pubertal periods, which may be a solution to the problem of correction of hyperprolactinemia, normalization of the menstrual cycle and gene-rative function. Given the urgency of this problem, the purpose of the current study was clarified[10;11]

Object of study. In the study Hypeprolactinemia syndrome was confirmed in girls and women in puberty and reproductive periods by clinical, instrumental, radiological and laboratory methods, 12-43 years aged girls and women were selected as the object of study.

The aim of the research. Study of the clinical and diagnostic features of HP in different ages, the state of the reproductive system and assessment of the effectiveness of the medicament treatment methods.

Research objectives:

1. To study the causes, frequency, complaints and clinical manifestations of hyperprolactinemia.
2. Determination of indicators of physical and sexual development of girls with hyperprolactinemia in puberty, the formation of menstrual function, hormones, echographic indicators of the uterus and ovaries.
3. To study the causes, frequency, the frequency of subjective and clinical symptoms, changes in the characteristics of hormones and echographic indicators of the reproductive organs in women with hyperprolactinemia in reproductive period.
4. To determine the features of radiological examinations of hyperprolactinemia of various origins.

[10] Klibanski A. Clinical practice. Prolactinomas // N.Engl.J.Med., 2010, №362, p.1219-1226.

[11] Mancini T., Casanueva F.F., Giustina A. Hyperprolactinemia and prolactinomas // Endocrinol.Metab.Clin.North Am., 2008, №37, p.67-99.

5. To study the incidence of thyroid pathology in girls and women with hyperprolactinemia, the effectiveness of hormones, echographic indicators of the small pelvic organs, the effectiveness of modern correction methods.
6. To determine the characteristics of menstrual, reproductive and generative functions, hormonal and echogenic indicators and the effectiveness of modern correction methods in girls and women with polycystic ovary syndrome against the background of hyperprolactinemia.
7. To study clinical and diagnostic features of hyperprolactinemia with neurogenic and iatrogenic origin.

Research methods. Clinical examination, ultrasound examination, assessment of physical and sexual development in girls in puberty, assessment of the degree of hirsutism, hormone, radiological examinations, method of statistical-mathematical analysis.

The main provisions for the defense:

1. High frequency of hypeprolactinemic hypogonadism is noted in girls and women with hyperprolactinemia. Causes of primary hypeprolactinemic hypogonadism include functional (idiopathic) disorders, pituitary gland adenoma, "empty" turkish saddle syndrome, pituitary adenoma combined with thyroid adenoma. In secondary (symptomatic) hypeprolactinemic hypogonadism, polycystic ovary syndrome, neurogenic factors, pathologies of the thyroid gland are very common.

2. In girls with hyperprolactinemia in puberty period, there is a delay in physical and sexual development, which is manifested by a delay in the anthropometric measurements, secondary sexual characteristics and formation of menstrual func - tion. In these girls, against the background of hyperprolactinemia, there is a decrease in follicle-stimulating hormone, luteinizing hormone, estradiol, and an increase in dehydroepiandrosterone sulfate.

3. Secondary hypeprolactinemic hypogonadism (symptomatic) predominates in the reproductive period. 32.7% of these women have polycystic ovary syndrome, 21.8% have neurogenic factors, and 23.6% have pathology of the thyroid gland.

Hyperprolactinemia with neurogenic origin is manifested by psychosis, traumatic brain injury, depressive states, chest injuries during sport exercise, post-traumatic encephalopathy. Iatrogenic factors are determined against the background of taking antipsychotic drugs, dopegid and antiepileptic drugs.

4. Treatment of hyperprolactinemia must be carried out in conjunction with endocrinology. First of all, the factors that cause hyperprolactinemia should be ruled out, the appointment of dopamine agonists - Dostinex is considered appropriate when the baseline is high.

Scientific novelty of research. As a result of the study, the frequency of nosological units of primary and secondary (symptomatic) hypeprolactinemic hypogonadism in girls and women with hyperprolactinemia was determined. For the first time, the characteristics of puberty in girls with hyperprolactinemia were studied, and it was found that in girls with hypeprolactinemic hypogonadism, there is a delay in physical and sexual development and in formation of menstrual function.

It has been established that hypeprolactinemic hypogonadism is accompanied by hyperprolactinemia in the background of hyperandrogenism. For the first time, the frequency of pathologies that cause primary and secondary (symptomatic) hypeprolactinemic hypogonadism, the criteria for clinical, hormonal, radiological (radiological) symptoms were determined.

As a result of the study, the incidence of neurogenic and iatrogenic hyperprolactinemia, the causative factors in girls and women in reproductive age were determined.

The effectiveness of dopamine agonists - Dostinex in hyperprolactinemia of various origins has been studied.

Practical significance of the research. As a result of the study, the frequency of subjective symptoms of hypeprolactinemic hypogonadism in girls and women with primary and secondary (symptomatic) hypeprolactinemic hypogonadism, the characteristics of menstrual and generative function were studied.

As a result of the study, the indicators of physical, secondary sexual developmental characteristics in women with hyperprolac-

tinemia in different ages, as well as the formation of the hypothalamus-pituitary-adrenal-ovarian system were studied. It has been established that hyperandrogenism is observed in girls and women with hyperprolactinemia, regardless of their origin.

For the first time, pathologies that cause hypeprolactinemic hypogonadism in girls and women in reproductive age and their frequency have been identified.

As a result of the study, polycystic ovary syndrome due to secondary hypeprolactinemic hypopogonadism was observed in 32.7%, thyroid pathology in 23.6%, neurogenic disorders in 21.8%, and iatrogenic factors in 12.7%.

In girls and women with hyperprolactinemia, X-ray craniography is recommended as a screening method. Magnetic resonance imaging of the pituitary gland is recommended in patients with "suspicious" and pathological signs in craniography results.

Treatment of hyperprolactinemia should be carried out under the joint supervision of an endocrinologist and gynecologist. Initial treatment of the causes (diseases) of hyperprolactinemia, determination of the amount of prolactin in the dynamics, in the case of hyperprolactinemia, dopamine agonists - 0.5 mg m tablets twice a week for 3-6 months with Dostinex is considered effective.

Approbation and application of research work. The results of the research have been discussed at the 5th International Medical Congress (Baku 2018). "Actual approaches to some problems of Obstetrics and Gynecology in Azerbaijan" (Baku 2019), The First International Scientific-Practical Virtual Conference "Clinical Endocrinology and Endocrine System Disease: Prognosis, Achievement and Challenges (virtual 2021).

The preliminary discussion of the dissertation work was conducted at the joint meeting of the staff of the I and II departments of Obstetrics and Gynecology of the Azerbaijan Medical University (July 5, 2018, protocol №19) and approbation of the work was reported and discussed at the scientific seminar of the Dissertation Council ED 2.06 under the Azerbaijan Medical University (April 1, 2021, protocol №5).

The obtained results were applied in the education of the I Department of Obstetrics and Gynecology, I Department of Obstetrics and Gynecology of the Educational Surgical Clinic of the Azerbaijan Medical University.

Publications. 12 scientific articles on the result of the dissertation were published. 7 of them are articles, 5 are theses and conference materials, including 2 articles and 2 theses were published abroad.

Volume and structure of the dissertation work. The dissertation work is written on 157 computer papers. It consists of the following chapters: introduction (- 14649 symbols), literature view (- 48165 symbols), chapter of materials and research methods (-11712 symbols), chapter of own research results (- 47689 symbols), conclusion (- 38124 symbols), findings (- 3949) and practical recommendations (-1099 symbols) Dissertation contains 47 tables, 17 figures and 14 schemes. The bibliographic index includes 217 works- 6 in Azerbaijan, 29 in Russian, 182 in English languages.

The total volume of dissertation is 165381 symbols (without contents, list of literature, tables, schemes and spaces).

MATHERIAL AND METHODS OF THE STUDY

The aim of this study was to study the clinical and diagnostic features of hyperprolactinemia at different ages, the state of the reproductive system and to assess the effectiveness of the drug treatment methods. In accordance with the purpose, 92 girls and women in puberty and reproductive age with hyperprolactinemia were examined at the Educational Surgical Clinic of the Azerbaijan Medical University and the Republic Family Planning Center. (Main group)

21 (22.8%) girls with hypeprolactinemia in puberty (main group 1) and 71 (77.2%) women with hyperprolactinemi in the reproductive period (main group 2) were examined.

The average age of women with hyperprolactinemia in the study was 25.1±0.81 (12-43) years. During examining the characterristics of reproductive function, it was found that 4 (4.3%) of girls and

women with hyperprolactinemia had a primary amenorrhea and the remaining 88 patients had menarche at 13.38±0.13 (10-16) years.

28 (30.4%) examined girls and women did not have a menstrual cycle disorders, but 64 (69.6%) had a menstrual cycle disorders. The duration of the menstrual cycle was 39.43±1.1 (15-60) days, and the menstrual period was 5.82±0.6 (2-10) days.

61 (66.3%) examined girls and women had a sexual life and 31 (33.7%) did not have sexual life The average age of beginning of sexual life was 22.1±0.46 years.

Clinical examination of the study

In girls with hypeprolactinemia during puberty, physical development indicators, including weight, height, size of the arms in the open position, shoulder width, chest circumference, leg length, and pelvic measurements were determined.

The prevalence of secondary sexual characteristic and the formation of menstrual function in girls with HP during puberty were determined. The assessment of the secondary developmental stages of sexual characteristics was carried out the J. Tanner scale.

The Ferriman-Gallway scale was used to determine the degree of hirsutism in the examined girls.

The results were compared with the anthropometric measurements and secondary sexual characteristics of practically healthy girls.

Hormonal examinations

In the study, the blood level of prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyrotropic hormone (TSH), estradiol (E2), dehydroepiandrosterone sulfate (DHEA-S), free triiodothyronine (T3),free tyroxin (T4) was analyzed.

Radiological examination

All patients included in the study underwent radiological craniography and, if necessary, Magnetic Resonance Imaging (MRI) examinations.

Ultrasound examination

The examined girls and women underwent an ultrasound examination of the pelvic organs with abdominal and vaginal transmission.

During the study, the length, width, anterior-posterior size of the uterus, the thickness of the endometrium, the length and width of both ovaries were determined.

Ultrasound examination of the thyroid gland was also performed on all patients. The size of the gland, pathological changes were found.

Statistical processing of clinical material.

The results of the study were statistically processed. Group indicators are placed in the order of variation. The average arithmetic mean (m), the square root of the average arithmetic mean (λ2), its standard error (Se), as well as the minimum (min) and maximum (max) values of the series were determined for each group.

The U (Wilcoxon-Manna-Whitney) criterion, a non-parametric method, was used to develop quantitative indicators in groups and subgroups.

OWN RESEARCH RESULTS

In the study the causes of hyperprolactinemia were divided into primary and secondary (symptomatic) hyperprolactinemic hypogonadism according to the classification presented by I.I. Dedov, G.A. Melnichenko and are shown in Figure 1.

It was found that 89 (96.7%) of girls and women with HP had breast secretions, 79 (85.9%) had headaches, and 86 (93.5%) had an emotional lability. There were other complaints as, irritability in 76 (82.6%), pallor of skin in 71 (77.2%), swelling of the face in 67 (72.8%), increased sweating in 70 (76.1%), nausea in 41 (44.6%), rough facial features in 36 (39.1%), swelling of the lower extremities in 39 (42.4%), weight loss in 31 (33.7%), weak nails in 24 (26.1%), and vision impairment in 33 (35.9%) patients.

As it seen from the figure, primary hyperprolactinemic hypogonadism was prescribed to 23 (25%) patients during puberty and reproductive periods. This form of hypogonadism is characterized by functional (idiopathic) disorders in 16 (69.6%) patients, pituitary adenoma in 5 (21.6%) women, including microprolactinoma in 3 pa-

tients (13%), and macroprolactinoma in 1 (4.3%), “empty sella” syndrome was diagnosed in 2 (8.7%) patients.

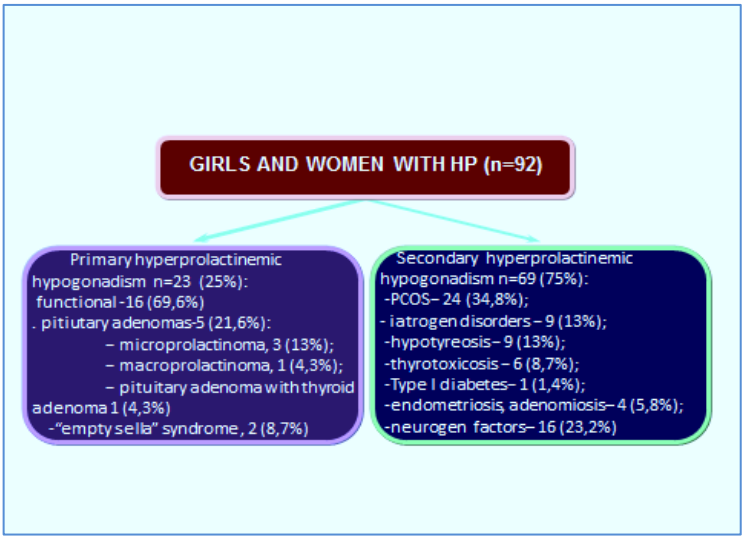


Figure 1.Causes of HP in girls and women in puberty and reproductive periods

Secondary hypeprolactinemic hypogonadism was found in 69 (75%) girls and women. Polycystic ovary syndrome (PCOS) in 24 (34.8%) patients, iatrogenic disorders in 9 (13%), hypothyroidism in 9 (13%), thyrotoxicosis in 6 (8.7%) patients, and 1 (1,1) Diabetes mellitus type 1 was diagnosed in 4%, endometriosis in 4 (5.8%), and hyperprolactinemic hypogonadism of neurogenic origin in 16 (23.2%) patients.

In girls in puberty, frequency of primary hyperprolactinemic hypogonadism was 33.3% and the secondary was 66.7%.

In the study it was found that 6 (85.7%) of girls with primary hyperprolactinemic hypogonadism had functional (idiopathic) disorders and 1 (14.3%) had pituitary microadenoma.

PCOS in 6 (42.9%), neurogenic causes in 4 (28.6%), hypothyroidism in 2 (14.3%) and iatrogenic factors in 2 (14.3%) girls with secondary hyperprolactinemic hypogonadism are noted.

FEATURES OF CHARACTERISTICS OF PHYSICAL AND SEXUAL DEVELOPMENT, FORMATION OF MENSTRUATION, HORMONES AND ECHOGRAPHIC INDICATORS IN GIRLS WITH HYPERPROLACTINEMIA

In the research, girls in puberty with HP were divided into 2 subgroups (13-15 year old girls (n=11) and 16-17 year old girls (n= 10)) to study the characteristics of physical and sexual development.

Antropometric indicators of physical development of 13-15 and 16-17 years subgoups with HP, including height, body weight, distance at the open position of the arms (DOA), length of the lower extremities (LLE), circumference of the chest (CC), width of shoulders (WS) and external measurements of the pelvis were statistically lower than the sizes of practically healthy girls at that ages. ($P < 0.05$)

Girls with HP during puberty had delay in mammary glands development than healthy girls, and there is a significant increase in pubic hairgrowth. The characteristics of menstrual function in girls with HP during puberty also were analyzed. It was found that 4 (19%) of 21 girls did not menstruate during the examination, 11 (52.4%) had irregular, painful menstruation, and 6 (28.6%) had secondary amenorrhea .

Statistically significant decrease of FSH, LH, and E2 levels, and increased DHEA-S level were observed in girls with HP during puberty ($P < 0.05$).

Thus, girls with HP during puberty show signs of central hypogonadotropic hypogonadism. Due to high levels of prolactin, it is appropriate to use the term hyperprolactinemic hypogonadism in this situation. In girls with HP, a statistically significant decrease in the size of the uterus and both ovaries is noted ($P < 0.05$).

Thus, hyperprolactinemic hypogonadism in girls with HP during puberty is manifested by physical and mammary glands developmental delay, increased hairgrowth in the armpits, pubic area and high hirsutism. At the same time, significantly lower levels of LH, FSH, E2, statistically significant lower echographic indicators of the uterus and both ovaries ($P < 0.05$).

DETERMINATION OF SUBJECTIVE AND CLINICAL SYMPTOMS IN GIRLS AND WOMEN WITH HYPERPROLACTINEMIA IN REPRODUCTIVE PERIOD

In the study, 71 (77.2%) of girls and women with 92 HP were in the reproductive period. The average age of examined girls and women was 34.41±0.71 (18-43) years.

28 (39.4%) girls and women with HP had no menstrual dysfunction, and 43 (60.6%) women with hyperprolactinemia had menstrual dysfunction. Menarche in girls and women with hyperprolactinemia in the reproductive period was at 11.46±0.13 (9-16) years.

70 (98.6%) girls and women in reproductive period with HP had mammary gland secretions (galactorrhea), 71 (100%) had irritability, 71 (100%) had pallor of skin, and 68 (95, 8%) emotional lability, 55 (77.5%) swelling of the face, 61 (85.9%) headaches, 57 (80.3) %) increased hairgrowth, visual impairment was in 42 (59%), swelling of the lower extremities in 39 (54.9%), weight gain in 32 (45%), rough facial features in 28 (39%) vomiting in 23 (32%), nausea in 41 (57.7%), fragility of the nails in 24 (33.85), chest pain during breathing in 18 (25%), obesity in17 (23.9%), weight gain in 16 (22.5%) patients.

Thus, the prevalence and high frequency of subjective symptoms in girls and women with HP during the reproductive period are noted.

HP manifests itself as primary and secondary (symptomatic) HPHG. In the study, the incidence of primary HPHG in girls and women in reproductive period was 22.5% and secondary HPHG was 77.5%.

Functional disorders were in 62.5%, pituitary adenomas in 25%, microprolactinoma in 12.5%, macroprolactinoma in 6.25%, pituitary adeoma with thyroid adenoma in 6.25%, "empty sella" syndrome in 12,5% examined girls and women in reproductive period. Secondary HPHQ (symptomatic hypogonadism) has a high incidence of PCOS (32.7%), neurogenic causes (21.8%), hypothyroidism (12.7%), iatrogenic factors (12.7%), thyrotoxicosis (10, 9%), type I diabetes (1.18%), endometriosis (7.3%).

Thus, in the reproductive period, HP manifests itself with symptomatic hypogonadism in 77.5% cases and with secondary HPHG in 22.5% patients.

In addition to the high levels of prolactin in girls and women with HP in the reproductive period, there is a statistically significant increase in the level of FSH, DHEA-S, free T3, free T4, and a significant decrease in the level of E_2. ($P < 0.05$).

Echographic characteristics of the uterus and ovaries of girls and women during the reproductive period were studied.

There is a statistically significant decrease in all echographic indicators of uterus in girls and women with HP during the reproductive period. It should be noted that in these women there is a significant increase in endometrial thickness. ($P < 0.05$)

Thus, the study found that in girls and women with HP during the reproductive period, a decrease in all sizes of the uterus, a significant increase in the thickness of the endometrium and the thickness of both ovaries were detected, indicating the frequency of endocrine diseases with HP, it can be explained by the frequency of pathological processes that cause HPHG.

DIAGNOSTIC FEATURES OF RADIOLOGICAL EXAMINATION METHODS OF HYPERPROLACTINEMIA WITH DIFFERENT ORIGINS

To determine the diagnostic value of radiological (radiological) examination methods 92 girls and women with HP were examined.

According to the study in 69 (75%) of 92 girls and women, no pathology was found according to radiological craniography. In 18 (19.6%) “suspicious” changes that did not correspond to physiological parameters were detected. The "suspicious" changes were the doubling of the contours of the sella turcica, the thickening or hardening of the hard meninges in the forehead, the presence of signs of calcification of the sella turcica, the thickening of the hard membranes behind the sella turcica, the strengthening of the vascularisation along the skull.

Organic pathologies of the sella turcica were diagnosed in 5 (5.4%) patients with HP. Pathological changes include an increase in the size of the sella, various degrees of deformation, doubling of the contours and a bulge of up to 3 mm, the presence of a balloon-like sella turcica.

Taking into account the results of radiological craniography, MRI was performed in girls and women with "suspicious" and pathological radiographic changes.

In 4 patients with hyperpolactinemia, MRI revealed microadenoma with weak and late contrast fluid collection in the right and left pituitary gland, coronal size of the pituitary gland was 8.0±0.05 mm, axial size 12.5±0.02 mm, anterior-posterior size 13.25±0,07 mm.

In addition, macroadenoma measuring 9 mm anteriorly, coronally 17 mm length, and axially 14 mm extending into the supracellular cistern was identified in 1 patient. The macroadenoma covered the intracavernous segment of both internal carotid arteries at 180 ° and displaced the pituitary gland toward the infundubulum superior.

In addition to the destructive changes in the walls of the sella turcica, increasing of sizes of the sella turcica, the deformation of the pituitary gland in the form of a hemisphere, the presence of a low-intensity T2W signal in the T1W mode of the pituitary gland, the asymmetric supra-cellular cistern and thinning and elongation of the pituitary gland were found in 2 patients. As a result of MRI, microadeomas of different sizes (4.3%), macroadenomas (1.1%), “empty” sella syndrome (2.2%) are identified.

CHARACTERISTICS OF PATHOLOGY OF THE THYROID GLAND IN GIRLS AND WOMEN WITH HYPERPROLACTINEMIA

The study found that 16 (17.4%) of girls and women with 92 HP had thyroid pathology, 9 (9.8%) of them had hypothyroidism and 6 (6.5%) had hyperthyroidism. Pituitary adenoma with thyroid adenoma was reported in 1 (1.1%) case. In the study, hirsute index in women with HP and hypothyroidism (HT) was 18.3 ± 2.24 (11-28) on the Ferriman-Gallway scale. In 8 women, sexual life started at age 21.8±1.46 (18-25) years. When analyzing the characteristics of reproductive function in women with HP and hypothyroidism, it was found that menarche was at 13.89±0.51 (12-16) years, the duration of the menstrual cycle was 39.67±4.13 (20-55) days, and the duration of menstruation was 7, it was 0±0.44 (5-10) days.

Infertility was reported in 5 patients from 8 with HP and HT in the reproductive period, 2 of them had a primary infertility, the duration of infertility was 5.6±4.4 (1.2-10) years, 3 (60%) patients had a secondary infertility and duration of infertility was 3.0±0.58 (2-4) years.

In 8 women with HP and HT, the number of pregnancies was 6.83±1.76 (1-7), 1.5±0.7 (1-2) of them deliveries, the number of miscarriages was 4.0±2.0 (2-6), the number of medical abortions was 1.33±0.33 (1-2).

Thus, the predominance of menstrual and generative dysfunction, spontaneous abortions in women with HP and HT has been reported.

In girls and women with HP and HT, a statistically significant decrease in LH, free T3, and free T4 in the background of HP, and an increase in TSH and DHEA-S were noted ($P < 0.05$).

Thus, in women with HP, there is a decrease in thyroid function and adrenal hyperandrogenism (HA).

Ultrasound examination of the thyroid gland was performed in all girls and women.

76 (82.6%) girls and women with HP had no thyroid pathology in ultrasound examination. The image of the vein is normal, no nodules are observed.

Various pathologies of the thyroid gland were found in 16 (17.4%) of the examined girls and women. In 9 of them (56.3%) there was a decrease in echogenecity of the thyroid gland, diffuse inhomogeneous in echostructure, and in 6 (37.5%) patients there were identified macronodular, hyperechoic, colloidal nodules of various sizes. The mean size of the nodules was 2.98±0.9 mm.

It should be noted that hypothyroidism was observed in 9 (56.3%) patients with thyroid pathology on the background of thyroiditis. In 1 (6.3%) woman with microprolactinoma, a mixed, hyperechoic derivative of the thyroid gland was noted. In 6 (37.5%) hyperthyroidism of different size and number of nodules was detected.

Thus, 82.6% of girls and women with HP did not show thyroid pathology due to ultrasound, 17.4% showed organic changes, 56.3% showed a decrease in echogenicity of tissue in the thyroid gland and hypothyroidism against the background of diffuse non-homogeneous structural thyroiditis, in 37.5% hyperechoic, colloidal nodules of various sizes with calcinate inside were detected, thyroid adenoma combined with pitiutary microprolactinoma in 6.3% were identified.

In girls and women with HP and HT in ultrasound examination there is a statistically significant decrease in all uterine indicators and the width of both ovaries, and a statistically significant increase in endometrial thickness.

In the study, hyperT was diagnosed in 6 girls and women with HP. Patients with hyperT had 21.5±2.92 (8-27) hirsute index by Ferriman-Gallway scale, indicating an average severity of hairgrowth.

Women's sexual life was started at the age of 23.7±1.6 (18-30) years, 4 out of 6 women with HP and HyperT had primary infertility, the duration was 7.5±2.5 (2-13) years. One of the main causes of infertility was the endocrine factor. In 2 patients the number of pregnancies was 4.0±1.5 (2-7), the number of miscarriages was 1.5±0.3 (1-3), and the number of deliveries was 1.8±0.51 (1-2).

In women with HP and HyperT, a statistically significant decrease in TSH and E_2 was noted against the background of increased Prl, DHEA-S, LH, FSH, free T_3, free T_4 ($P < 0.05$).

It should be noted that along with Prl, there is an increase in the amount of FSH, LH, which reflects an increase in the activity of the hypothalamic-pituitary system.

Thus, in women with HP, HyperT manifests itself with an increase in thyroid hormones, hyperandrogenism, hypoestrogenism and a decrease in TSH.

In women with HP and HyperT, a significant decrease in all sizes of the uterus, a statistically significant increase in the thickness of the endometrium and the size of both ovaries were noted during ultrasound examination ($P<0.05$).

CHARACTERISTICS OF OVERVIEW OF POLYCYSTIC OVARIAN SYNDROME AGAINST THE BACKGROUND OF HYPERPROLACTINEMIA

In the study, 24 (34.8%) of 69 patients with symptomatic hypogonadism had PCOS. 6 of them (25%) were in puberty and 18 (75%) were in the reproductive period. The average age of examined girls and women was 23.2±0.94 (16-34) years.

20 (83.3%) girls and women with HP and PCOS had the menstrual cycle disorders, and 4 (16.7%) had a normal menstrual function. Disorders of the menstrual cycle as opsomenorrhea 65%, amenorrhea 25%, proyomenorrhea 10% were detected.

16.7% of girls and women in the reproductive period did not started sexual life, and 83.3% of patients had sexual life at the age of 20.13±0.85 (17-29) years.

Infertility was in 13 (86.7%) and reproductive function was normal in 2 (13.3%) women with HP and PCOS.

9 (69.2%) infertile women had type primary infertility and 4 (30.8%) had secondary infertility. The duration of primary infertility was 4.12±0.6 (1.5-7) years, and the duration of secondary infertility was 2.1±0.13 (1.5-3) years.

In women with normal reproductive function, the number of pregnancies was 5.63±1.19 (1-9), the number of deliveries was 1.8± 0.37 (1-3), and the number of medical abortions was 2.5±1.9 (1-6), the number of miscarriages was 1.33±0.33 (1-2).

Thus, 83.3% of women with HP and PCOS were diagnosed with menstrual disorders, 69.2% with primary infertility, and 30.8% with secondary infertility.

The hormonal parameters of girls and women with HP and PCOS are presented in Table 1.

Table 1. Hormone indicators of the girls and women with HP and PCOS

Hormones	Examination group		P
	Girls and women with HP and PCOS	Practically healthy girls and women	
FSH, mIU/ml	9,12±2,0 (1,0-30,8)	5,9±0,13 (3,7-3,8)	>0,05
LH, mİU/ml	19,93±1,42 (2,2-21,4)	8,21±0,39 (2,6-11,5)	<0,05
TSH, uİ/ml	2,23±0,28 (0,2-50)	2,12±0,11 (1,2-3,23)	>0,05
Prl, ng/ml	46,2±1,15 (25-250)	16,36±1,15 (3,8-25,2)	<0,05
E_2,pg/ml	67,24±4,75 (19,4-137,6)	89,23±0,35 (40-128)	<0,05
DHEA-S, pg/ml	4,97±0,88 (1,24-9,0)	1,28±0,18 (0,6-2,1)	<0,05
T_3, pg/ml	2,37±0,45 (1,3-3,43)	2,18±0,08 (1,4-3,0)	>0,05
T_4, ng/dL	1,2±0,1 (0,97-2,4)	1,0±0,08 (0,7-1,71)	>0,05

As can be seen from Table 1, girls and women with HP and PCOS had statistically high levels of LH, DHEA-S, and a decrease in E_2 ($P<0.05$).

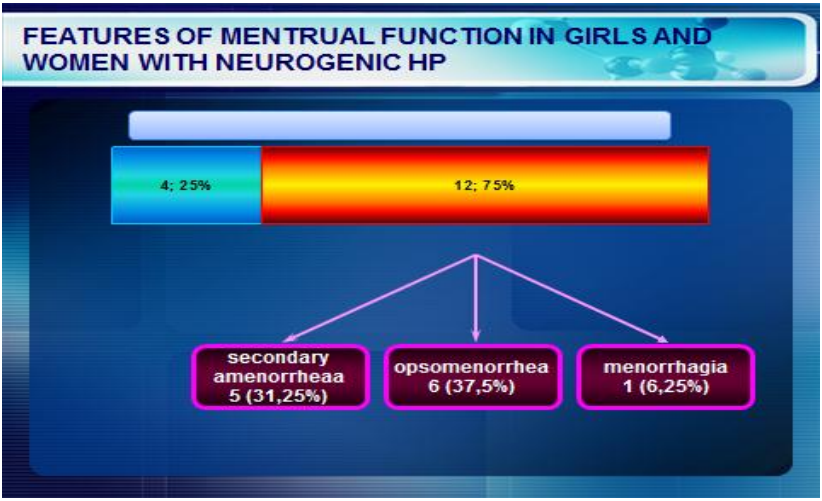
Thus, in women with HP and PCOS hyperandrogenism and hypoestrogenism are noted in the background of HP.

In girls and women with HP and PCOS, a significant decrease in all uterine sizes and an increase in endometrial thickness are noted ($P<0.05$). Statistically significant increase in the length and thickness of both ovaries is determined in ultrasound examination.

CHARACTERISTICS, CAUSES OF NEUROGENIC AND IATROGENIC HYPERPROLACTINEMIA, CLINICAL FEATURES AND DIAGNOSIS

Patients with neurogenic HPHG had a history with mental illness, including 5 (31.3%) patients with psychosis, schizophrenia, and traumatic brain injury, and 6 (37.5%) women with a depressive condition, 4 (25%) with posttraumatic encephalopathy was reported and 1 (6.3%) patient with chest injuries.

Characteristics of menstrual function in girls and women with neurogenic HP are presented in Figure 2.



As can be seen from Figure 2, 25% of girls and women with neurogenic HP had normal menstrual function, 75% had menstrual dysfunction.

It was determined that 31.3% of girls and women with neurogenic HP had secondary amenorrhea, 37.5% opsomenorrhea, and 6.3% menorrhagia.

FSH, DHEA-S, free T_3, and free T_4 are statistically significant increased in girls and women with neurogenic HP. At the same time,

statistically significant decreases in TSH and E_2 were observed in the examined girls and women ($P < 0.05$).

It was detected, that there is a decrease in the size of the uterus and both ovaries, and a significant increase in endometrial thickness in girls and women with neurogenic HP. ($P < 0.05$)

In the study, 9 (13%) girls and women had HP of iatrogenic origin. The average age of the patients was 28.0±3.0 (16-43) years. Antipsychotic drugs for mental illness were prescribed in 5 out of 9 patients (55.6%), Dopegit use in 2 (22.2%) patients, 2 antiepileptic drugs (22.2%) women. In women with iatrogenic HP, a statistically significant increase in DHEA-S and T_4 and a decrease in E_2 were noted ($P < 0.05$). In women with iatrogenic HP, there is a statistically significant reduction in the length and width of the uterus and both ovaries, and a significant increase in endometrial thickness.

TREATMENT METHODS OF HYPERPROLACTINEMIA WITH DIFFERENT ORIGIN IN GIRLS AND WOMEN

In the study, HP was treated depending on the cause, and all treatments were performed under the supervision of an endocrinologist. In girls in puberty with primary HPHG, Dostinex 0.25 mg twice a week is administered under the control of Prl level.

The treatment lasted for 6-12 months, resulting in a decrease in Prl levels to normal levels in girls, an increase in physical development and the development of secondary sexual characteristics, as well as the formation of the menstrual cycle.

As a result of the study, the determination of 0.125-1.0 mg of cabergoline in 95% of Prl-secreting microadenomas twice a week for 12-24 months results in a decrease in Prl to normal levels.

It should be noted that in patients with HP and other endocrine pathologies, it is advisable first of all to treat the main disease, to check level of Prl after treatment and then use dopamine agonist (DA).

Women with HP and HT were gradually prescribed L-thyroxine in their treatment. In women with hyperT, thiamazole (tyrosol) 30 mg daily or propylthiouracil 300 mg daily, metimazole is

prescribed for 4-8 weeks. After the thyroid function is restored, the regulatory dose of Dostinex 0.5 mg twice a week was prescribed and the amount of prolactin was studied in dynamics.

In the study, girls and women were treated in the first phase with combined oral contraceptives (COC) for 3-6 months, including Rigevidon and Diana 35. Treatment is carried out for 3-6 months from the 5th to the 25th day of menstruation. Treatment of HP is 0.5 mg ½ tab. twice a week with Dostinex for 3-6 months. Dosage and duration of administration of drugs were determined in accordance with the dynamic control of hormones.

In the study, 55.6% of women with iatrogenic HP received antipsychotic drugs, so a change of these drugs was recommended by a psychiatrist because of the effect on the course of the underlying disease. The same trend has not been considered appropriate by a neurologist, given that the replacement of antiepileptic drugs may adversely affect the treatment of epilepsy. Replacement of the antihypertensive Dopegit was observed with a change in the dynamics of Prl to physiological parameters, resulting in the restoration of menstrual function.

FINDINGS

1. In girls and women with hyperprolactinemia, primary hyperprolactinemic hypogonadism is 25% and secondary (symptomatic) hypeprolactinemic hypogonadism is 75%. Functional (idiopathic) disorders are in 69.6%, pituitary adenoma in 21.6%, including microprolactinoma (13%), macroprolactinoma (4.3%), 8.7% of cases of "empty" sella syndrome, 4.3% of adenomas of the thyroid gland and pituitary adenoma in girls and women with primary hypeprolactinemic hypogonadism. In patients with secondary hypeprolactinemic hypogonadism in 34.8% of cases of polycystic ovary syndrome, 23.2% of neurogenic causes, 21.7% of pathologies of the thyroid gland, endometriosis in 5.8%, 1.4% type I diabetes are noted in [2,8].
2. In girls with hyperprolactinemia during puberty, there is a delay in sexual development against the background of delayed

physical development. 19% of girls with hyperprolactinemia have irregular menstruation, 52.4% have irregular, painful menstruation, and 28.6% have secondary amenorrhea. In 13-15 years girls with hyperprolactinemia, the hirsut figure is 18.4±0.48 points, and in girls aged 16-17 years it is 21.6±0.36 points.

In girls with hypeprolactinemic secondary hypogonadism during puberty decrease in follicle-stimulating (2.23±0.3 mIU / ml), luteinizing hormone (3.28±0.13 mIU/ml), estradiol (39.56± 7.78 pg/day) ml), in thyroxine (1.17±0.08 ng/dL) and increase in prolactin (31.68±2.3 ng/ml), dehydroepiandrosterone sulfate (14.9±3.88 pg / ml) is reported. ($P < 0.05$) [3.5].

3. In women with hyperprolactinemia in reproductive period there is an icrease in prolactin (43.1±3.82 ng/ml), follicle-stimulating (9.61±1.65 mIU/ml), dehydroepiandrosterone sulfate (5.23± 0.56 pg/ ml), free triiodothyronine (4.36±0.86 pg/ml), free thyroxine (6.64±0.9 ng/dL) level and decrease in estradiol (59.1±6.12 pg/ml) level. According to echographic indicators, a decrease in all sizes of the uterus, an increase in the thickness of the endometrium (7.8±0.36 mm), an increase in the thickness of the right and left ovaries are reported ($P < 0.05$) [6,7].
4. According to radiological craniography, 75% of girls and women with hyperprolactinemia have no pathology of the sella turcica, and 19.6% of women have "suspicious" radiological changes. Organic pathology was detected by radiological craniography in 5.4%, which is manifested by an increase in the size of the sella turcica, varying degrees of deformation, doubling of the contours, and the presence of a ball-like sella turcica. According to radiological craniography, magnetic resonance imaging is mandatory for women with "suspicious" and pathological changes [1].
5. Levels of luteinizing hormone (4.4±0.95 mIU/ml), estradiol (60.85±4.84 pg/ml), triiodothyronine (1.88±0.05 pg/ml) and thyroxine (0.67±0.06 ng/dL) in women with hyperprolactinemia and hypothyroidism are decreased, the levels of pro-

lactin (32.54±2.84 ng/ml), thyrostimulating hormone (6.15± 0.07 uI/ml), dehydroepiandrosterone sulfate (4.38±0.45 pg/ml) are significantly higher (P <0.05).

In women with hyperprolactinemia and hyperthyroidism increase in levels of follicle-stimulating hormone (9.8±1.7 mIU/ml), luteinizing hormone (23.0±0.4 mIU/ml), dehydroepiandrosterone sulfate (3.2±0.2 pg/ml) the level of triiodothyronine (7.37±0.87 pg/ml), thyroxine (7.6±0.62 ng/dL), a decrease in levels of estradiol (76.2±3.51 pg/ml), thyrostimulating hormone (1.14±0.17 uI/ml) are determined [4,11].

6. Polycystic ovary syndrome is noted in 34.8% of patients with symptomatic hypogonadism. Infertility is diagnosed in 86.7% of women with hyperprolactinemia and polycystic ovary syndrome, 69.2% of them have primary infertility, and 30.8% have secondary infertility.

   In women with hyperprolactinemia and polycystic ovary syndrome an increase of luteinizing hormone (19.93±1.42 mIU/ml), dehydroepiandrosterone sulfate (4.97±0.88 pg/ml), prolactin (46.2±1.15 ng/ml) and decrease of estradiol level (67.2±4.75 pg/ml) is observed [10].
7. Hyperprolactinemic hypogonadism of neurogenic origin is diagnosed in 23.2% and iatrogenic origin in 13% of women with hyper. 31.3% of women with neurogenic hypeprolactinemic hypogonadism, had psychosis, traumatic brain injury, 37.5% had depression, 25% had chest injuries during exercise, and 6.3% had post-traumatic encephalopathy.

   55.6% of women with iatrogenic hyperprolactinemia are taking antipsychotic drugs, 22.2% are taking dopegid, and 22.2% are taking antiepileptic drugs [9].

PRACTICAL RECOMMENDATIONS

1. In girls with delayed physical and sexual development during puberty, it is important to determine the amount of follicle-stimulating, luteinizing hormone, as well as to study the level of prolactin.

2. X-ray craniography should be performed in girls and women with hyperprolactinemia. The presence of "suspicious" and pathological signs on radiological craniography is an indication for magnetic resonance imaging.
3. The level of prolactin in thyroid disease should be studied, and in the case of hyperprolactinemia in the first stage of treatment correction of the underlying disease, the determination of prolactin in the dynamics, in the case of hyperprolactinemia using of dopamine agonists - Dostinex.
4. Diagnosis and treatment of girls and women with hyperprolactinemia in puberty and reproductive period, correction of reproductive pathology must be carried out under the joint supervision of an endocrinologist and gynecologist.
5. Drugs used in the treatment of the underlying disease in hyperprolactinemia of iatrogenic origin should be administered by a qualified specialist and take into account the characteristics of the underlying disease.

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