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DIAGNOSIS AND TREATMENT OF HYPERPROLACTINEMIA SYNDROME IN CASE OF INFERTILITY IN WOMEN

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The article is an independent study.

Introduction. Prolactin (lactotropic hormone) is a human peptide hormone that is synthesized in the anterior pituitary gland [1, 2, 3, 4]. An increase in the activity of prolactin can be regarded as a biochemical marker of problems of the hypothalamic-pituitary system. Hyperprolactinemia can occur primarily and act as an independent form of the disease, or form secondarily as a result of endocrine disorders, gynecological and somatic diseases [2, 5].

Regardless of the etiology, hyperprolactinemia may be accompanied by hypogonadism, infertility, galactorrhea, or be asymptomatic. The development of hyperprolactinemia in women is manifested by insufficiency of the corpus luteum, which leads to a violation of reproductive function. The frequency of detection of hyperprolactinemia in female infertility is 19-40% [6, 7, 8].

According to the latest clinical guidelines for the diagnosis and treatment of hyperprolactinemia, issued by a group of international experts of the American Society of Endocrinology, to establish a diagnosis of hyperprolactinemia, it is enough to determine the level of prolactin in the blood serum once [5].

The widespread introduction of dopamine agonist drugs into clinical practice has practically solved the problem of treating hyperprolactinemic conditions. Currently, in order to normalize the level of prolactin, a drug of the third generation of dopamine agonists, Dostinex, is used. The pharmacological effects of the drug Dostinex are based on the fact that it is an ergoline derivative that has a long-term prolactin-lowering effect. This drug has a selective effect, without affecting the basal secretion of other pituitary hormones. A decrease in plasma prolactin levels is observed 3 hours after administration and persists for 7-28 days in patients with hyperprolactinemia [7, 8].

The purpose of the study. To evaluate the effectiveness of the drug Dostinex in the treatment of infertile women with hyperprolactinemia.

Object and methods of the research. We examined 50 women of reproductive age with functional hyperprolactinemia, suffering from infertility of endocrine origin and with a completely excluded male factor of infertility. Inclusion criteria: female age ≥19 years and <42 years; a history of infertility are more than one year. Exclusion criteria: presence of precancerous or malignant neoplasms; positive test for HIV, syphilis, hepatitis, tuberculosis, gonorrhea, trichomoniasis; alcohol or drug addiction. It should be emphasized that among the examined women there were no women with macroadenoma and neurological symptoms. All patients had a neurologist's opinion about the possibility of conservative treatment. The main complaints of the examined patients were menstrual disorders, galactorrhea of various degrees of severity and infertility. The average age of the examined patients was 29.2±0.27 years.

The control group consisted of 30 women with a history of spontaneous pregnancies, which did not have infertility, reproductive losses and increased prolactin levels. The average age of women in the control group was 28.9±0.32 years.

Blood serum was used as a material for quantitative determination of prolactin content. For the analysis, blood was taken from the cubital vein in the morning on an empty stomach on the 3rd-5th day of the cycle. All patients were assessed for total prolactin by Macro ELISA using the Access 2 laboratory system. Hyperprolactinemia was diagnosed at prolactin levels above 25 ng/ml. All patients, in addition to the level of total prolactin (PRL), were determined by the level of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) and dehydroepiandrosterone (DHEA) in the blood serum.

When diagnosed with hyperprolactinemia, Dostinex was prescribed. The dose and duration of the drug were determined individually, taking into account the initial level of prolactin. The treatment was carried out for 3 months under the control of serum prolactin and individual tolerability of the drug. The criteria for discontinuation of the drug were reduction/normalization of prolactin levels in the blood, cessation of galactorrhea, normalization of the menstrual cycle, and restoration of ovulation.

Assessment of treatment efficacy was based on normalization of laboratory parameters and clinical settings: restore regular menstrual cycle, ovulation, the cessation of galactorrhea, pregnancy. A comparative analysis of the effectiveness of the therapy was performed based on the study of the results before treatment and 6 months after the start of therapy.

The effectiveness of therapy was evaluated by comparing the level of prolactin, mammography and ultrasound examination of the mammary glands at the beginning and at the end of the 3-month course of treatment. In addition, the presence and nature of pain in the mammary glands and discharge from them were compared.

Statistical processing of the obtained data was carried out by the methods of variation statistics using the Microsoft Excel spreadsheet editor. The reliability of the differences between the indicators was determined by the Student's method (t-test) and the exact Fisher method. The critical significance level for testing the null hy-

Table 1 – Indicators of hormonal status in patients with functional hyperprolactinemia

indicators	Patients (n=50)	Control (n=30)	Confidence (p)
PRL	63,6±3,49 (37,6-100,5)	20,8±1,29 (6,8-32,6)	p<0,001
LH	6,8±0,25 (3,5-9,9)	7,1±0,36 (3,2-9,9)	p>0,05
FSH	7,9±0,24 (4,5-10,6)	8,1±0,34 (4,6-10,9)	p>0,05
E2	107,8±1,88 (76,0-150,0)	106,7±1,98 (96,0-150,0)	p>0,05
DHEA	291,2±2,08 (269,2-320,3)	142,3±6,20 (110,0-260,6)	p_1<0,001

pothesis was assumed to be less than or equal to 0.05 (p<0.05).

The results of the study and their discussion. In hyperprolactinemia syndrome, regardless of the cause, the key link is an increase in prolactin levels. In this regard, the assessment of the basal level of prolactin is the first most important criterion for the diagnosis of hyperprolactinemia syndrome. The basal level of prolactin in the blood plasma of patients with functional hyperprolactinemia varied widely – from 37.6 ng / ml to 100.5 ng / ml. The mean value was 63.6±3.49 ng / ml. The average prolactin level in women in the control group was 20.8± 1.29 ng / ml (p<0.001) **(Table 1).**

The average levels of LH, FSH, and E2 in patients with functional hyperprolactinemia were within the standard values and did not significantly differ from the control group (p>0.05). At the same time, the average level of LH in the blood serum of patients was 6.8±0.25 ng/ml, FSH-7.9±0.24 ng/ml, E2-107.8±1.88 ng/ml. In the control group, these parameters were equal, respectively: LH-7.1±0.36 ng/ml, FSH-8.1±0.34 ng/ml, E2– 106.7±1.98 ng/ml. In the group of patients, along with prolactin, there were significant changes in the content of DHEA, the average value of which was 291.2±2.08 ng/ml versus 142.3±6.20 ng/ml in the control group (p<0.001).

Violation of the hormonal balance of the body with hyperprolactinemia directly affects the functional state of the mammary glands. Changes in the echostructure of the mammary glands in patients with hyperprolactinemia were represented by various variants of benign dysplasia and fat involution. The most common changes in the structure of the mammary glands in patients with hyperprolactinemia were various variants of benign dysplasia. Diffuse-fibrotic mastopathy was observed in 6 (12.0%) patients, diffuse-cystic mastopathy – in 1 (2.0%) women. Nodular forms of pathology (fibroadenomas) were detected in 2 (4.0%) patients, fibrous-fat involution -in 1 (2.0%) patient. In the remaining patients, there were no changes in the structure of the mammary glands. The dependence of the frequency of breast pathology on the age of the patient, the presence or absence of a history of childbirth and lactation, galactorrhea has not been established.

Table 2 – Indicators of hormonal status in the dynamics of treatment

Indicators	Patients (n=50)		Control (n=30)
	Before the examination	Before the examination	
PRL	63,6±3,49 (37,6-100,5)	28,2±0,76 (18,2-36,8) p<0,001	20,8±1,29 (6,8-32,6)
LH	6,8±0,25 (3,5-9,9)	7,0±0,25 (3,6-10,1) p>0,05	7,1±0,36 (3,2-9,9)
FSH	7,9±0,24 (4,5-10,6)	8,1±0,23 (4,9-10,7) p>0,05	8,1±0,34 (4,6-10,9)
E2	107,8±1,88 (76,0-150,0)	107,3±1,78 (76,0-148,0) p>0,05	106,7±1,98 (96,0-150,0)
DHEA	291,2±2,08 (269,2-320,3)	251,6±1,58 (220,1-263,1) p<0,001	142,3±6,20 (110,0-260,6)

Thus, in patients with hyperprolactinemia, changes in the structure of the mammary glands were usually represented by hypoplastic processes.

In order to reduce the level of prolactin, all patients were prescribed the drug Dostinex. Taking into account the individual baseline level of prolactin, the average therapeutic dose of the drug was determined, that was 0.35±0.1 mg per week. To obtain a clinical effect, 26 (52.0%) patients had enough 0.25 mg, and 24 (48.0%) – 0.5 mg of the drug per week. **Table 2** shows the indicators of the hormonal status of patients 3 months after the start of treatment.

As can be seen from the data obtained, in patients treated with Dostinex, changes in the dynamics of treatment related to the following laboratory parameters. The PRL level decreased 2.3-fold (28.2±0.76 ng/ml versus 63.6±3.49 ng/ml before treatment; p<0.001). Pronounced changes in the dynamics of treatment also related to the level of DHEA (251.6±1.58 ng/ml vs 291.2±2.08 ng/ml before treatment; p<0.001). No significant changes were observed for LH, FSH, and E2 (p>0.05).

The study of the effectiveness of therapy with Dostinex after 1 month of therapy showed that the level of prolactin in the observed patients was within the laboratory norms in 43 (86.0%) patients. In 7 (14.0%) patients whose prolactin values did not reach laboratory standards after a month, it returned to normal after 3 months. The prolactin level was within the standard values in all patients receiving Dostinex, 3 months after the start of therapy. The concentration of prolactin in the blood serum did not exceed normal values for the next 3 months after discontinuation of the drug. The prolactin level was within the normal range in all patients (p<0.001) at the control examination 6 months after the start of treatment.

The results of restoring the menstrual cycle in patients in the first month of therapy showed its normalization in 30 (60.0%) women. Menstrual cycle recovery was observed in 41 (82.0%) women after 3 months of medical treatment. At the control examination, 6 months after the start of treatment, the normalization of prolactin levels in the blood led to the restoration of the menstrual cycle in 100.0% of patients, which became regular, ovulatory.

When using the drug Dostinex, a decrease in the density of glandular tissue and the thickness of the ducts was revealed (according to mammography and ultrasound examination of the mammary glands). The study of the regression dynamics of the galactorrhea symptom in patients treated with Dostinex showed the following. After a month of therapy, the frequency of discontinuation of galactorrhea was noted in 40 (80.0%) patients. After 3 months of therapy galactorrhea persisted in only one (2.0%) patient. After 6 months from the start of treat-

ment, all 100.0% of patients had no symptoms of galactorrhea.

Side effects of treatment with Dostinex were observed in 9 (18.0%) patients in the form of headache, dizziness, nausea, dry mouth. These symptoms were observed in the first days of taking the drug and passed during the first month of treatment.

The results of the treatment of the patients showed the effectiveness of the therapy in correcting disorders of the reproductive system. After therapeutic measures, pregnancy in the early follow-up period (within 3-6 months after treatment) occurred in 44 (88.0%) patients with hyperprolactinemia.

For the successful treatment of patients with infertility due to functional hyperprolactinemia, an individual approach to the choice of the drug, therapeutic dose, regimen and duration of treatment in accordance with specified recommendations and based on the tolerability of the using drugs.

Conclusions. Drug therapy of hyperprolactinemia with Dostinex allows to achieve a normal level of prolactin, normalize menstrual function and eliminate galactorrhea in all observed patients.

Prospects for further research. It is planned to further study the methods of treatment of endocrine disorders, gynecological and somatic diseases.

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ДІАГНОСТИКА ТА ЛІКУВАННЯ СИНДРОМУ ГІПЕРПРОЛАКТИНЕМІЇ ПРИ БЕЗПЛІДДІ У ЖІНОК

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Резюме. *Мета*. Оцінити ефективність препарату Достинекс при лікуванні безпліддя у жінок з гіперпролактинемією.

Об'єкт і методи дослідження. Були обстежені 50 жінок репродуктивного віку, що страждають безпліддям ендокринного ґенезу і повністю виключеним чоловічим фактором безпліддя. Критерії включення до обстеження: вік жінки ≥19 років та <42 років; наявність в анамнезі безпліддя понад один рік. Контрольну групу склали 30 жінок зі спонтанними вагітностями в анамнезі, у яких не було ознак безпліддя, репродуктивних втрат і підвищеного рівня пролактину. Всім пацієнткам визначали рівень загального пролактину методом Macro ELISA за допомогою лабораторної системи Access 2. Гіперпролактинемію було діагностовано при рівні пролактину вище 25 нг/мл. При встановленій гіперпролактинемії було призначено Достинекс. Доза та тривалість застосування препарату визначалися індивідуально, з урахуванням вихідного рівня пролактину. Критеріями припинення прийому препарату були зниження/нормалізація рівня пролактину в крові, припинення галактореї, нормалізація менструального циклу, відновлення овуляції.

Результати дослідження. При синдромі гіперпролактинемії, незалежно від причини її виникнення, ключовою ознакою є підвищення рівня пролактину. Базальний рівень пролактину в плазмі крові пацієнток з функціональною гіперпролактинемією коливався в широкому діапазоні – від 37,6 нг/мл до 100,5 нг/мл. Середнє значення склало 63,6±3,49 нг/мл. Середній рівень показника пролактину у жінок контрольної групи склав 20,8±1,29 нг/мл (p<0,001).

З метою зниження рівня пролактину всім пацієнткам призначено препарат Достинекс. З урахуванням індивідуального вихідного рівня пролактину було визначено середню терапевтичну дозу лікарського засобу, яка становила 0,35±0,1 мг в тиждень. Для отримання клінічного ефекту26 (52,0%) пацієнткам було достатньо 0,25 мг, а 24 (48,0%) - 0,5 мг препарату в тиждень. У пацієнток, що отримували терапію Достинексом, зміни в динаміці лікування стосувалися наступних лабораторних показників: рівень PRL знизився у 2,3 рази (28,2±0,76 нг/мл проти 63,6±3,49 нг/мл до початку лікування; p<0,001).

Вивчення ефективності терапії препаратом Достинексу через один місяць лікування показало, що рівень пролактину у пацієнток, що спостерігалися став у межах лабораторних норм у 43 (86,0%) хворих. У 7 (14,0%) пацієнток, у яких показник пролактину не досяг лабораторних нормативів через місяць, він нормалізувався через 3 місяці.

Висновки. Медикаментозна терапія гіперпролактинемії препаратом Достинекс дозволяє досягти референтних показників рівня пролактину, нормалізувати менструальну функцію, припинити галакторею у всіх пацієнтів, що спостерігалися.

Ключові слова: безпліддя, пролактин, гіперпролактинемія, лікування, Достинекс.

DIAGNOSIS AND TREATMENT OF HYPERPROLACTINEMIA SYNDROME IN INFERTILITY IN WOMEN

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Abstract. Goal. To evaluate the effectiveness of Dostinex in the treatment of infertile women with hyperprolactinemia.

Methods. We examined 50 women of reproductive age with functional hyperprolactinemia, suffering from endocrine infertility and with completely excluded male factor of infertility. Inclusion criteria: female age ≥19 years and <42 years; history of infertility over one year. The control group consisted of 30 women with a history of spontaneous pregnancies, who did not have infertility, reproductive losses, or increased prolactin levels. All patients were assessed for total prolactin by Macro ELISA using the Access 2 laboratory system. Hyperprolactinemia was diagnosed with prolactin levels above 25 ng/ml. When diagnosed with hyperprolactinemia, Dostinex was prescribed. The dose and duration of the drug were determined individually, taking into account the initial level of prolactin. The criteria for discontinuation of the drug were reduction/normalization of prolactin levels in the blood, cessation of galactorrhea, normalization of the menstrual cycle, and restoration of ovulation.

Results. In hyperprolactinemia, regardless of the cause, the key link is an increase in prolactin levels. The basal level of prolactin in the blood plasma of patients with functional hyperprolactinemia varied widely – from 37.6 ng/ml to 100.5 ng/ml. The average value was 63.6±3.49 ng/ml. The average prolactin level in women in the control group was 20.8±1.29 ng/ml (p<0.001).

In order to reduce the level of prolactin, all patients were prescribed the drug Dostinex. Taking into account the individual initial level of prolactin, the average therapeutic dose of the drug was determined, which was 0.35±0.1 mg per week. To obtain a clinical effect, 26 (52.0%) patients had enough 0.25 mg, and 24 (48.0%) - 0.5 mg of the drug per week. In patients treated with Dostinex, changes in the dynamics of treatment related to the following laboratory parameters. The PRL level decreased 2.3 times (28.2±0.76 ng/ml vs 63.6±3.49 ng/ml before treatment; p<0.001). The study of the effectiveness of therapy with Dostinex after 1 month of therapy showed that the level of prolactin in the observed patients was within the laboratory norms in 43 (86.0%) patients. In 7 (14.0%) patients whose prolactin values did not reach laboratory standards after one month, it returned to normal after 3 months.

Conclusion. Drug therapy of hyperprolactinemia with Dostinex allows to achieve a normal level of prolactin, normalize menstrual function, and eliminate galactorrhea in all observed patients.

Key words: infertility, prolactin, hyperprolactinemia, treatment, Dostinex.

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CLINICAL AND DIAGNOSTIC ASPECTS OF GENITAL ENDOMETRIOSIS IN WOMEN OF REPRODUCTIVE AGE

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The connection of the publication with planned research works. This work is a fragment of the dissertation for the degree of Doctor of Philosophy in medicine "Clinical and diagnostic aspects of optimal diagnosis of genital endometriosis in women of reproductive age»

Introduction. In recent years, special attention has been paid to the problem of women's reproductive health. The issues related to the study of genital endometriosis (GE) in women of reproductive age are of particular relevance and practical significance from the point of view of the modern view of this problem [1, 2, 3]. It is known that the frequency of genital endometriosis varies from 12 to 60% according to various literature sources. Endometriosis occupies the third place in the structure of gynecological diseases [4]. The relevance of the study of pathology is associated not only with the high frequency of occurrence [5].

Despite numerous studies devoted to various aspects of endometriosis, many questions related to both the features of the clinical picture, depending on the localization of the process, and the issues of modern and informative diagnosis and treatment, which is of fundamental practical importance, remain open. These issues are caused by a number of factors: 1) long-term, chronic and recurrent course of GE, leading to the suppression of the reproductive function of women; 2) the tendency to a steady and progressive growth of endometrioid heteropathies with a subsequent rapid spread in the body, the development of serious complications from other organs and systems, eventually leading to organ loss in the reproductive system; 3) a decrease in working capacity, a change in the psychoemotional sphere and a deterioration in the quality of life of a woman [6, 7].

Currently, laparoscopy is recognized as the most informative and indispensable method of diagnosing GE [8]. The effectiveness of this method is not only in the diagnosis of genital endometriosis, but also infertility of uncertain origin, etc. At the same time, the use of laparoscopy for therapeutic purposes in infertility is also relevant. Undoubtedly, the significance of the use of laparoscopy is not in doubt, since diagnostic findings of pathology on the part of the pelvic organs in the form of external GE or adhesive process in the pelvis, obstruction of the fallopian tubes, etc., allows it to be used as a method for expert analysis in the most difficult diagnostic situations.

Thus, genital endometriosis is the leading medical and social problem of modern gynecology and indicates the feasibility of conducting a comprehensive clinical and instrumental study of women of reproductive age with this pathology.