

© 2024 by the author(s).

This work is licensed under Creative Commons Attribution 4.0 International License
<https://creativecommons.org/licenses/by/4.0/>



How to cite / Як цитувати статтю: Kopytsia T, Sukhostavets N, Sukharev A. Effectiveness of complex therapy of hyperprolactinemia in women of the Sumy region, associated with stress against the background of armed aggression. *East Ukr Med J.* 2024;12(3):533-539

DOI: [https://doi.org/10.21272/eumj.2024;12\(3\):533-539](https://doi.org/10.21272/eumj.2024;12(3):533-539)

ABSTRACT

Tetiana Kopytsia

<https://orcid.org/0000-0001-8208-0902>

Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine

Natalia Sukhostavets

<https://orcid.org/0000-0002-2132-5037>

Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine

Anatoly Sukharev

<https://orcid.org/0009-0003-6993-6296>

Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine

EFFECTIVENESS OF COMPLEX THERAPY OF HYPERPROLACTINEMIA IN WOMEN OF THE SUMY REGION, ASSOCIATED WITH STRESS AGAINST THE BACKGROUND OF ARMED AGGRESSION

Introduction. Ukrainians have been living under martial law for the last two years. As a result of a constant stress, physical and especially mental health is affected. Chronic stress can cause functional hyperprolactinemia, which is characterized by an increase of the level of prolactin in the blood. Elevated serum prolactin is a level that is > 25 ng/ml or 530 mIU/L, which affects the functioning of various levels of the reproductive system.

The purpose of the study: to study the effectiveness of complex therapy of hyperprolactinemia in women of the Sumy region, which is associated with chronic stress against the background of armed aggression.

Materials and methods. The study was conducted at the Municipal Non-Profit Enterprise "Clinical Maternity Hospital of the Blessed Virgin Mary" and the Municipal Non-Profit Enterprise "Central City Clinical Hospital". A comprehensive clinical and laboratory examination was carried out of 81 women of the Sumy region who had reproductive plans, aged from 22 to 39 years old, who were divided into the following clinical groups: I (main) group, which included 31 women – was prescribed anti-stress therapy, drugs with Vitex agnus castus and cognitive behavioral therapy with a psychotherapist. II (comparison) group – 28 women who received anti-stress therapy and drugs with Vitex agnus castus and III (control) group – healthy women ($n = 22$). Exclusion criteria were the age of the patients less than 22 and more than 39 years, pituitary tumor confirmed (using magnetic resonance imaging) at the time of the study, taking medications that could affect the results of the studied hormones.

Research results. The analysis of the obtained prolactin level data indicated that in the majority of women from the study groups, the prolactin level was elevated within the range of 24–35 ng/ml. Before treatment, the average concentration of prolactin in patients of group I was 36.74 ± 2.72 ng/ml ($p < 0,05$), after 3 months, a decrease in concentration was noted to 20.54 ± 1.74 ng/ml ($p < 0,05$). In the comparison group, the average concentration of prolactin before treatment was 31.64 ± 2.48 ng/ml ($p < 0,05$), while after 3 months, it equaled 27.04 ± 2.02 ng/ml ($p < 0,05$). Also, in patients of the I group, the level of estradiol, progesterone and a thickness of the endometrium were increased.

Conclusion. The scheme of a differentiated approach to the treatment of Sumy region women with hyperprolactinemia against the background of stress, which we have outlined, contributes to the normalization of prolactin, estrogen, progesterone levels, and the growth of the functional endometrial layer.

Keywords: anti-stress therapy, cognitive -behavioral therapy, drugs with Vitex Agnus Castus, estradiol, functional hyperprolactinemia, progesteron, prolactin, stress.

Corresponding author: Kopytsia Tetiana, Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine
e-mail: t.kopica@med.sumdu.edu.ua

РЕЗЮМЕ

Тетяна Копиця

<https://orcid.org/0000-0001-8208-0902>

Кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна

Наталія Сухоставець

<https://orcid.org/0000-0002-2132-5037>

Кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна

Анатолій Сухарев

<https://orcid.org/0009-0003-6993-6296>

Кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна

ЕФЕКТИВНІСТЬ КОМПЛЕКСНОЇ ТЕРАПІЇ ГІПЕРПРОЛАКТИНЕМІЇ У ЖІНОК СУМСЬКОГО РЕГІОНУ, ЩО ПОВ'ЯЗАНА ЗІ СТРЕСОМ НА ТЛІ ЗБРОЙНОЇ АГРЕСІЇ

Вступ. Останні два роки українці живуть в умовах воєнного стану. Унаслідок постійного стресу відбувається враження фізичного та особливо психічного здоров'я. Хронічний стрес може викликати функціональну гіперпролактинемію, що характеризується підвищенням рівня пролактину у крові. Підвищений рівень пролактину в сироватці крові – це рівень, що становить > 25 нг/мл або 530 мМЕ/л та негативно позначається на функціонуванні різних рівнів репродуктивної системи.

Мета дослідження: вивчити ефективність комплексної терапії гіперпролактинемії у жінок Сумського регіону, що пов'язана з хронічним стресом на тлі збройної агресії.

Матеріали та методи. Дослідження проводилось на базі КНП «Клінічний пологовий будинок Пресвятої Діви Марії» СМР та КНП «Центральна міська клінічна лікарня» СМР. Комплексне клініко-лабораторне обстеження було проведене у 81 жінки Сумського регіону, які мали репродуктивні плани, віком від 22 до 39 років, яких було розподілено на наступні клінічні групи: I (основна) група, яка включала 31 жінок – їм було призначено антистресорну терапію, препарати прутняка та когнітивно-поведінкову терапію у психотерапевта, II (порівняння) група – 28 жінок, які отримували антистресорну терапію та препарати прутняка та III (контрольна) група – здорові жінки ($n = 22$). Критеріями виключення з дослідження були вік пацієнтів менше 22 і більше 39 років, наявність пухлини гіпофіза, підтвердженої (за допомогою магнітно-резонансної томографії) на момент дослідження, прийом ліків, які могли б вплинути на результати досліджуваних гормонів.

Результати дослідження. Аналіз отриманих даних рівнів пролактину вказував, що у переважної більшості жінок з груп дослідження рівень пролактину був підвищений в межах 24–35 нг/мл. До лікування середня концентрація пролактину у пацієток I групи складало $36,74 \pm 2,72$ нг/мл ($p < 0,05$), через 3 місяці відмічено зменшення концентрації до $20,54 \pm 1,74$ нг/мл ($p < 0,05$). У групі порівняння середня концентрація пролактину до лікування склала $31,64 \pm 2,48$ нг/мл ($p < 0,05$), через 3 місяці – $27,04 \pm 2,02$ нг/мл ($p < 0,05$). Також у пацієток I групи відмічалось стійке підвищення рівня естрадіолу та прогестерону та достовірне збільшення товщини ендометрію.

Висновок. Викладена нами схема диференційованого підходу до лікування жінок з гіперпролактинемією на тлі хронічного стресу, сприяє нормалізації рівнів пролактину, естрогену, прогестерону, зростанню функціонального шару ендометрію.

Ключові слова: антистресорна терапія, когнітивно-поведінкова терапія, препарати прутняка, естрадіол, функціональна гіперпролактинемія, прогестерон, пролактин, стрес.

Автор, відповідальний за листування: *Копиця Тетяна Володимирівна, кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна*
e-mail: t.kopica@med.sumdu.edu.ua

Скорочення:

E2 – estradiol,
FSH – follicle-stimulating hormone,
LH – luteinizing hormone,
PRG – progesterone,
PRL – prolactin,
VAC – Vitex agnus castus

INTRODUCTION / ВСТУП

For the last two years, Ukrainians have been living under martial law: "airborne" alarms, "alarming" backpacks, shelters, explosions, evacuations, a state of constant expectation of bombings. As a result of disturbed sleep, insufficient rest, fatigue and exhaustion, a constant state of stress, physical and especially mental health is affected [1, 2]. As you know, stress is a non-specific protective reaction of the body in response to stimulus [3]. It should be noted that women are significantly more vulnerable to stress disorders than the men. Studies indicate that the frequency of such disorders among the female population exceeds the indicators among men three times. As a result of pathological stimulation of the hypothalamic-pituitary-adrenal system, an increased level of cortisol is secreted, which, in turn, contributes to the disruption of the reproductive system of the female body. There are changes in the functions of the ovaries, hypothalamus, and pituitary gland [4,5,6]. Stress can cause functional hyperprolactinemia, which is characterized by an increase in the level of prolactin (PRL) in the blood [6, 7].

PRL is a pituitary hormone that is secreted by the lactotrophic cells of the anterior part of the pituitary

gland in a pulsating mode during the day: during sleep, the secretion increases, during the day it decreases, reaching a maximum before lunch [8]. The maximum level of PRL in women is noted between 1 and 5 in the morning. PRL affects the reproductive system, ensuring reproduction and lactation, water-electrolyte exchange, has an anabolic effect on morphogenesis and growth, a metabolic effect on metabolism, a psychogenic effect on behavioral reactions, as well as an immune effect, affecting immunoregulation [9].

One of the main properties of PRL is the ability to influence the development of mammary glands and lactation. Together with ovarian estrogens, it contributes to the growth of mammary glands, stimulates the production of milk in them, enhances the synthesis of milk proteins. PRL is also a luteotropic hormone, as it supports the function of the corpus luteum and its production of progesterone (PRG) [10].

Increased level of PRL is a level that is $> 25\text{ng/ml}$ or 530 mIU/L and negatively affects the functioning of various levels of the reproductive system. In the hypothalamus, under the influence of its increased level, the synthesis and release of globulin, which binds sex hormones, decreases, and the sensitivity of the

hypothalamus to estrogens decreases. Excessive levels of PRL reduce the sensitivity of the ovaries to gonadotropins, reduce the secretion of PRG by the corpus luteum of the ovaries, which can be cause of it's early disintegration, causing disorders of the menstrual cycle, contribute to the pathological proliferation of the mammary gland [10, 11].

The duration of stress is an important factor for understanding the mechanisms of pathological effects of hormones. Thus, with acute stress, the level of testosterone in the circulating blood increases, and with chronic stress, it decreases. And this process does not depend on the level of luteinizing hormone (LH), but is associated with blockade of receptors on the Leydig cells of the ovarian medulla. These pathological changes occur under the stimulating influence of adrenocorticotrophic hormone on hypothalamic neurons, which promote increased secretion of the corresponding hypothalamic releasing factors, and the latter, in turn, affect pituitary gonadotropins, in particular LH. In this regard, a paradoxical effect arises: against the background of an increase in the blood level of LH, there is a further significant decrease in the level of testosterone and, secondarily, estradiol (E2), a decrease in which is the main cause of reproductive disorders [12, 13].

Stress-induction of cortisol and oxidative stress lead to apoptosis of granulosa cells, which, in turn, leads to a decrease in estradiol levels and induction of apoptosis of oocytes [14].

The purpose of the study: to study the effectiveness of complex therapy of hyperprolactinemia of women of Sumy region, which is associated with chronic stress against the background of armed aggression.

Materials and methods. The study was conducted on the basis of the CNP "Clinical Maternity Hospital of the Blessed Virgin Mary" of the and the CNP "Central City Clinical Hospital" during 2022-2023. A comprehensive clinical and laboratory examination was conducted in 81 women who had reproductive plans, aged from 22 to 39 years old, who were divided into the following clinical groups:

- I (main) group - women with hyperprolactinemia against the background of stress associated with armed aggression using our proposed differentiated approach, which included anti-stress therapy, drugs with Vitex agnus castus (VAC) in dose 20 mg for a day and cognitive -behavioral therapy with a psychotherapist (n = 31);

- II (comparison) group – women with hyperprolactinemia on the background of armed aggression, whose management was anti-stress therapy and drugs with VAC, used the same dose 20 mg (n = 28);

- III (control) group – healthy women (n = 22).

When selecting patients for the study group, the inclusion criteria were: women with infertility on the background of hyperprolactinemia (PRL level in blood serum > 25ng/ml or 530 mIU/l); absence of any treatment of patients 3 months before the examination; compensated state of accompanying pathology of women; availability of informed consent of patients for comprehensive examination and treatment.

When selecting patients for the control group, the inclusion criteria were: women aged 22 to 39 without hyperprolactinemia and menstrual disorders.

The examination included the collection of anamnesis, an objective examination –general and special, and additional methods. A thorough study of the main and accompanying complaints, anamnesis collection, analysis of outpatient charts was carried out. Menstrual function was evaluated according to menograms, the condition of a woman before and during menstruation (nausea, pain, changes in general condition), the nature and severity of menstrual function disorders, the age of their occurrence and possible causes that can provoked them, the results of psychological tests, the available treatment mandatory assessment of efficiency. The gynecological examination included an examination of the external and internal genitalia, the color and degree of moisture of the mucous membrane, the presence or absence of inflammatory processes. A bimanual vaginal and rectal examination was conducted. Laboratory diagnostics were carried out in accordance with the existing standards of medical care, the following were evaluated: general blood analysis, biochemical analysis and hormonal examination – determination of the content of follicle-stimulating hormone (FSH), LH, PRL, E2 (2-7 th days of menstrual cycle), PRG was checked at 20-22 th days of menstrual cycle. Psychometric, clinical, laboratory, instrumental methods of research, as well as studies of hormonal homeostasis were carried out before treatment, 1, 3 and 6 months after the start of treatment. PRL was determined by enzyme immunoassay in serum blood, women donated venous blood on an empty stomach after 2 hours from moment of awakening, at 2-7 th day of menstrual cycle.

Ultrasound was performed on the 7–9th day of the menstrual cycle in the dynamometer before treatment, 3 and 6 months after the start of therapy. For this, a Mylab Seven ultrasound machine was used. All patients with hyperprolactinemia at the beginning of the study, who were under observation, excluded the tumor nature of hyperprolactinemia with the help of brain magnetic resonance imaging. To study the psycho-emotional sphere, and the impact of stressors on them, an

assessment of anxiety indicators was carried out in the examined women. Used the Spielberger-Hanin anxiety scale questionnaire before the start of treatment and 1, 3 and 6 months after the start of treatment. The results were interpreted as follows: up to 30 points – low anxiety; 31–45 points – moderate; 46 or more points – high anxiety.

Research results and discussion. Group I patients were prescribed the complex differentiated treatment offered by us, which included anti-stress therapy (femibut + mebikar), drugs with VAC and cognitive-behavioral therapy by a psychotherapist.

Patients of the II group were prescribed anti-stress therapy (femibut + mebikar) and drugs with VAC.

Statistical processing and analysis of the obtained data was performed using «Microsoft Excel» programs using the methods of mathematical statistics and the software package Statistica 8.0.

The analysis of the obtained PRL level data indicated that in the vast majority of women from the research groups, the PRL level was elevated within the range of 24-35 ng/ml, which confirmed the stress-induced genesis of prolactinemia against the background of armed aggression.

Before treatment, the average concentration of PRL in patients of group I was $36,74 \pm 2,72$ ng/ml ($p < 0,05$), after 3 months a decrease in concentration was noted to $20,54 \pm 1,74$ ng/ml ($p < 0,05$), and after 6 months – up to $10,74 \pm 0,89$ ng/ml ($p < 0,05$). In the comparison group, the average concentration of PRL before treatment was $31,64 \pm 2,48$ ng/ml ($p < 0,05$), after 3 months – $27,04 \pm 2,02$ ng/ml ($p < 0,05$), and after 6 months – up to $23,47 \pm 1,64$ ng/ml ($p < 0,05$).

Therefore, no patient from the main group had a decrease in PRL below 10 ng/ml. A decrease of the level of PRL was accompanied by an increase in the level of E2 and PRG, their levels 6 months after the start of treatment did not differ from those of healthy women. In the comparison group, PRL levels decreased, however, after 3 and 6 months, they remained at the upper limit of normal. E2 and PRG levels were significantly lower than in healthy women.

The level of E2 before treatment in patients of the first group was $56,87 \pm 1,34$ ng/ml ($p < 0,05$), after 3

months it was $93,28 \pm 3,52$ ng/ml ($p < 0,05$), and after 6 months – $120,94 \pm 8,44$ ng/ml ($p < 0,05$). In patients of the II comparison group, E2 before treatment was $57,12 \pm 1,28$ ng/ml ($p < 0,05$), after 3 months it was $85,42 \pm 3,17$ ng/ml ($p < 0,05$), and after 6 months – $90,23 \pm 7,44$ ng/ml ($p < 0,05$).

The level of PRG in patients of the first group was before treatment – $7,45 \pm 0,49$ ng/ml ($p < 0,05$), after 3 months – $12,45 \pm 0,89$ ng/ml ($p < 0,05$), after 6 months – $19,31 \pm 1,52$ ng/ml ($p < 0,05$). In the II comparison group, the level of PRG – before treatment – $9,15 \pm 0,49$ ng/ml ($p < 0,05$), after 3 months – $11,45 \pm 0,79$ ng/ml ($p < 0,05$), after 6 months – $10,59 \pm 1,36$ ng/ml ($p < 0,05$).

When analyzing sonographic studies of the increase in the thickness of the endometrium in the first group of patients before treatment, the thickness was $4,54 \pm 0,56$ mm ($p < 0,05$), after 3 months – $8,15 \pm 0,27$ mm ($p < 0,05$), after 6 months – $9,15 \pm 0,7$ mm ($p < 0,05$). In the II group – before treatment, the thickness of the endometrium was $4,20 \pm 0,28$ mm ($p < 0,05$), after 3 months – $6,68 \pm 0,29$ mm ($p < 0,05$), after 6 months – $6,89 \pm 0,49$ mm ($p < 0,05$).

A significant increase in the thickness of the endometrium was observed in the patients of group I, after 6 months its thickness did not differ from that of healthy women.

When testing behavior using the Spielberger-Hanin anxiety scale questionnaire, in a 1 month after the start of treatment, 8 (25%) women in group I were in a state of high anxiety, after 3 months – 8 (30%), after 6 months – 10 (35%) women. Before treatment, 22 (70%) women of the main group were in a state of high anxiety.

In the II group, the specific weight of patients with a high level of anxiety after 1 month also decreased and amounted to 11 (40%), after 3 months – 30% ($n=8$), after 6 months – 35% ($n=10$). Before treatment – 65% ($n=18$) women of the comparison group were in a state of high anxiety. Therefore, 6 months after the start of treatment, the achieved levels of anxiety reduction in the I group were maintained, and an increase in anxiety levels was observed in the II group.

levels of PRL, E2, PRG, and the growth of the functional layer of the endometrium.

Thus, it can be concluded that patients with hyperprolactinemia against the background of the chronic stress can be offered the treatment scheme that we have developed.

CONCLUSIONS / ВИСНОВКИ

The scheme of a differentiated approach to the treatment of women with hyperprolactinemia of Sumy region against the background of stress associated with armed aggression, which included anti-stress therapy, drugs with VAC and cognitive-behavioral therapy by a psychotherapist, contributes to the normalization of the

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

In the future, it is possible to include cognitive-behavioral therapy by a psychotherapist in the complex treatment of hyperprolactinemia against the background of chronic stress which can increase the effectiveness of therapy in the corresponding patients.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

REFERENCES/СПИСОК ЛІТЕРАТУРИ

- Rooney KL, Domar. The relationship between stress and infertility. *Dialogues Clin Neurosci*. 2018;20:41–47. <https://doi.org/10.31887/DCNS.2018.20.1/krooney>
- Haimovici F, Anderson JL, Bates GW, Racowsky C, Ginsburg ES, Simovici D, Fichorova RN. Stress, anxiety, and depression of both partners in infertile couples are associated with cytokine levels and adverse IVF outcome. *J Reprod Immunol*. 2018;79:116–122. <https://doi.org/10.1111/aji.12832>
- Dong Y, Cai Y, Zhang Y, Xing Y, Sun Y. The effect of fertility stress on endometrial and subendometrial blood flow among infertile women. *Reprod. Biol. Endocrinol*. 2017;15:15–19.
- Tatarchuk TF, Kosei NV, Reheda SI, Jarotska NV, Gorokhova CO. The role of hyperprolactinemia in the genesis of stress-induced infertility and the possibility of its correction. *Health of woman*. 2017;6(122):31–39.
- Sanders R. Blocking hormone could eliminate stress-induced infertility. *J.Berkeley news online*. 2015:201–211. <https://doi.org/10.15574/HW>
- Geraghty AC, Muroy EC, Zhao SH. Knockdown of hypothalamic RFRP3 prevents chronic stress-induced infertility and embryo resorption. *University of California, Berkeley, United States. Canadian Institute for Advanced Research, Canada*. 2015;4:59–64. <https://doi.org/10.7554/eLife.04316>
- Piekarski DJ, Zhao S, Jennings K.J. Gonadotropin-inhibitory hormone reduces sexual motivation but not lordosis behavior in female Syrian hamsters (*Mesocricetus auratus*). *Hormones and Behavior*. 2015;64: 501–10. <https://doi.org/10.1016/j.yhbeh.2015.06.006>
- Louis GM, Lum KJ, Sundaram R. Stress reduces conception probabilities across the fertile window: evidence in support of relaxation. *J.Fertil Steril*. 2017;95:2184–9. <https://doi.org/10.1016/j.fertnstert.2010.06.078>
- Tatarchuk TF, Kosei NV, Reheda SI, Jarotska NV, Gorokhova C.O. Stress infertility. *REPRODUCTIVE ENDOCRINOLOGY*. 2016;31:12–21. <https://doi.org/10.18370/2309-4117.2016.31.12-21>
- Lee DY, Oh YK, Yoon BK. Prevalence of hyperprolactinemia in adolescents and young women with menstruation-related problems. *J. Obstet. Gynecol*. 2019; 206:213–223. <https://doi.org/10.1016/j.ajog.2011.12.010>
- Besnard I, Auclair V, Callery G, Gabriel-Bordenave C, Roberge C. Hyperprolactinémies induites par les antipsychotiques: physiopathologie, clinique et surveillance. *L'Encéphale*. 2014; 40(1):86–94. <https://doi.org/10.1016/j.encep.2012.03.002>
- Shatcovska AS, Grygorenko AP, Gorbatyk OG, Mincovska AM. [Stress-induced disorders of the hypothalamic-pituitary and peripheral endocrine system in a woman's body]. *Medical aspects of women's health*. 2021; 4(139):23–27
- Eagan SH. Menstrual suppression for military women. Barriers to care in the United States. *Obstet. Gynecol*. 2019; 134(1):726. <https://doi.org/10.1097/AOG.0000000000003318>
- Levkina OL, Masibroda NG, Muntyan OA, Voznyc AV. [The influence of today's chronic stress on women's menstrual function]. *Bulletin of the Vinnytsia National Medical University*. 2023; 27(2):331–335

Received 20.01.2024

Accepted 22.05.2024

Одержано 20.01.2024

Затверджено до друку 22.05.2024

INFORMATION ABOUT THE AUTHORS / ВІДОМОСТІ ПРО АВТОРІВ

Копиця Тетяна Володимирівна, к.м.н., асистент кафедри акушерства гінекології та планування сім'ї, тел. +380(50)160-18-67 t.kopica@med.sumdu.edu.ua
<https://orcid.org/0000-0001-8208-0902>

Сухоставець Наталія Перівна, к.м.н., асистент кафедри акушерства гінекології та планування сім'ї, n.sukhostavets@med.sumdu.edu.ua
<https://orcid.org/0000-0002-2132-5037>

Сухарев Анатолій Борисович, к.м.н., доцент кафедри акушерства гінекології та планування сім'ї, тел. +380(95)119-74-75 zalivna7308@gmail.com
<https://orcid.org/0009-0003-6993-6296>