

Features of women's reproductive dysfunctions associated with prolonged stressful situations

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The number of appeals of migrant women and servicewomen for specialized gynecological care has increased during the years of the armed conflict in Eastern Ukraine.

The aim of the work was a comprehensive study of the hormonal function of pituitary gland, ovaries, thyroid gland and adrenal glands in women of reproductive age with various types of menstrual cycle disorders caused by a prolonged stressful situation.

Materials and methods. With the help of immune-enzyme analysis the authors have conducted a study of pituitary hormones (FSH, LH, prolactin), ovarian hormones (estradiol, progesterone, free T), thyroid hormones (TSH, FT₄) and thyroid peroxidase antibodies, as well as adrenal glands hormones (ACTH, cortisol (urine), DHEA-s) of 74 migrant women and servicewomen with menstrual disorders caused by a stressful situation. According to complaints, women were divided into 2 subgroups: with amenorrhea 34 (45.9 %) and abnormal uterine bleeding – 40 (54.1 %).

Results. Women with stressed amenorrhea had a significant 2 times ($P < 0.05$) increase in FSH; 1.9 times – LH; 1.6 times – prolactin (which is not typical for classical hyperprolactinemia) and 3.2 times decrease in estradiol, 3.9 times – progesterone in comparison to the control group. Dysfunction of the thyroid gland was recorded, in particular 2 times decrease in FT₄ and 1.7 times increase in thyroperoxidase antibodies relative to the control. A significant 1.6 times increase in ACTH, 1.8 times increase in cortisol (urine) and 1.6 times increase in DHEA-s were detected compared with the control. Women with abnormal uterine bleeding had a significant 1.5 times ($P < 0.05$) increase in prolactin, 1.3 times increase in estradiol, and a 2.5 times decrease in progesterone compared to the control women group. 90.5 % of women of reproductive age with menstrual cycle disorders caused by the influence of prolonged stress factor had hormonal disorders of the ovaries, adrenal glands and thyroid gland.

Conclusions. In women with stress-related amenorrhea there is a violation of the relationship in the hypothalamic – pituitary system while maintaining the negative feedback loops of the pituitary-ovarian axis or ovarian depletion; post-traumatic stress disorders have a significant pathological effect on the reproductive system of women who have experienced such suffering.

Ключові слова:

стрес, менструації
порушення,
менструальний
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Особливості порушень репродуктивного здоров'я жінок, що пов'язані з тривалими стресовими ситуаціями

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За роки збройного конфлікту на сході України збільшилась кількість звернень жінок-переселенок і жінок-військовослужбовців за спеціалізованою гінекологічною допомогою.

Мета роботи – комплексне дослідження гормонопродукувальної функції гіпофіза, яєчників, щитоподібної залози та надниркових залоз у жінок репродуктивного віку при різних видах порушень менструального циклу, що спричинені тривалою стресовою ситуацією.

Матеріали та методи. За допомогою імуноферментного аналізу здійснили дослідження гіпофізарних гормонів (ФСГ, ЛГ, пролактину), яєчникових гормонів (естрадіолу, прогестерону, вільного тестостерону), а також гормонів щитоподібної залози (ТТГ, Т₄ вільного) та антитіл до тиреопероксидази, гормонів надниркових залоз (АКТГ, кортизолу (сечі), ДГЕА-с) у 74 жінок-переселенок і жінок-військовослужбовців із порушеннями менструального циклу, що спричинені стресовою ситуацією. На підставі скарг жінок поділили на 2 підгрупи: з аменореєю – 34 (45,9 %), з аномальними матковими кровотечами – 40 (54,1 %).

Результати. У результаті дослідження в жінок з аменореєю виявили вірогідне ($p < 0,05$) збільшення ФСГ удвічі, ЛГ в 1,9 раза, пролактину в 1,6 раза (не властиве класичній гіперпролактинемії), а також зниження естрадіолу у 3,2 раза, прогестерону у 3,9 раза щодо контрольної групи. Зафіксували відхилення в роботі щитоподібної залози: зниження Т₄ вільн., удвічі та підвищення АТГО в 1,7 раза щодо контролю. Виявили вірогідне ($p < 0,05$) підвищення АКТГ у 1,6 раза, кортизолу (сечі) – в 1,8 раза та ДГЕА-с – в 1,6 раза порівняно з контролем. У жінок з аномальними матковими кровотечами відбувалось вірогідне ($p < 0,05$) підвищення пролактину в 1,5 раза, естрадіолу в 1,3 раза та зниження прогестерону у 2,5 раза порівняно з контрольною групою жінок. У 90,5 % жінок репродуктивного віку з порушеннями менструального циклу, що виникли під впливом тривалого стресового фактора, виявили гормональні порушення в роботі яєчників, надниркових залоз чи щитоподібної залози.

Висновки. У жінок зі стресогенною аменореєю виявили порушення взаємовідносин у системі гіпоталамус – гіпофіз при збереженні негативного зворотного зв'язку між яєчниками та гіпофізом або виснаження яєчників; посттравматичні стресові порушення мають значущий патологічний вплив на репродуктивну систему жінок, які їх перенесли.

Особенности нарушения репродуктивного здоровья женщин, связанные с длительными стрессовыми ситуациями

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За годы вооруженного конфликта на востоке Украины увеличилось количество обращений женщин-переселенок и женщин-военнослужащих за специализированной гинекологической помощью.

Цель работы – комплексное исследование гормонопродуцирующей функции гипофиза, яичников, щитовидной и надпочечниковых желез у женщин репродуктивного возраста с разными видами нарушений менструального цикла, которые возникли под влиянием длительного стрессового фактора.

Материалы и методы. С помощью иммуноферментного анализа проведено исследование гипофизарных гормонов (ФСГ, ЛГ, пролактина), яичниковых гормонов (эстрадиола, прогестерона, свободного тестостерона), а также гормонов щитовидной железы (ТТГ, свободного T_4) и антител к тиреопероксидазе, гормонов надпочечниковых желез (АКТГ, кортизола (мочи), ДГЭА-с) у 74 женщин-переселенок и женщин-военнослужащих с нарушениями менструального цикла, которые произошли на фоне стрессовой ситуации. На основании жалоб женщин разделили на 2 подгруппы: с аменореей – 34 (45,9 %), с аномальными маточными кровотечениями – 40 (54,1 %).

Результаты. В результате исследования у женщин с аменореей установлено достоверное ($p < 0,05$) увеличение ФСГ в 2 раза, ЛГ в 1,9 раза, пролактина в 1,6 раза (что не характерно для классической гиперпролактинемии), а также снижение эстрадиола в 3,2 раза и прогестерона в 3,9 раза относительно контрольной группы. Зафиксировано отклонение в работе щитовидной железы, а именно снижение $T_{4\text{своб}}$ в 2,0 раза и увеличение АТПО в 1,7 раза по отношению к контролю. Установлено достоверное увеличение АКТГ в 1,6 раза, кортизола (мочи) в 1,8 раза, ДГЭА-с в 1,6 раза в сравнении с контролем. У женщин с аномальными маточными кровотечениями отмечено достоверное ($p < 0,05$) повышение пролактина в 1,5 раза, эстрадиола в 1,3 раза, снижение прогестерона в 2,5 раза по сравнению с контрольной группой женщин. У 90,5 % пациенток репродуктивного возраста с нарушениями менструального цикла, которые возникли под влиянием длительного стрессового фактора, диагностированы гормональные нарушения в работе яичников, щитовидной и надпочечниковых желез.

Выводы. У женщин со стрессогенной аменореей имеет место нарушение взаимоотношений в системе гипоталамус – гипофиз при сохранении негативной обратной связи между яичниками и гипофизом либо же истощение яичников; посттравматические стрессовые нарушения имеют значительное патологическое влияние на репродуктивную систему женщин, которые их перенесли.

Ключевые слова:

стресс, менструации нарушения, менструальный цикл.

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The number of local military conflicts which are mostly harmful for women and children is increasing each year in the world. A local armed conflict continues from 2014 to the present time in the East of Ukraine, which has caused an increase in the number of migrant women and service-women seeking specialized gynecological care.

Post-traumatic stress dysfunctions of military and civilian population that arise as a result of warfare (in different countries) have been studied mainly by neurologists and psychiatrists. The results of these studies indicate the long-term and serious medical and social consequences for the population. According to the scientific literature, 42–50 % of the female population after extreme stresses has psycho-emotional and neurological disorders [1,2]. The peculiarity of stress and strong emotional experiences is that through the central nervous system, which is the highest coordination center in the system “cortex – hypothalamus – hypophysis – ovaries – uterus”, they affect the function of the ovaries and the reproductive system as a whole [1,2]. Nowadays, these processes are poorly understood and the scientific literature on this problem is very limited.

It is proved that endorphins are produced in the central nervous system during high stress or psycho-emotional strain; they reduce pain and facilitate the perception of negative situations [1,3,4]. This is so-called protective reaction of the organism. But the prolonged release of endorphins in the blood has its negative consequences. An increase in the level of endorphins causes a decrease in the synthesis of another neurotransmitter, dopamine, which increases the formation of corticotropin by the hypothalamus and ad-

renocorticotropin hormone (ACTH) by the hypophysis. The adrenal glands are intensively stimulated under the action of ACTH and the amount of cortisol is increased that can cause hypertension, steroid diabetes, obesity, immunodepressive state etc. Clinically, such patients may develop a hypothalamic syndrome with the appearance, first of all, of menstrual cycle disorders, since the hypothalamic-ovarian system is most sensitive to stress-related changes in the central nervous system. In addition, an elevated level of cortisol blocks follicle maturation, ovulation in the ovaries, which is the cause of anovulatory cycles, amenorrhea, infertility [4–6].

As a result of the increase in endorphins and dopamine depletion, prolactin (PRL) secretion, which is also a stress hormone, is exacerbated. The high concentration of PRL inhibits secretion of gonadotropic hormones of the hypophysis and, as a result, there is a decrease in the synthesis of estrogens and progesterone in the ovaries, that is the cause of menstrual cycle disorders, early ovarian depletion, amenorrhea, infertility, dys hormonal breast diseases, tumors of uterine and ovaries [7–10].

In addition, during the interaction between ecological and genetic factors, inherited defects of the gonadotropin-releasing hormone biology can reduce the threshold at which external stressors suppress the hypothalamic-pituitary-ovarian axis [1,3].

Despite the achievements of modern science, the mechanisms of stress-dependent hormonal implementation at the level of target organs are not sufficiently studied [11,12]. There is no evidence of chronic stress effect on premature ovarian insufficiency [13,14].

Aim

The aim of the research was a comprehensive study of the hormonal function of pituitary gland, ovaries, thyroid gland and adrenal glands in women of reproductive age with various types of menstrual cycle disorders caused by a prolonged stressful situation.

Materials and methods

Over the past 3 years, 74 women with complaints of menstrual disorder (the main group), which manifested for the first time after resettlement (return) from the zone of armed conflict, have asked for medical help. Among 74 women, there were 63 migrant women (85.1 %) and 11 servicewomen (14.9 %). All patients were 18–37 years old. The average age of these women was 27.7 ± 8.7 years. The control group consisted of 23 women of reproductive age (19–36 years) who were in a state of psychological comfort and had no menstrual cycle violations. The average age of women in the control group was 27.2 ± 7.9 years.

Randomization of the main group patients to subgroups was conducted taking into account complaints about the absence of menstruation or the presence of vaginal bleeding.

The level of hormones in blood plasma was measured by means of ELISA test system sets (DRG International Inc., USA) by immunosorbent methods. We studied such hormones as luteinizing hormone (LH), follicle-stimulating hormone (FSH), PRL, estradiol, progesterone, free testosterone (free T), adrenocorticotrophic hormone (ACTH), sulfate dehydroepiandrosterone (DHEA-s). Free cortisol (24 urine) was measured by the same ELISA test system sets. Hormonal function of the thyroid gland was also studied: thyroid stimulating hormone (TSH), free thyroxine (FT₄). Thyroid peroxidase antibodies (TPO Ab) were detected by a sequential ELISA method.

In women with preserved menstrual cycle, hormonal examination was carried out at early follicular phase (2–4th day of a menstrual cycle). The levels of prolactin, ACTH, cortisol and thyroid hormones did not change during the menstrual cycle, but for the convenience of studied women, these hormones were assayed together with other hormones on day 2–4 of the menstrual cycle.

All women of the main group were subjected to an ultrasound examination of the uterus and ovaries by the Ultrasound scanner General Electric Voluson E8 Expert with an endovaginal transducer 3.0–9.5 MHz. Magnetic resonance imaging and other examinations and consultations were conducted for the main group women according to indications.

Statistical data were processed by means of Excel adapted for medical and biological research. Wilcoxon non-parametric criterion for the paired samples was used for quantitative data comparison before and after the treatment period. When a difference was found, paired comparisons between groups by means of Mann–Whitney test were used. Differences were recognized statistically significant at $P < 0.05$ [15].

Hormonal examination of the main group women and controls was carried out in Khmelnytskyi Municipal Perinatal Center and Khmelnytskyi Military Hospital between 1.09.2015 and 31.08.2018.

A written informed consent was signed by women who made up the main group and those who volunteered to participate in the study.

Results

The patients of the main group were randomized to 2 subgroups based on complaints: amenorrhea and abnormal uterine bleeding. Women from the first subgroup (34 people) complained about delay in menstruation from 3 to 6 months – 27 patients (79.4 %), absence of menstruation for 6 months and more – 7 patients (20.6 %). Patients from the second subgroup (40 people) were troubled by frequent menstruation (twice a month) – 14 (35.0 %) patients, duration of menstrual bleeding more than 7 days – 15 women (37.5 %), heavy menstrual bleeding accompanied by clots – 11 patients (27.5 %). Hormone measurements in women of the main group showed a significant imbalance in the main endocrine organs functioning.

A significant ($P < 0.05$) increase in the hypothalamic hormones (FSH – 2 times, LH – 1.9 times, prolactin – 1.6 times) was observed in women of the first subgroup compared to controls, and there was a decrease in the ovarian hormones (except for free T): estradiol – 3.2 times, progesterone – 3.9 times in relation to the control group (Table 1).

A significant 2 times decrease in FT₄ and 1.7 times increase in TPO Ab relative to the control indicated a violation of the thyroid gland function in the patients of this subgroup (Table 2).

A significant 1.6 times increase in ACTH, 1.8 times increase in cortisol (urine) and 1.6 increase in DHEA-s in patients of the first subgroup compared with the control indicated an adrenal dysfunction (Table 3).

The following pathological changes were detected among 34 patients of the first subgroup: the levels of FSH and LH in 18 (52.9 %) patients deviated above the norm. The PRL level in 14 (41.2 %) patients was above the reference value. 16 (47.1 %) patients had a high level of cortisol in daily urine, 13 (38.2 %) patients had an elevated level of ACTH, which is considered to be a stress hormone suppressing the gonadotropic function of the hypophysis and the ovarian function (indirectly). 8 women (23.5 %) had an increased DHEA-s. An increase in TSH and reduction in FT₄ beyond the reference values were observed in 7 patients (20.6 %), 2 (5.9 %) of them showed elevated level of ATPO and 1 patient (2.9 %) had a reduction of TSH and increased FT₄. In general, among this group of examined women, the hormonal abnormalities were found in 33 women (97.1 %).

Clinically, women of the first subgroup had the following changes: according to ultrasound, the average thickness of the endometrium in women from this group was 5.7 ± 0.8 mm, 1 (2.9 %) patient had an atrophic changes in the endometrium (2.2 mm thickness). A hyperplasia of adrenal tissues was detected in 4 patients (11.8 %) during the ultrasonography of the adrenal glands; they also had an elevated level of ACTH. Microadenoma (prolactinoma) of the pituitary gland was detected in 1 woman (2.9 %). Hypothyroidism (including subclinical form) was diagnosed for the first time in 7 patients (20.6 %), thyrotoxicosis – 1 (2.9 %), autoimmune thyroiditis – 2 (5.9 %).

Women with amenorrhea lasting more than 6 months, in addition to reproductive abnormalities, had vegetative-vascular and psycho-emotional disorders.

Table 1. Reproductive hormones (M ± m)

Hormone, measurement unit	Main group of women (n=74)		Control group (n = 23)	P ₁₋₃	P ₂₋₃
	subgroup 1 (n = 34)	subgroup 2 (n = 40)			
	1	2	3		
FSH, mIU/mL	11.9 ± 2.6	4.8 ± 1.5	5.9 ± 1.3	<0.05	>0.05
LH, mIU/mL	13.4 ± 3.1	7.3 ± 1.8	7.2 ± 1.7	<0.05	>0.05
PRL, ng/mL*	27.3 ± 4.2	24.9 ± 3.5	16.7 ± 3.1	<0.05	<0.05
Estradiol, pg/mL	22.0 ± 4.7	89.2 ± 7.9	70.4 ± 8.5	<0.05	<0.05
Progesterone, ng/mL	0.21 ± 0.1	0.33 ± 0.09	0.82 ± 0.08	<0.05	<0.05
Free T, pg/mL	5.58 ± 0.5	4.59 ± 0.3	4.78 ± 0.3	>0.05	>0.05

*: reference values according to the laboratory data 4.79–23.3 ng/mL.

Table 2. Indicators of the thyroid gland function (M ± m)

Hormone, measurement unit	Main group of women (n = 74)		Control group (n = 23)	P ₁₋₃	P ₂₋₃
	subgroup 1 (n = 34)	subgroup 2 (n = 40)			
	1	2	3		
TSH, mIU/L*	4.8 ± 0.7	4.3 ± 0.6	3.5 ± 0.7	>0.05	>0.05
FT ₄ , ng/dL**	0.7 ± 0.1	1.2 ± 0.2	1.4 ± 0.1	<0.05	>0.05
TPO Ab, IU/mL	38.4 ± 6.5	34.6 ± 5.8	22.2 ± 6.9	<0.05	>0.05

*: reference values according to the laboratory data 0.3–4.0 mIU/L; **: reference values according to the laboratory data 0.8–2.0 ng/dL.

Table 3. Hormones of the adrenal glands and ACTH (M ± m)

Hormone, measurement unit	Main group (n = 87)		Control group (n = 23)	P ₁₋₃	P ₂₋₃
	subgroup 1 (n=34)	subgroup 2 (n=40)			
	1	2	3		
ACTH, pg/mL*	47.6 ± 8.3	37.4 ± 7.1	29.3 ± 4.7	<0.05	>0.05
Free cortisol (24 urine), mkg/24 hour	177.0 ± 32.5	112.4 ± 27.1	97.6 ± 19.2	<0.05	>0.05
DHEA-S, ng/mL	9.9 ± 1.8	7.7 ± 1.4	6.1 ± 1.2	<0.05	>0.05

*: reference values according to the laboratory data 1.0–46.3 pg/mL.

We consider these changes as a consequence of the long-term stressful situation in which these women were.

Patients of the second subgroup of the examined women had a significant 1.5 times ($P < 0.05$) increase in prolactin, 1.3 times increase in estradiol and a 2.5 times reduction of progesterone (*Table 1*) compared with the controls. There were no significant ($P < 0.05$) changes detected in the thyroid gland and adrenal glands (*Table 2, 3*); although there was a clear tendency to increase in TSH, ACTH, free cortisol (24 urine) and FT₄ reduction.

After the examination of 40 women of the second subgroup, 33 of them (82.5 %) had estradiol at the control level, 7 patients (17.5 %) had increased estradiol level, progesterone levels in all patients were within the lower limit of normal values. FSH and LH levels were within reference values for all women in this subgroup, but the LH / FSH ratio was <1.5. The level of PRL was within the upper normal limit in 31 (77.5 %) women, an elevated PRL level – in 9 (22.5 %) women. 7 (17.5 %) patients of the second subgroup showed an increased level of ACTH and cortisol.

An increase in TSH and reduction of FT₄ from the reference values were observed in 3 patients (7.5 %), an increase in TPO Ab was found in 2 patients (5.0 %). Clinically, according to the ultrasound, hypertrophic changes of the endometrium (thickness of the endometrium – 20 ± 4.8 mm) in 19 patients (47.5 %), adenomyosis – in 4 patients (10 %), rapid growth of myoma – in 1 patient (2.5 %), myoma with the presence of submucous nodes – in 5 (12.5 %) patients of the second subgroup were detected.

A subclinical form of hypothyroidism (according to the levels of TSH and FT₄) was first diagnosed in 3 patients (7.5 %) and formation of autoimmune thyroiditis (the appearance of TPOAb without thyroid gland function disturbance) was diagnosed in 2 (5.0 %) patients. Anemia of 1 or 2 degree was detected in 19 patients (47.5 %). Pathological changes of hormones were found in 34 (85.0 %) out of 40 examined women.

Discussion

Consequently, there are complex biochemical processes associated with a negative influence of chronic stress on the central nervous system in a woman's body in a stressful state [2,3]. Mechanisms of menstrual disorders are realized through neurosecretory structures of the brain that regulate tonic and cyclic secretion of gonadotropins. Clinically, these violations are manifested in anovulatory cycles, hyperplastic processes of the endometrium, abnormal uterine bleeding, amenorrhea, endocrine forms of infertility and others [1,8].

Our research shows that a menstrual dysfunction associated with stress-induced hyperprolactinemia occurred in 31.1 % of patients. However, classical hyperprolactinemia is characterized by a decrease in FSH and LH levels and, accordingly, a decrease in estradiol and progesterone [5,7]. In our study, in presence of hyperprolactinemia (subgroup 1), an increase in FSH and LH levels with low peripheral hormones is observed (*Table 1*), which may indicate a disturbance in the hypothalamic-pituitary gland relationship while maintaining

the negative feedback loops of the pituitary-ovarian axis or depletion of the ovaries. Such changes may indicate the depth of the impact of chronic stress on the woman's body and the severe degree of the reproductive system dysfunction.

ACTH and cortisol are also stress hormones which suppress gonadotropins of the pituitary gland and folliculogenesis in the ovaries. Among the examined groups of women, 27.0 % of patients had high ACTH values and 31.1 % – cortisol.

In addition, the 1.7 times increase in TPO Ab in women with stress-induced amenorrhea relative to the control indicates an impairment of immunological tolerance, which in combination with hormonal dysfunction, in fact, can rule out the menstrual cycle at all.

Hormonal disorders were more presented in the group of women with stress-induced amenorrhea than in women with abnormal uterine bleeding. Significant changes were detected according to 10 indicators in the subgroup of women with amenorrhea and in the subgroup of women with abnormal uterine bleeding – according to 3 out of 12 examined hormonal indicators in comparison to the control group. Pronounced hormonal dysfunction was found in 67 (90.5 %) out of 74 examined women with menstrual cycle disorders which appeared after stress.

Conclusions

1. Thus, out of 74 examined women with menstrual cycle disorders caused by a stressful factor, pronounced hormonal abnormalities were found in 67 women (90.5 %).

2. In women of the main group with stressful amenorrhea, pronounced hormonal disorders were found in 97.1 %, and in women of the main group with abnormal uterine bleeding – in 85.0 %.

3. In the studied women with stress-induced amenorrhea, not inherent to hyperprolactinemia levels of FSH and LH in low peripheral hormones were observed, which may indicate a disturbance in the hypothalamic-pituitary gland relationship while maintaining the negative feedback loops of the pituitary-ovarian axis or ovarian depletion.

4. Thus, post-traumatic stress disorders lead to significant pathological changes not only in the psycho-emotional sphere, but also in the reproductive system of women, suffering from them, and require not only prolonged psychological rehabilitation, but also a serious gynecological examination and treatment. Since both amenorrhea and abnormal uterine bleeding are accompanied by infertility, the problem of rehabilitation of such women acquires both medical and social significance.

Prospects for further research. The effect of long-term stress-related factors on the interaction of pituitary hormones: prolactin, FSH and LH, the mechanisms of this interaction, as well as the impact of stress-induced immunological disorders on the hormonal profile of women, require further in-depth studies.

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