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Stress-induced endocrine changes in adolescent girls with menstrual cycle disorders in under the influence of the war in Ukraine

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Hormonal functioning against the background of stress is almost the most discussed problem in Ukraine today. The menstrual cycle as a vital indicator of life activity reacts sharply to changes in the environment. Russian military aggression in Ukraine forced the majority of the population to experience the hardships of war. Research of hormonal support of menstrual cycle disorders in the emergency situations will expand the understanding of the interaction of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes.
The objective: **to compare the hormonal determinants of stress-related menstrual disorders in adolescent girls in the prewar period and against the background of war.**
Materials and methods**. 331 adolescent girls with menstrual disorders (in 2018–2021 – 184 girls and in 2022–2024 – 147 girls) aged 11–17 years were examined. 149 girls were diagnosed with abnormal uterine bleeding (AUB) (84 girls before the war and 65 – after the war), and 182 patients with oligomenorrhea (OM) (100 adolescents before the war and 82 – after the war). All patients lived in the territory of the city of Kharkiv and the Kharkiv region, which are subject to constant military attacks during the war. The hormonal examination complex included determination of blood serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, testosterone, cortisol, estradiol (E_2), dehydroepiandrosterone sulfate (DHEA-S), and their ratios were calculated (LH/FSH, cortisol/DHEA-S, prolactin/cortisol, testosterone/cortisol, testosterone/E_2).**
Results**. In adolescents with menstrual disorders of the AUB and OM type, who were in the epicenter of constant bombardment, hormonal determinants changed. The level of stress-dependent hormones probably increased. These are the DHEA-S and prolactin concentrations. Accordingly, the ratio prolactin/cortisol increased and ratio cortisol/DHEA-S decreased, which indicates an increased resistance to a stressful situation. Being in a zone of armed conflict leads to the classic relationship between cortisol and DHEA-S, their correlation appears. Sex hormones also participate in the reaction to a stressful situation, and in AUB – testosterone, and in OM – E_2. In girls in a zone of constant air raids and bombardments, against the background of a strong positive relationship between cortisol and DHEA-S, a rather weak correlation between cortisol and testosterone is found, which may indicate a less sensitive relationship between stress and sex hormones.**
Conclusions**. Menstrual disorders are accompanied by impaired regulation of the pituitary-adrenal and pituitary-gonadal axes. Being in a zone of armed conflict increases the tension of stress-dependent and sex hormones in this contingent of patients, which can provoke a complicated course of AUB and OM.**
Keywords: *adolescent girls, stress, war, gonadotropic, adrenal, sex hormones, menstrual disorders, oligomenorrhea, abnormal uterine bleeding.*

Стрес-індуковані ендокринні зміни при порушеннях менструального циклу в дівчат-підлітків під впливом війни в Україні

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Гормональне функціонування на тлі стресу – чи не найбільш обговорювана сьогодні проблема в Україні. Менструальний цикл як життєво важливий показник життєдіяльності гостро реагує на зміни навколишнього середовища. Російська військова агресія в Україні змусила більшість населення переживати труднощі війни. Дослідження стану гормонального забезпечення при розладах менструального циклу в умовах надзвичайних ситуацій розширить уявлення щодо взаємодії гіпоталамо-гіпофізарно-надниркової та гіпоталамо-гіпофізарно-гонадної осей.
Мета дослідження: порівняння гормональних детермінант стресозалежних порушень менструальної функції у дівчат-підлітків у довоєнний період і на тлі війни.
Матеріали та методи. Обстежено 331 дівчину з порушеннями менструальної функції (у 2018–2021 рр. – 184 дівчини й у 2022–2024 рр. – 147 дівчат) віком 11–17 років. У 149 дівчат діагностовано аномальні маткові кровотечі (АМК) (у 84 дівчат до війни та в 65 – після початку війни), а у 182 пацієнток – олігоменорею (ОМ) (у 100 підлітків до війни й у 82 – після початку війни). Усі пацієнтки проживали на території Харкова та Харківської області, які зазнають постійних бойових атак під час війни. Комплекс гормонального обстеження включав визначення в сироватці крові концентрацій лютеїнізувального гормону (ЛГ), фолікулостимулювального гормону (ФСГ), пролактину, тестостерону,

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кортизолу, естрадіолу (E_2), дегідроепіандростерону сульфату (ДГЕА-С), обчислювали їх співвідношення (ЛГ/ФСГ, кортизол/ДГЕА-С, пролактин/кортизол, тестостерон/кортизол, тестостерон/E_2).
Результати. У підлітків із розладами менструальної функції за типом АМК і ОМ, які опинилися в епіцентрі постійного бомбардування, змінилися гормональні детермінанти. Вірогідно, підвищився рівень стресозалежних гормонів. Це вміст ДГЕА-С, пролактину. Відповідно, зросло співвідношення пролактин/кортизол і знизилося кортизол/ДГЕА-С, що свідчить про збільшення протидії стресовій ситуації. Перебування в зоні збройного конфлікту призводить до класичних взаємовідношень кортизолу і ДГЕА-С, з'являється їхній кореляційний зв'язок. У реакції на стресову ситуацію беруть участь і статеві гормони, причому при АМК – тестостерон, а при ОМ – E_2. У дівчат, які перебували в умовах постійних повітряних тривог і бомбардування, на тлі міцного позитивного зв'язку кортизолу з ДГЕА-С реєструються доволі слабкі кореляційні відношення між кортизолом і тестостероном, що може свідчити про менш чутливий зв'язок між стресовими та статевими гормонами.
Висновки. Розлади менструальної функції супроводжуються порушеннями регуляції функції гіпофізарно-адреналової й гіпофізарно-гонадної осей. Перебування в зоні збройного конфлікту збільшує напруження стресозалежних і статевих гормонів у цього контингенту хворих, що може провокувати ускладнений перебіг АМК і ОМ.
Ключові слова: *дівчата-підлітки, стрес, війна, гонадотропні, адреналові, статеві гормони, розлади менструальної функції, олігоменорея, аномальні маткові кровотечі.*

Adolescence is a unique period in human life. It is characterized by a multitude of changes associated with sexual maturation, linear growth, immunological transformation, emotional and cognitive development.

The female reproductive system is susceptible to the modulating effects of stress due to the interconnected nature of the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes. Given the impact of stress on the HPG and HPA axes, it is likely that the high levels of stress experienced by Ukrainian girls during military events may alter menstrual cycle patterns and symptoms [1]. In the 21st century, in the age of technological progress, stress has become a silent pandemic that affects people, especially the younger generation, all over the world. Ukrainian adolescents have also encountered traumatic factors as a result of the war unleashed by russia. In addition to its negative impact on mental well-being, stress affects both physiological processes and the menstrual cycle [2, 3].

The physiological response to stress is mediated by activation of the HPA axis. The HPA axis is a complex system of neuroendocrine pathways and feedback loops that regulates homeostasis in the body through adaptive responses to internal and external stressors, and is a key component of the "stress system" [4, 5]. Cortisol (C) is the major stress hormone involved in the management of the stress response from the onset of stress to recovery from stressful events. It is often considered a key logical indicator of stress and is commonly known as the "hormonal endpoint" of the HPA axis and is responsible for the body's responses to stressors [6, 7]. Among the putative biomarkers of acute stress secreted by the adrenal cortex are dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S), which are produced by the *zona reticularis* in response to adrenocorticotropic hormone [8, 9]. In addition to being a precursor of sex steroids, DHEA-S is an anabolic steroid with a regenerative role [10]. Thus, secretion of DHEA-S after acute stress has been postulated to play a protective role as an antagonist of other stress hormones. DHEA (and its sulfate, DHEA-S) is the most abundant steroid hormone in humans and is the sex steroid with the greatest androgenic activity in females [11–13]. C and DHEA-S regulate different (mostly opposing) physiological functions. When sufficient circulating C concentrations are reached, a negative feedback loop is triggered, which again reduces the activity of the HPA and allows to avoid the systemic dysfunction caused by prolonged exposure to C. While C is a catabolic hormone and thus exerts an energy-mobilizing effect on the body, DHEA and DHEA-S are anabolic hormones that play a protective and regenerative role. DHEA-S has neuroprotective and antiglucocorticoid effects and may help counteract some of the negative effects of excess C. Thus, a sensitive balance between C and DHEA-S is important for regulating the body's homeostasis [14, 15]. Quantifying the relationship between C and DHEA is an important characteristic for objectively measuring stress and its manifestations in the human body. The ratio of C to DHEA is considered an accurate method for assessing the functionality of the HPA axis and is considered a simple way to simultaneously analyze the action of two independent hormones [16–18].

The body's response to stress disrupts hormonal balance, which plays a significant role in the occurrence of menstrual problems. Reproductive steroids, such as estradiol (E_2) and testosterone (T), are important factors in the regulation of homeostasis caused by stress [19–23]. Dysregulation of adrenal and sex hormones is associated with increased symptoms of depression and anxiety, changes in the regulation of emotions and behavior [24–26].

The most important and widely studied role of prolactin (PRL) is its modulation of stress responses, and the most studied are the features of its production during pregnancy and lactation. PRL can control numerous forms of behavior and affect homeostasis. Incentives that promote the release of prolactin include many factors, and one of the leading places is stress [27, 28].

It is assumed that the possible effects of hormones are determined by the balance between interdependent hormones – the ratio of C/DHEA-S, PRL/C, T/C. That is, the ratio of hormones is a simple way to simultaneously analyze the action of several hormones [29].

Although the stress system has been widely studied, the complexity of the various interactions is still not sufficiently defined, especially in relation to menstrual disorders in adolescence. In addition to the fact that menstrual disorders are formed under the influence of stress, today Ukrainian girls have additional psychotraumatic factors, namely the full-scale war unleashed by russia. Menstruation is a cyclical process that requires the harmony of all endogenous and environmental factors.

Permanent residence in the zone of military (combat) operations certainly cannot but affect the formation of menstrual disorders. According to the Decree of the President of Ukraine dated February 24, 2022, No. 64/2022 "On the imposition of martial law in Ukraine", approved by the Law

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of Ukraine dated February 24, 2022, No. 2102-IX, the laws of Ukraine "Law on the Legal Regime of Martial Law", "On the defense of Ukraine", orders of the Commander-in-Chief of the Armed Forces of Ukraine determine the areas of military (combat) operations. These orders are issued monthly, for the previous month.

From February 24, 2022, Kharkiv region was monthly designated by orders of the Commander-in-Chief of the Armed Forces of Ukraine as areas of military operations. In the media for the period from February 2022 to June 2025, more than 1,720 explosions were reported, almost 6.5 thousand alarms, the longest of which lasted more than 18 hours [30].

The objective of our study was to determine the features of hormonal determinants of stress-related menstrual disorders in adolescent girls in the pre-war period and against the backdrop of war events.

MATERIALS AND METHODS

In the period 2018–2021 years – before the war – was examined 184 girls aged 11–17 years with menstrual disorders (84 with abnormal uterine bleeding (AUB) and 100 with oligomenorrhea (OM)) who were treated at the clinic of the State Institution (SI) "Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences (NAMS) of Ukraine" and against the background of a full-scale war 2022–2024 years was examined 147 patients with menstrual disorders (65 with AUB and 82 with OM) who continued to live in Kharkiv and the Kharkiv region after the start of the full-scale war.

The diagnosis of menstrual disorders was established on the basis of anamnestic data, complaints, clinical and laboratory research methods. Physiological parameters of the menstrual cycle in girls were considered to be 21 to 45 days long, 3–8 days of menstruation, and 25–40 mL of blood loss. According to the International Federation of Gynecology and Obstetrics (FIGO) AUB System 2 classification (2018), AUB is defined as uterine bleeding with an intermenstrual interval of less than 21 days and/or a duration of more than 8 days and/or between menstrual bleedings. In the cohort of girls with AUB who were examined, blood diseases, thrombocytopenia, and blood coagulation insufficiency were excluded using screening for hemostasis disorders. All patients underwent a complete clinical blood test with measurement of clotting time. Structural causes and inflammatory diseases of the pelvic organs were also excluded. According to the PALM-COEIN classification, all girls were classified as AUB for non-structural reasons related to endocrine disorders (ovulatory dysfunction – AUB-O) [31, 32]. The diagnosis of OM was defined as spontaneous menstruation with an intermenstrual interval of more than 45 days with a normal duration of bleeding [33] and its onset during puberty according to ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) is considered primary OM.

The examination algorithm consisted of determining the level of luteinizing hormone (LH), follicle-stimulating hormone (FSH), PRL, E_2, T, C and DHEA-S in the blood serum. The coefficients of LH/FSH, C/DHEA-S, PRL/C, T/C, T/E_2 were calculated.

All hormonal studies were performed by enzyme-linked immunosorbent assay (ELISA) using a Rayto RT-2100C photometer (Rayto, China) and reagent kits from "Best Diagnostic" (Kyiv, Ukraine). The level of DHEA-S was measured using commercially available ELISA kits from a German manufacturer.

The results of the study were analyzed using the software Statgraphics Plus for Windows 5.0. The mean value (M) and standard deviation (SD) were calculated for all variables. The difference in group statistics was assessed using Student's t-test. The difference was considered statistically significant at $p < 0.05$. The relationship between quantitative indicators was assessed using the Pearson correlation coefficient (r). The value of p below 0.05 indicates statistically significant non-zero correlations at the 95% confidence level.

Written informed consent was obtained from each registered participant or their parents/guardians for all medical procedures. The study protocol was approved by the Bioethics and Deontology Committee of the SI "Institute for Children and Adolescents Health Care of NAMS of Ukraine".

RESULTS AND DISCUSSION

In order to identify the characteristics of the concentration of gonadotropic and steroid hormones, their levels in the blood serum in the morning hours were studied in girls examined in the pre-war period and after the war. The average values are given in Table 1.

As can be seen from Table 1, patients with AUB have a significant difference in the indicators of gonadotropic and steroid hormones before the start of the full-scale war and after. Among the gonadotropic hormones, a significant increase in the level of LH was found in girls examined after the start of the war. Due to this, there is a significant increase in the ratio of LH/FSH. PRL secretion increases. Considering that the war in Ukraine provokes stress disorders, adrenal hormones deserve special attention, namely C and DHEA-S. In girls living in the front-line city of Kharkiv, the C content did not change in relation to the values in the pre-war period. The concentration of DHEA-S increased statistically significantly. And accordingly, the C/DHEA-S ratio decreased. The content of the sex hormone E_2 did not change, but the level of T decreased significantly. Accordingly, the ratios T/E_2 and T/C also decreased. The PRL/C ratio increased due to the increased PRL values.

Among patients with OM, almost similar changes occurred (Table 2).

A significant increase in PRL, DHEA-S, E_2, PRL/C ratio was recorded. Such indicators as T level, T/E_2, C/DHEA-S ratios were significantly reduced.

Correlations between sex and adrenal hormones were revealed. In AUB before the full-scale war, a medium-strength relationship was observed between DHEA-S and T ($r = 0.60$; $p < 0.0001$) and a somewhat weaker one between C and T ($r = 0.24$; $p < 0.07$). In OM, a relationship was also observed between DHEA-S and T ($r = 0.41$; $p < 0.0001$) and C and T ($r = 0.28$; $p < 0.008$), but, unlike girls with AUB, in OM there was also a relationship between DHEA-S and E_2 ($r = 0.25$; $p < 0.02$). Against the background of the ongoing war in Ukraine, these relations have a bit changed. In addition to the existing ones, a relationship was added between C and DHEA-S (AUB – $r = 0.30$; $p < 0.04$; OM – $r = 0.35$; $p < 0.004$), and in OM there was also a correlation between C and E_2 ($r = 0.36$; $p < 0.004$).

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Table 1

Mean values and standard deviations of gonadotropic, steroid hormones in patients with AUB before the start of military aggression and after

Hormonal indicators	Before the war 2018–2021 (n = 84)	Against the background of a full-scale war 2022–2024 (n = 65)	p
LH, mIU/mL	8.01 ± 5.81	10.01 ± 7.55	< 0.05
FSH, mIU/mL	7.33 ± 2.95	7.10 ± 3.36	> 0.05
LH/FSH, Units	1.21 ± 0.91	1.64 ± 1.25	< 0.01
PRL, mIU/mL	360.63 ± 174.82	479.15 ± 241.94	< 0.0008
E_2, nmol/L	0.36 ± 0.26	0.39 ± 0.25	> 0.05
T, nmol/L	1.92 ± 1.13	1.51 ± 1.20	< 0.03
C, nmol/L	404.76 ± 196.34	367.08 ± 193.24	> 0.05
DHEA-S, mcmol/L	4.34 ± 3.31	5.79 ± 4.39	< 0.03
C/DHEA-S, Units	121.68 ± 90.42	91.26 ± 70.09	< 0.02
PRL/C, Units	0.99 ± 0.46	1.46 ± 0.73	< 0.0001
T/E_2, Units	7.32 ± 5.45	5.32 ± 5.24	< 0.02
T/C, Units	0.005 ± 0.004	0.004 ± 0.003	< 0.002

Notes: LH – luteinizing hormone; FSH – follicle-stimulating hormone; PRL – prolactin; E_2 – estradiol; T – testosterone; C – cortisol; DHEA-S – dehydroepiandrosterone sulfate.

Table 2

Mean values and standard deviations of gonadotropic, steroid hormones in patients with OM before the start of military aggression and after

Hormonal indicators	Before the war 2018–2021 (n = 100)	Against the background of a full-scale war 2022–2024 (n = 82)	p
LH, mIU/mL	12.94 ± 12.62	14.69 ± 12.50	> 0.05
FSH, mIU/mL	7.76 ± 6.41	8.76 ± 8.75	> 0.05
LH/FSH, Units	1.77 ± 1.22	1.79 ± 1.11	> 0.05
PRL, mIU/mL	360.73 ± 182.04	476.29 ± 261.26	< 0.0005
E_2, nmol/L	0.32 ± 0.35	0.43 ± 0.37	< 0.04
T, nmol/L	2.43 ± 1.23	2.13 ± 1.17	< 0.03
C, nmol/L	415.97 ± 220.88	390.22 ± 177.63	> 0.05
DHEA-S, mcmol/L	6.81 ± 4.02	8.86 ± 5.80	< 0.01
C/DHEA-S, Units	86.02 ± 65.33	64.29 ± 52.45	< 0.03
PRL/C, Units	0.97 ± 0.67	1.42 ± 0.88	< 0.0001
T/E_2, Units	11.58 ± 8.57	7.42 ± 5.74	< 0.0003
T/C, Units	0.007 ± 0.005	0.006 ± 0.004	> 0.05

Notes: LH – luteinizing hormone; FSH – follicle-stimulating hormone; PRL – prolactin; E_2 – estradiol; T – testosterone; C – cortisol; DHEA-S – dehydroepiandrosterone sulfate.

The russian-Ukrainian war, which began on February 24, 2022, has become one of the largest and fastest-growing humanitarian emergencies since World War II. Various consequences of war (damage to property, death of a loved one, lack of psychological preparedness for a disaster, negative consequences of overcoming difficulties, etc.) negatively affect mental health. Emotional instability, stress reactions, anxiety cannot but affect the physical condition and menstrual function, which is a vital indicator [34, 35]. Recently, there has been an increasing amount of discussion in the literature about the role of adrenal hormones in the implementation of stress in various diseases, tumor development, and pregnancy [36, 37]. DHEA-S and C are the most prevalent hormones of the human adrenal glands, released as end products of a tightly coordinated endocrine response to stress. Together, they mediate short-term and long-term responses to stress and provide physiological and behavioral adjustments necessary to maintain homeostasis [38]. It is believed that the first response to stress is an increase in C. In our study, this does not occur. Most likely, due to chronic stress, because Kharkiv was a front-line city for all three years of the war, a stage of exhaustion occurs, when energy and resources for long-term adaptive responses to the stressor are depleted. The level of DHEA-S, on the contrary, increases. This is a positive reaction, since DHEA-S is a "protective" hormone, it counteracts the action of C. A decrease in the level of DHEA-S is associated with a negative mood, the formation of pathological states [39]. The C/DHEA-S ratio

decreases due to an increase in DHEA-S. An increase in this coefficient implies a higher level of stress against the background of a low level of the "protective" hormone, which can negatively affect mental health. An increase in PRL content is noted in girls who are in a combat zone. One of the functions of PRL is to modulate stress. On the one hand, an increase in this hormone is positive, since it is a reaction to stress, on the other hand, a long-term increase in PRL causes hormonal abnormalities, which leads to disorders in the menstrual cycle and contributes to a complicated course of the disease, increases the risk of insulin resistance and dyslipoproteinemia [40]. The PRL/C ratio also increases. These changes are characteristic of both AUB and OM. Sex hormones (T, E_2) behave differently depending on the type of menstrual dysfunction. The T level decreases against the background of ongoing military events. E_2, on the contrary, increases, but only in adolescents with OM. The T/C ratio decreases only in girls with AUB. The T/E_2 ratio decreases, but in AUB, mainly due to a decrease in T content, and in OM – due to an increase in E_2.

However, today the focus is not on the individual hormones but on the relationships between hormones originating from the HPA and HPG axes, as these axes regulate each other throughout life. Each of these endocrine axes, as well as their connections, respond to stress. The HPA and HPG axes perform regulatory functions that help the body adapt to new contexts. Traditionally, these systems were thought to inhibit each other in stressful and challenging circumstances. However, it has now been shown that positive hormonal connection (or positive correlation) – when an increase in the level of hormones in one axis is associated with an increase in the level of hormones in the other axis – is both normative and adaptive during adolescence [41]. The identified correlations between stress and sex hormones indicate a positive relationship of hormones derived from the HPA and HPG axes, including all hormone pairs (namely C–T, C–DHEA-S, DHEA-S–T). Changes in this hormonal triad are primarily due to stressful events occurring in Ukraine. Both before the war and during the martial law period, a closer positive relationship was noted between DHEA-S and T, and it was most pronounced in adolescents with AUB than OM. A less close relationship was recorded in girls with menstrual cycle disorders between C and T. There is evidence in the literature that gonadal hormones (T and E_2) are associated with changes in mood and behavior. T can also modulate symptoms of depression [22, 42]. It is possible to assume that during the destructive events of war, there are changes in the interaction of T with adrenal hormones, it increases with DHEA-S – a "protective" hormone and decreases with C. The connection between C and DHEA-S appeared in girls with increased stress under the influence of war events. That is, stressful situations associated with the war factor affect the relationship between the hormones HPA and HPG. The association of hormones of interacting processes between HPA and HPG expands the possibilities of studying stress not only on the example of C, as the final product of the HPA axis, but also makes it possible to consider the connectivity of the functioning of the HPA-HPG axes.

CONCLUSIONS

1. Adolescents with menstrual disorders had significant differences in their hormonal background in the pre-war period and after the start of a full-scale war. Against the backdrop of war, AUB was accompanied by increased shifts in gonadotropic (LH, LH/FSH), adrenal hormones (DHEA-S) and decreased sex hormones (T). In adolescents with OM, only steroid hormones underwent significant changes: T significantly decreased and E_2 increased.

2. With a long-term stay in the stress center, the greatest changes occurred among such hormones as DHEA-S, PRL, T and the ratios C/DHEA-S, PRL/C, T/C, which are directly responsible for stress reactions.

3. The stress reacting depends not only on the response of adrenal hormones, but also on the interaction of stress and sex hormones.

Conflict of interest. The authors declare no conflicts of interest.

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