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The relationship between the level of psychological stress and hormone markers of stress in the case of menstrual cycle disorders in adolescent girls against the Russian–Ukrainian war

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Prolonged residence in a war zone may adversely affect menstrual function in adolescent girls.
Aim – to determine the relationship between psychological stress and adrenal stress hormones in adolescent girls with menstrual disorders living in a frontline city.
Materials and methods. Between 2022 and 2024, 142 girls aged 11–17 years with menstrual disorders were examined, including 69 with abnormal uterine bleeding (AUB) and 73 with oligomenorrhea (OM). Psychological stress was assessed in all participants. Serum cortisol and dehydroepiandrosterone sulfate (DHEA-S) levels were measured, and the cortisol/DHEA-S ratio was calculated as an indicator of hypothalamic-pituitary-adrenal (HPA) axis activity.
Results. Hormonal stress markers were associated with psychological stress severity. Elevated cortisol levels were observed only in girls with moderate stress in both groups. Increased DHEA-S was uncommon in AUB but occurred in nearly half of the girls with OM, particularly those with moderate stress. In the AUB group, low stress was mainly associated with a normal cortisol/DHEA-S ratio, indicating balanced HPA axis function, whereas high stress was more often accompanied by an elevated ratio, suggesting impaired adaptive capacity. In contrast, girls with OM predominantly exhibited normal or reduced cortisol/DHEA-S ratios across all stress levels, reflecting a more adaptive hormonal response. Hormonal responses also varied according to physical and sexual development.
Conclusions. Psychological stress is associated with alterations in adrenal stress hormones in adolescent girls with menstrual disorders. Understanding these relationships may facilitate the development of strategies to prevent and mitigate the effects of chronic war-related stress.
The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their parents or legal guardians.
The authors declare no conflict of interest.
Keywords: psychological stress, abnormal uterine bleeding, oligomenorrhea, adolescent girls, cortisol, dehydroepiandrosterone sulfate, war.

Зв'язок між рівнем психологічного стресу і гормональними маркерами стресу при порушеннях менструального циклу у дівчат-підлітків на тлі російсько-української війни

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Постійне проживання в зоні бойових дій є важливим чинником ризику порушень менструальної функції.
Мета – визначити взаємозв'язок між рівнем психологічного стресу та адреналовими гормонами (маркерами стресу) при порушеннях менструального циклу в дівчат-підлітків прифронтового міста.
Матеріали та методи. У 2022–2024 рр. обстежено 142 дівчат 11–17 років із розладами менструального циклу: 69 – з аномальними матковими кровотечами (АМК) та 73 – з олігоменореєю (ОМ). Усіх учасниць оглянуто психологом. Визначали рівні кортизолу, дегідроепіандростерону сульфату (ДГЕА-С) та розраховували співвідношення кортизол/ДГЕА-С.
Результати. Гормональні маркери стресу були пов'язані з рівнем психологічного стресу. Підвищення кортизолу виявляли лише при середньому рівні стресу в обох групах. Підвищення ДГЕА-С при АМК спостерігалося рідко, тоді як при ОМ, особливо за середнього рівня стресу, майже у половини дівчат. При АМК низький рівень стресу супроводжувався переважно нормальним співвідношенням кортизол/ДГЕА-С, що свідчило про збалансованість гіпоталамо-гіпофізарно-надниркової системи. За високого рівня стресу частіше реєстрували підвищений коефіцієнт кортизол/ДГЕА-С, що вказувало на виснаження адаптаційних механізмів. Для ОМ характерним було переважання нормальних і знижених значень кортизол/ДГЕА-С при всіх рівнях стресу, що свідчило про більш адаптовану відповідь. Вираженість гормональної реакції залежала також від фізичного та статевого розвитку.
Висновки. Психологічний стрес асоціюється зі змінами гормональних маркерів стресу у дівчат із порушеннями менструального циклу. Вивчення цих взаємозв'язків сприятиме розробці стратегій профілактики та корекції наслідків хронічного стресу, зумовленого війною.
Дослідження виконано відповідно до принципів Гельсінської декларації. Отримано інформовану згоду батьків і дітей.
Конфлікт інтересів відсутній.
Ключові слова: психологічний стрес, аномальні маткові кровотечі, олігоменорея, дівчата-підлітки, кортизол, дегідроепіандростерону сульфат, війна.

Introduction

On February 24, 2022, Russia's invasion of Ukraine marked the beginning of a full-scale war. According to United Nations International Children's Emergency Fund (UNICEF), the escalation of the conflict in Ukraine poses a direct threat to the lives and well-being of 7.5 million children in the country.

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More than 250,000 children are regularly exposed to shelling and the effects of landmines and unexploded ordnance, making them more vulnerable to injuries and mental health problems. Children from the southeastern regions are especially affected. Armed conflicts always threaten freedom, justice, and democratic values. The impact of war on mental and physical health is long-term. Ukraine is currently experiencing a situation potentially catastrophic for its future, as, apart from human casualties, the war endangers the mental and physical health of children and adolescents [7,28].

Stress is defined as a state in which homeostasis is threatened or perceived as such. The human body and mind respond to stress by activating adaptive reactions of the central and peripheral nervous systems. The adaptive response to stressors plays a protective role in human survival. In circumstances where stressors are stronger or more prolonged-such as in Ukraine, particularly in frontline areas-the stress response may become maladaptive or inadequate. A maladaptive stress response can contribute to health deterioration and the development of menstrual function disorders [16,25].

The menstrual cycle involves a highly coordinated set of interactions between the hypothalamus, anterior pituitary, and ovaries. The term «menstrual health» is increasingly used in the literature. Menstrual health is defined as a state of complete physical, mental, and social well-being, and not merely the absence of disease or disorders related to the menstrual cycle [10].

According to the Committee on Adolescent Health Care of the American College of Obstetricians and Gynecologists (ACOG), which has also been endorsed by the American Academy of Pediatrics (AAP), the menstrual cycle should be regarded as a «vital sign», similar to temperature, pulse, respiration, and blood pressure. Using the menstrual cycle as an additional vital sign provides a powerful tool for assessing normal development and detecting pathological conditions [1,6,11].

Stress is considered a common cause of menstrual irregularities. The body's response to stress involves changes in the levels of many hormones, which can disrupt hormonal balance [13].

To date, we have not encountered studies addressing the specific relationship between the level of psychological stress and hormonal stress markers in adolescent girls with menstrual disorders in the context of war.

The aim of the study was to determine the relationship between the level of psychological stress and adrenal hormones (hormonal stress markers) in adolescent girls with menstrual disorders in a frontline city.

Materials and methods of the study

A total of 142 adolescent girls aged 11–17 years with menstrual disorders (69 with abnormal uterine bleeding (AUB) and 73 with oligomenorrhea (OM)) who received treatment at the State Institution «Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine» (Kharkiv) during 2022–2024 were examined. The menstrual status was assessed based on self-reported data regarding the date and duration of the last menstrual cycle and cycle regularity. According to the International Federation of Gynecology and Obstetrics (FIGO) classification system (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 intermenstrual bleeding [22]. According to the PALM-COEIN classification, all girls were classified as having AUB of non-structural causes associated with endocrine disorders (anovulatory disorders) [29]. In the cohort of girls with AUB who were examined, diseases of the blood, thrombocytopenia, and coagulation deficiencies were excluded using screening for hemostatic disorders. The diagnosis of OM was defined as spontaneous menstruation with an intermenstrual interval of more than 45 days, with normal duration [11]. Patients with congenital or postnatal forms of adrenogenital syndrome, gonadal dysgenesis, and severe disabling extragenital diseases (diabetes mellitus, idiopathic rheumatoid arthritis, autoimmune thyroiditis, and others) were excluded from the study. All patients underwent a general clinical examination. Anthropometry included measurements of height, body weight, calculation of body mass index (BMI): BMI = weight (kg) / (height (m) × height (m)), and classification was performed using age percentile tables according to the order of the Ministry of Health of Ukraine [20]. For each patient, depending on age, the percentile range of BMI was determined individually. If it was below the 15th percentile, it was considered underweight. If it was between the 15th and 85th percentiles, it

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Table 1

Mean levels of stress markers in girls with menstrual cycle disorders

Indicator	Groups					
	AUB			OM		
	Stress level			Stress level		
	low	moderate	high	low	moderate	high
Cortisol, nmol/l	350.75±120.91	301.65±168.56	292.98±150.03	332.04±132.23	451.84±243.18	328.16±120.01
DHEA-S, μmol/l	5.21±2.85	5.43±3.46	5.03±4.41	9.19±5.03	10.64±6.45	7.09±4.47
Cortisol/DHEA-S, units	99.53±84.01	67.38±38.91	130.31±101.57	49.47±36.75	52.28±28.33	56.66±33.98

was considered physiological variation, and above the 85th percentile, it was considered overweight. The development of secondary sexual characteristics was assessed according to the corresponding developmental stages proposed by J. Tanner.

The assessment of hormonal status was based on the determination of cortisol and dehydroepiandrosterone sulfate (DHEA-S) in serum using an immunoenzymatic photometer Rayto RT 2100C (China) with «Best Diagnostic» kits (Kyiv), and the cortisol/DHEA-S ratio was calculated – the morning value of cortisol was divided by the morning value of DHEA-S.

All girls were consulted by a psychologist using psychodiagnostic methods and a questionnaire to assess stress indicators (Lüscher test). The severity of stress was determined as the sum of points for frustration of basic needs and points for decompensation, distributed according to the level of intensity as follows: 0 points – stress-free choice; 1–2 points – low level of stress; 3–5 points – moderate level of stress; 6–9 points – high level of stress; 10–12 points – excessively high level of stress.

Descriptive statistics included quantitative variables presented as mean (M) and standard deviation (SD), and qualitative variables were described as frequencies (%). To determine statistically significant differences, Student's t-test, Fisher's test, Wilcoxon–Mann–Whitney test, and chi-square test were applied. Differences in indicators were considered significant at $\rho<0.05$. Data analysis was performed using SPSS version 17.0 and «Statgraphics Plus for Windows 5.0» software.

Prior to the study, informed consent was obtained from each adolescent girl, as well as from their parents or legal guardians for participants under 14 years of age. The implementation of this study fully complied with the Declaration of Helsinki and was approved by the Committee on Bioethics and Deontology of the State Institution «Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine».

Results of the study

Analysis of the psychological state of adolescent girls with menstrual disorders showed that most of them exhibited varying levels of stress. The absence of a stress response and an excessively high level of stress were recorded only in isolated cases. The most common level of stress among adolescents with AUB was moderate, while in patients with OM it was high (Figure 1).

The mean values of adrenal hormones in both AUB and OM groups did not show significant differences depending on the level of stress (Table 1). However, in cases of AUB, the cortisol/DHEA-S ratio remained within reference limits at low and moderate stress levels, while at high stress levels it exceeded the normal range. This indicates that girls with AUB and high stress levels require additional monitoring, as this condition may have adverse health consequences. In girls with OM, the mean values of the cortisol/DHEA-S ratio remained within the normal range across all levels of stress response.

The assessment of individual characteristics revealed that cortisol levels were mostly within physiological ranges or decreased (Figure 2). Elevated

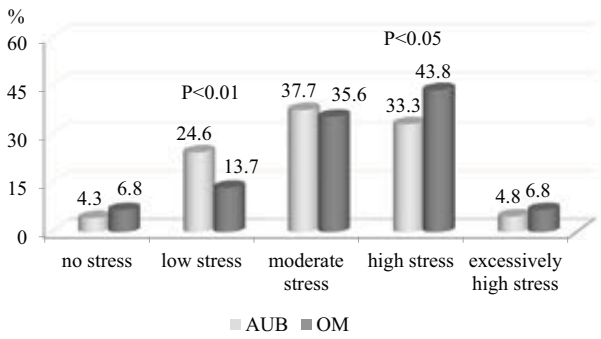

Fig. 1. Percentage of girls with different levels of stress

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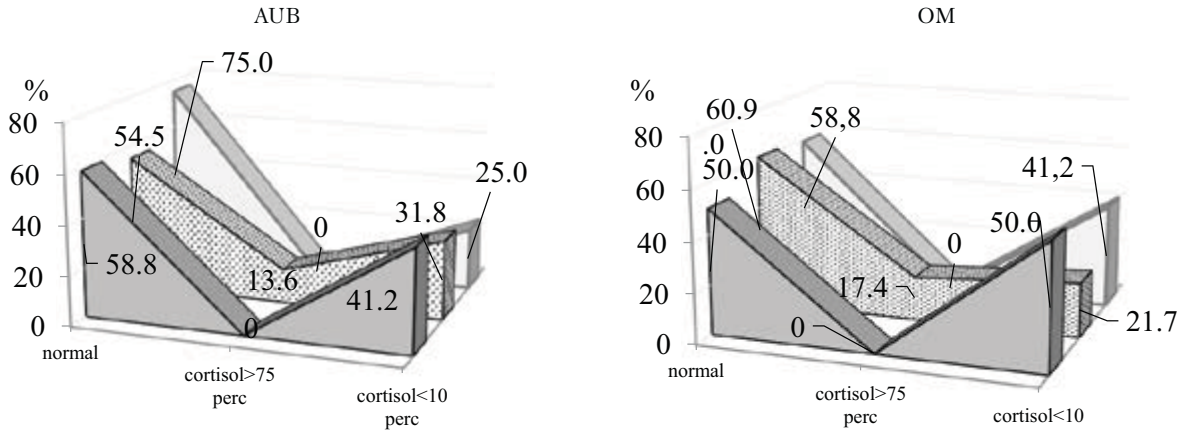

Fig. 2. Percentage of different cortisol levels in girls with menstrual cycle disorders depending on the level of stress

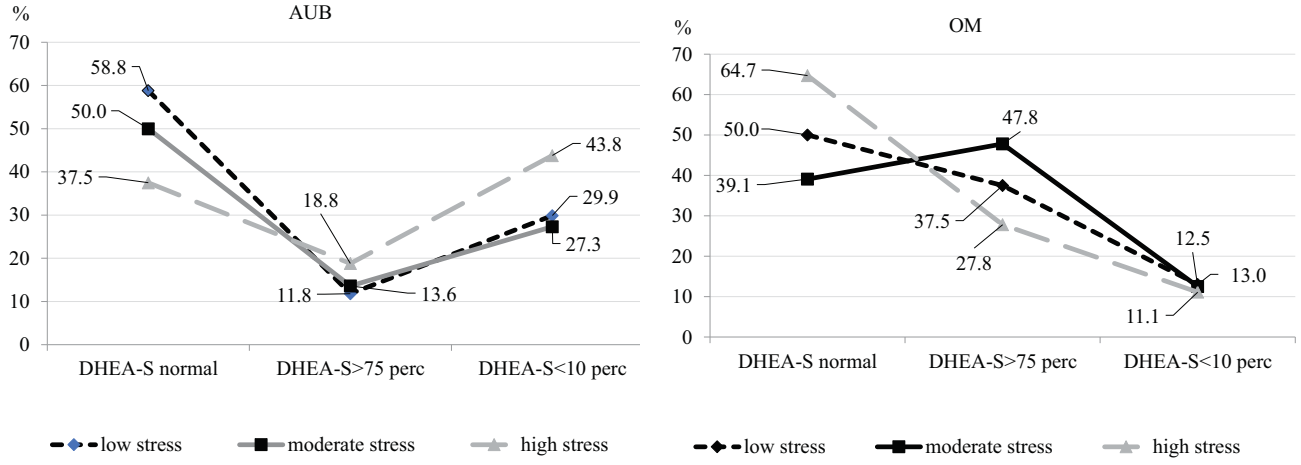

Fig. 3. Percentage of different DHEA-S levels in girls with menstrual cycle disorders depending on the level of stress

cortisol levels were observed only in cases of moderate stress, both in girls with AUB and those with OM.

The hormone with an opposite physiological effect to cortisol–DHEA-S – in most patients with AUB also varied within normal reference ranges (Figure 3). More than one-third of the girls had decreased DHEA-S levels, while elevated values were observed only in isolated cases. In girls with OM, as in those with AUB, reference values were most frequently recorded. However, unlike AUB, more than one-third of OM patients had elevated DHEA-S levels, and at moderate stress levels, nearly half showed increased concentrations, whereas low DHEA-S values were found only in isolated cases.

The cortisol/DHEA-S ratio was within normal limits in 45.6% of girls with AUB and 37.1% of those with OM. Elevated levels of this ratio were observed significantly more often in the AUB group (32.9% versus 21.3% in OM; $p<0.04$), whereas reduced levels were more common in OM (41.0% versus 22.8% in AUB; $p<0.005$). Under conditions of persistent stressors, an exhaustion stage may develop when the energy and resources for prolonged adaptive responses to stress are depleted, and this occurs more frequently in AUB than in OM, as evidenced by the elevated cortisol/DHEA-S index.

The cortisol/DHEA-S ratio depended not only on the type of menstrual dysfunction but also on the level of stress (Figure 4). In AUB, with a low stress level, nearly half of the girls had physiological values of the ratio, a little more than one-third had elevated values, and only isolated cases showed decreased levels. A moderate stress level was accompanied in almost half of the cases by normal ratio values, a smaller percentage with elevated levels, and slightly more than one-third with reduced ratios. At high stress levels, an increase in the cortisol/DHEA-S ratio was most frequently observed.

OM was characterized by a different pattern. At all stress levels, the direction of changes in the cortisol/DHEA-S ratio remained similar. Normal reference values were recorded in more than one-

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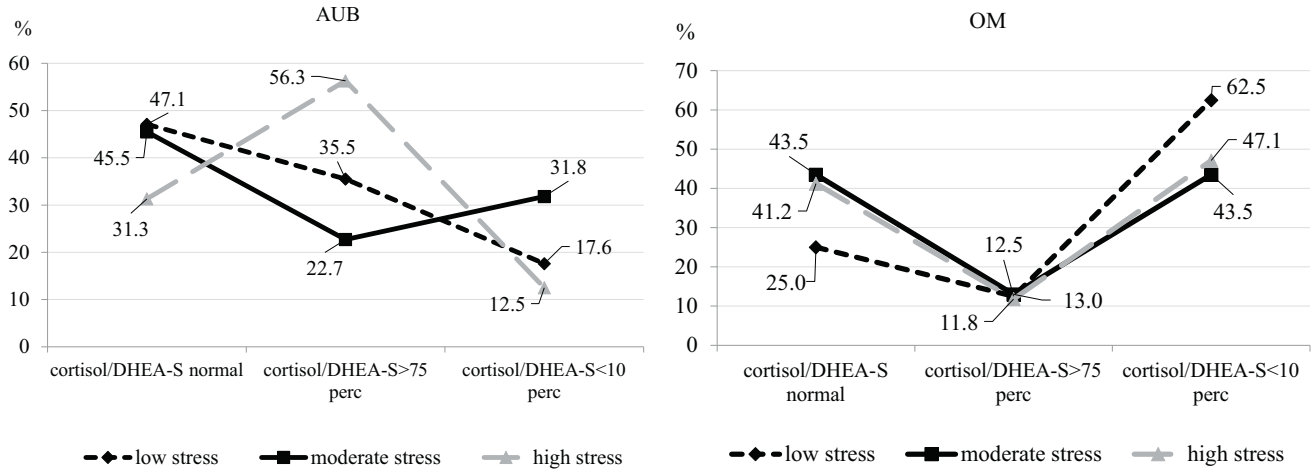

Fig. 4. Percentage of different cortisol/DHEA-S ratio values in girls with menstrual cycle disorders depending on the level of stress

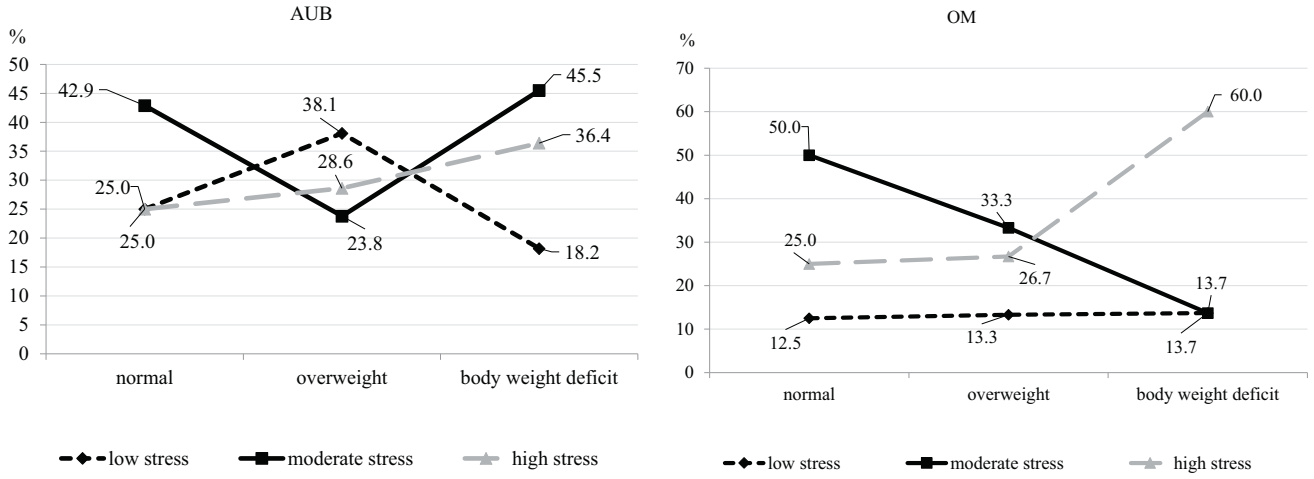

Fig. 5. Percentage of girls with menstrual cycle disorders and different levels of stress depending on BMI

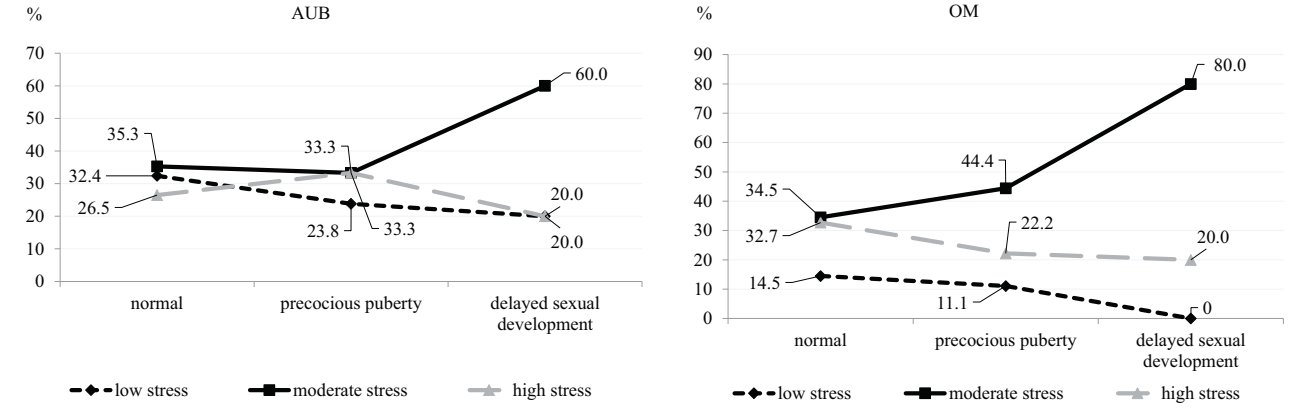

Fig. 6. Percentage of girls with different levels of stress depending on sexual development

third of patients (on average 35.3%), elevated values were rare, and more than half of the girls had decreased cortisol/DHEA-S ratios. The most frequent combinations were normal cortisol levels with elevated DHEA-S or decreased cortisol with normal DHEA-S levels. On one hand, this may represent an adaptive response to stress; on the other hand, according to the literature, a reduced cortisol/DHEA-S ratio is often found in adolescents with depressive states [2].

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Comparison of physical development with the level of stress in menstrual function disorders revealed that patients with AUB and OM, depending on their BMI, responded to stress differently (Figure 5).

In patients with AUB, a moderate level of stress predominated among those with normal or deficient BMI, while a low level of stress was more common in girls with excess body weight. In girls with OM, a slightly different picture was observed. With physiological BMI variations, as in AUB, a moderate level of stress was most frequently recorded, and unlike AUB, this pattern was also observed in those with excess body weight. In contrast, among girls with low body weight, a high level of stress predominated.

In adolescents with AUB whose sexual development corresponded to their chronological age or was advanced, various stress levels (low, moderate, and high) were observed with equal frequency. Among those with delayed sexual development, a moderate level of stress predominated (Figure 6). A similar pattern was observed in girls with OM.

Discussion

Studies of the effects of chronic stress on female reproductive function convincingly demonstrate the role of external provoking factors in the formation and functioning of the menstrual cycle, which serves as a marker of reproductive health [26]. The body's response to stress involves changes in the levels of many hormones, disrupting hormonal balance and other physiological processes [13]. Armed conflicts and wars are public health emergencies that affect people's lives at multiple levels. War-affected regions are often associated with higher levels of psychosocial stress and increased susceptibility to mental and psychiatric symptoms. This is especially true for children and adolescents, who are at high risk during crises. Therefore, there is growing interest in psychosocial health among populations living in war zones. Unfortunately, the effects of war on mental and physical health are long-term [24]. It was found that among girls with menstrual disorders living in front-line areas, some level of stress was almost always present. The distribution pattern of stress levels depended on the type of disorder. Girls with AUB more often had low stress levels, while adolescents with OM demonstrated significantly higher levels of stress.

Stress primarily activates two systems: the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is the central component of the stress response system. SNS activation triggers the release of adrenaline and noradrenaline, while HPA activation initiates a hormonal cascade culminating in cortisol secretion – often considered the key physiological indicator of stress. Chronic stress disrupts the normal function of this axis and affects the balance of other hormones. Altered cortisol levels serve as a catalyst for hormonal imbalance [12,18]. Another important biomarker of stress is DHEA-S. Beyond its role as a precursor of sex steroids, DHEA is an anabolic steroid with regenerative properties. DHEA secretion after stress exposure is considered protective. DHEA-S plays a protective role during the stress response, counteracts cortisol's effects, serving as an antagonist to other stress hormones [5]. Based on the average values of adrenal hormones, no significant differences depending on the level of stress were found, except for the cortisol/DHEA-S ratio. In girls with AUB, mean cortisol/DHEA-S ratios at low and moderate stress levels were within normal ranges, but significantly exceeded normal values at high stress levels. In OM, mean ratios were within normal limits at all stress levels. Therefore, girls with AUB and high stress levels may require additional monitoring due to possible negative health implications.

Conducting individual analysis made it possible to identify differences in the response to stressful events of girls with various menstrual disorders and the peculiarities of associations between levels of psychological stress and hormonal markers of stress. Regardless of the type of menstrual disturbance, elevated cortisol levels were recorded only at moderate stress levels. Increased cortisol during chronic stress may indicate insufficient counterregulation by DHEA-S [15]. Across all stress levels, normative and low cortisol values predominated – a pattern that may signal vulnerability to post-traumatic stress disorder symptoms [23].

HPA axis activation was further assessed by DHEA-S levels, which varied significantly by menstrual disorder type and stress level. In AUB, DHEA-S changes were mainly unidirectional: predominantly normal or reduced, and rarely elevated. Literature suggests that low DHEA-S levels form a link between long-term stress and adverse health conditions and may be an early sign of the negative

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physiological consequences of long-term stress [9,17]. OM presented a different hormonal pattern – over one-third had elevated DHEA-S levels, nearly half had moderate stress, and only isolated cases showed low levels. Literature indicates that adolescents with OM may exhibit more adaptive stress responses [4,14], although elevated DHEA-S could also be associated with increased anxiety [3,21].

The relationship between cortisol and DHEA-S, two steroids with opposing actions, is of particular interest. Cortisol, a catabolic hormone, and DHEA-S, an anabolic one, are both products of the HPA axis – the central stress-regulation system. The cortisol/DHEA-S ratio is considered an accurate measure of HPA axis functionality. Monitoring changes in these biomarkers may reveal important insights into stress regulation and mental health [2,8].

In a subset of girls, cortisol/DHEA-S ratios were within normal limits, suggesting balanced HPA function. Elevated ratios were more common among adolescents with AUB, whereas decreased ratios predominated in OM. An elevated ratio may indicate depressive tendencies and greater long-term health risks, while a decreased ratio could either represent a protective adaptation or reflect differing physiological processes [27]. Data on this system in adolescents with menstrual disorders remain scarce.

The cortisol/DHEA-S ratio depended not only on menstrual disorder type but also on stress level. In AUB, this ratio showed variable trends: at low stress, values were mainly normal or elevated; at moderate stress, normal or reduced; and at high stress, significantly more often elevated ($p<0.012$). It can be assumed that at moderate stress levels, the HPA response was primarily adaptive, supporting physiological resilience, whereas high stress led to greater HPA dysfunction.

In OM, ratio changes were unidirectional across stress levels – normal and decreased values predominated.

Adaptive stress responses may also be influenced by physical and sexual development, impacting reproductive and immune functions [19]. Stress responses in girls with different BMI values depended on both physical parameters and menstrual disorder type. In AUB, moderate and high stress levels were observed with equal frequency in girls with excess body weight, while low stress was slightly more common. In girls with body weight deficit, moderate and high stress levels predominated. Among adolescents with OM, a moderate stress level was most frequent at normal BMI, while both moderate and high levels were seen in those who were overweight. Low stress occurred 2–2.5 times less frequently, but without statistical significance. Adolescents with body weight deficit mainly exhibited high stress levels. It can be assumed that girls with a reduced level of energy resources have the greatest reaction to stressful events, that is, the demands of the situation exceed the resources.

Girls whose sexual development matched or exceeded chronological expectations demonstrated similar distributions of low, moderate, and high stress. In those with delayed sexual development (both AUB and OM), moderate stress was the most common.

Thus, the results of this study suggest that the response to stress load depends not only on endocrine reactions and hormone sensitivity but also on the girl's physical and sexual development. However, the complexity of these interactions remains insufficiently understood and warrants further research.

Conclusions

Almost all girls with menstrual disorders living in a front-line city exhibited varying levels of psychological stress. Girls with AUB more often demonstrated low stress levels, whereas adolescents with OM significantly more frequently exhibited high stress levels.

Hormonal stress markers showed distinct patterns depending on the type of menstrual dysfunction and stress level. Only at moderate stress levels did cortisol concentrations exceed the 75th percentile in both the AUB and OM groups. The distribution of DHEA-S levels in girls with AUB was unidirectional across all stress levels: in most cases within normal limits or decreased, and only occasionally elevated. In OM, physiological or elevated DHEA-S levels predominated, while low values were rare.

The cortisol/DHEA-S ratio ranged from 37.1% to 45.6% within normal limits. In AUB, elevated ratios were more common, especially under high stress-indicating reduced HPA axis regulation in response to psychological stressors, which may contribute to more negative health outcomes. In ado-

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lescents with OM, normal or decreased cortisol/DHEA-S ratios predominated across all stress levels, suggesting a more adequate adaptive response to psychological stress.

The stress level correlated with physical and sexual development. Among girls with AUB and normal or low BMI, moderate stress predominated, while in those with excess body weight, low stress was 1.3–1.6 times more frequent. In OM, as in AUB, a moderate stress level was most typical for girls with physiological BMI, and unlike AUB, the same pattern was observed in those who were overweight. In girls with body weight deficit, high stress was dominant. Among adolescents whose sexual development corresponded to or exceeded their chronological age, various stress levels (low, moderate, high) occurred with nearly equal frequency. For girls with delayed sexual development – both with AUB and OM – moderate stress was the most characteristic.

The authors guarantee the absence of a conflict of interest.

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