

FEATURES OF STEROID HORMONE LEVELS IN GIRLS WITH MENSTRUAL CYCLE DISORDERS AND MENTAL HEALTH DISORDERS

INTRODUCTION

Reproductive health of women is a crucial factor for addressing the demographic parameters of contemporary society and preserving its socioeconomic potential. Quite often, the initial signs of disturbances in the functioning of the female reproductive system are attributed to adolescence due to disruptions in the formation of connections within the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal complexes, which collectively constitute a system responsible for the development of a young girl into a future mother. Correcting these disturbances that arise during adolescence is the most effective way to ensure and maintain a woman's fertility. Puberty is the process through which reproductive competence is achieved. Sexual maturation is best regarded as one of the stages in the ongoing process of growth and development, which commences during pregnancy and continues throughout a woman's reproductive life, accompanied by hormonal changes [1–4].

Today, the characteristics of menstrual function in adolescent girls are considered one of the fundamental physiological indicators of health [5–8].

Regular menstrual cycles reflect the normal functioning of the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal systems. The most common cause of menstrual dysfunction is disturbances in the coordinated functioning of these axes, which, in turn, may contribute to various mental health issues [9–11]. The timing of sexual maturation, physical characteristics of pubertal development, and hormones are closely interconnected, and all of these factors can individually contribute to the risk of developing mental health disorders [12–14]. It is believed that testosterone, dehydroepiandrosterone (DHEA), and estradiol are key hormonal markers of pubertal development, which have an impact on cognitive functions. In girls, DHEA is the steroid with the highest androgenic activity. There is also a suggested link between DHEA levels and anxiety states. DHEA protects psychological well-being from the detrimental effects of elevated cortisol levels [15–17]. The complex interaction between cortisol and dehydroepiandrosterone sulfate (DHEA-S) is crucial for maintaining the balance of the stress

system [18–21]. The rationale for studying DHEA and cortisol together is supported by physiological data on the coordinated synthesis and release of these hormones in the adrenal glands and their opposing physiological actions [22, 23].

There is limited information available regarding these interactions in adolescents with menstrual dysfunction.

Objectives of the study: to investigate the peculiarities of the steroid hormone status in girls with menstrual function disorders, depending on comorbid psychopathology.

MATERIALS AND METHODS

A total of 174 girls aged 11–17 years with menstrual function disorders (78 with abnormal uterine bleeding (AUB) and 96 with oligomenorrhea (OM)) who were undergoing treatment at the Pediatric Gynecology Department of the SI "Institute of Health of Children and Adolescents of the NAMS of Ukraine" were examined. The comparison group consisted of 35 girls of the same age with a normal menstrual cycle who were examined during the early follicular phase.

The diagnosis of psychopathology was based on the clinical picture at the time of examination and corresponded to the ICD-10 criteria for neurasthenia (F48), depressive neurotic disorder (F34.1 – dysthymia), and anxious-depressive disorder (F41.2). Exclusion criteria included manifest psychoses (organic/endogenous); severe somatic illness in a decompensated stage, the presence of a current organic central nervous system disorder, disorders of hallucinatory-mare-like registry in the status at the time of examination; intellectual disability (F70); and oligophrenic-like defect within the framework of childhood-type schizophrenia (F20.58).

The complex laboratory examination included the determination of the plasma levels of estradiol (E_2), testosterone (T), and cortisol (C) in the morning, using the enzyme immunoassay method on the "Rayto RT 2100C" analyzer (Germany) with standard commercial kits from "Best Diagnostics" (Kyiv, Ukraine). DHEA-S was analyzed using an immunoassay kit from "Astra Biotech" (Germany). The C/DHEA-S ratio was calculated using the unprocessed, raw values. The morning cortisol value was divided by the morning DHEA-S value to obtain the initial ratio.

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DOI: <http://dx.doi.org/10.18370/2309-4117.2024.71.39-44>

The research materials underwent statistical analysis. Differences between the compared samples were determined using non-parametric methods (Wilcoxon-Mann-Whitney test, Fisher's exact test, χ^2). The critical level of significance for testing the statistical hypotheses was set at $p < 0.05$.

The study followed the principles of the World Medical Association Helsinki Declaration, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, and relevant legislation of Ukraine. The research protocol was approved by the Committee on Bioethics and Deontology of the SI «Institute of Health of Children and Adolescents of the National Academy of Medical Sciences of Ukraine» (protocol No. 1 from 10.01.2023). All patients and their parents provided informed written consent to participate in the clinical study.

RESULTS AND DISCUSSION

The individual comparative analysis of steroid hormones showed that normal levels of E_2 , T, and C in serum were in most girls with AUB, regardless of the presence of comorbid psychopathology. The proportion of girls with DHEA-S levels within physiological limits did not significantly differ depending on the presence of comorbid psychopathology and ranged from 33.3% in adolescents without psychopathology to 50% in girls with AUB and depression. The C/DHEA-S ratio within normal limits did not show significant differences in girls, regardless of comorbid psychiatric pathology.

A similar situation was observed for hormonal levels in girls with OM. In the vast majority, fluctuations of E_2 , T, and C remained within the physiological range. The percentage of patients with reference values of DHEA-S ranged from 48 to 58%. The proportion of girls with normal C/DHEA-S ratios was lowest with comorbid depressive states (44.4%) and increased in patients without psychopathology (50%).

The percentage of patients with elevated or reduced E_2 levels showed probable differences depending on comorbid psychopathology. In girls without mental health deviations, AUB was more often associated with elevated estradiol levels. In contrast, hypoestrogenia prevailed in cases with comorbid depressive states ($up = 1.65$; $p < 0.05$) (Fig. 1).

The study of the T/ E_2 ratio (hyperandrogenism index (HI)) in adolescents with AUB revealed that its deviations were more common in girls without comorbid mental disorders. Changes in this coefficient were less frequent in patients with neurotic disorders and depressive states (54.6 versus 25.7% for neurotic disorders and 19.0% for depression; $u_p = 2.21$; $p_1 < 0.03$, $u_p = 2.49$; $p_2 < 0.006$). It is worth noting that a significant decrease in HI occurred more often. Although up to 10% of girls had elevated HI levels. So hyperandrogenism was observed in some patients. Given that in the absolute majority of girls with AUB, the estradiol level was within the reference range, and changes in testosterone levels mainly occurred due to slight increases, the increase in HI can be interpreted in this cohort of patients as relative hyperandrogenism. On the other hand, reproductive steroids can influence the activating and organizational structure of affective neural networks, thus contributing to the regulation of emotions and behavior [24]. It can be assumed that the disruption of the balance of these hormones contributes to the formation of comorbid psychopathology.

High C levels were observed in 5–8% of AUB patients, whereas low levels were detected 3–6 times more often (from 16 to 30%).

The content of DHEA-S was mostly reduced (Fig. 2). An increase in DHEA-S levels was observed in 5.6–18.5% of cases.

The C/DHEA-S ratio was elevated in more than half of the patients (Fig. 3).

An increase in the C/DHEA-S ratio suggests higher levels of the stress hormone C and lower levels of the «protective» hormone, which may be associated with negative consequences for mental health.

Hypoestrogenia predominated in all patients with OM. The E_2 level was low in almost half of the patients (below the 25th percentile), and it was significantly reduced in 15.5% (below the 10th percentile) (Fig. 4). This occurred 2.3–1.6 times more often in comorbid depressive states.

The percentage of girls with reduced E_2 levels among patients with AUB significantly increased in adolescents with psychological pathology. The percentage of girls with with hypoestrogenia among patients with OM showed no significant difference based on the presence or absence of comorbid psychological pathology.

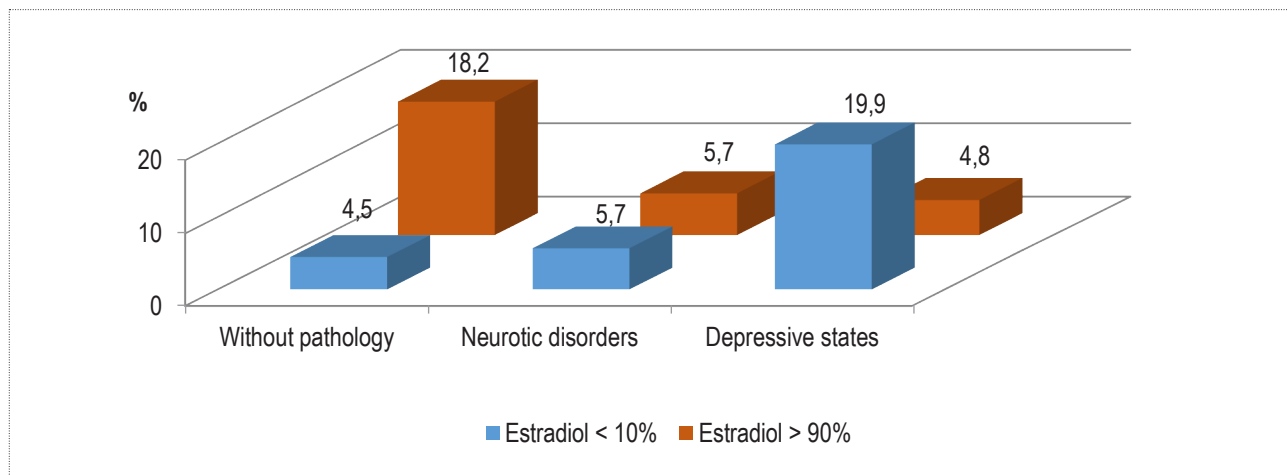


Figure 1. Percentage of girls with AUB with different E_2 levels depending on psychopathology

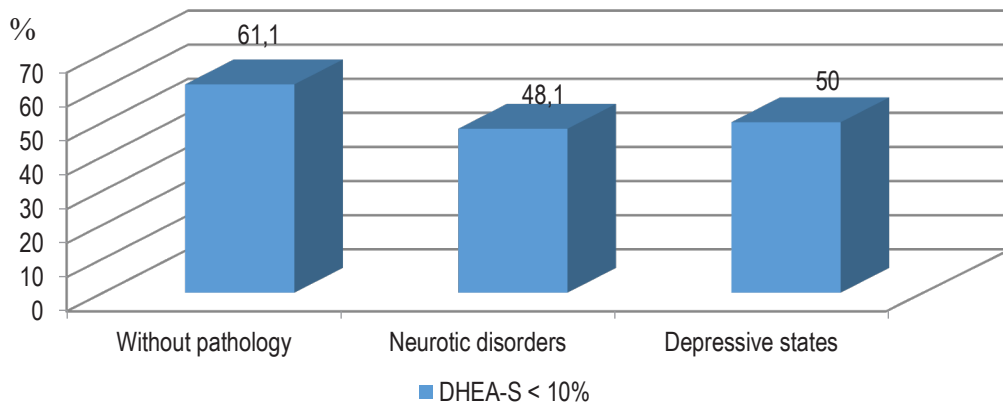


Figure 2. Percentage of AUB patients with low DHEA-S levels by comorbid psychopathology

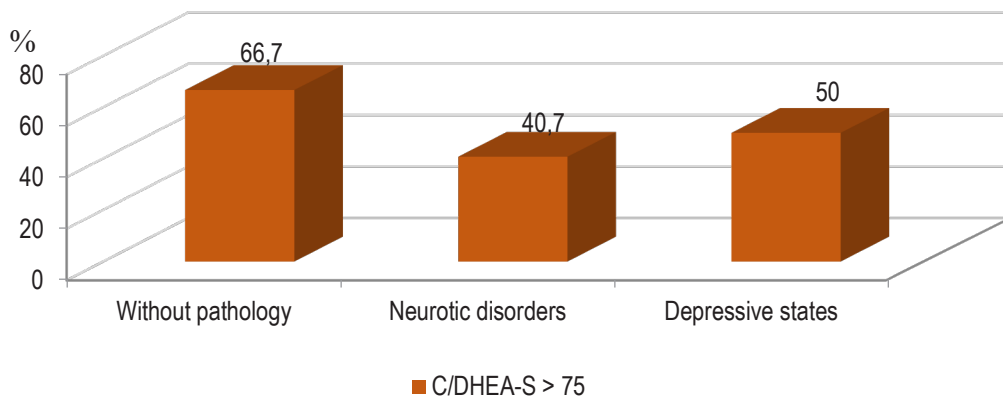


Figure 3. Percentage of AUB patients with high C/DHEA-S ratios depending on psychopathology

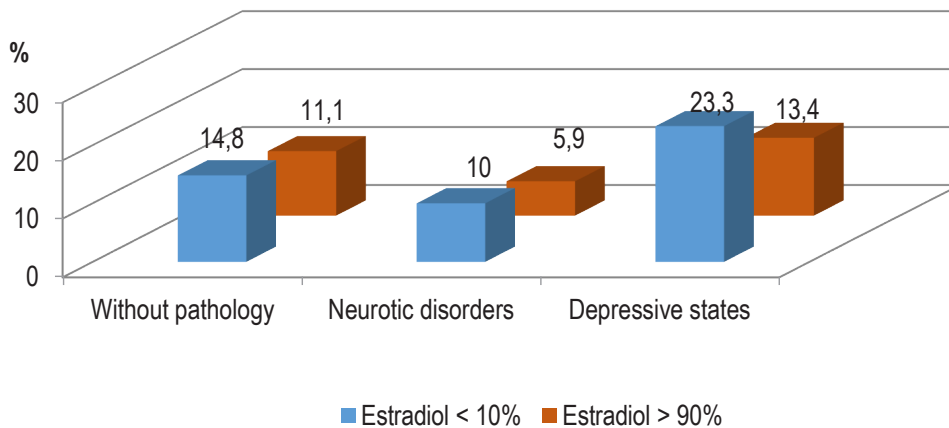


Figure 4. Percentage of girls with OM and different E₂ levels depending on psychopathology

An increase in the HI in adolescents with OM was observed much more frequently than in AUB, especially when there was psychopathology, particularly in comorbid depressive states. There is literature evidence indicating that T and E₂ can be considered as neurosteroids. Considering their neurotrophic role, neurosteroids are of increasing interest in psychiatry and neurology research. It is assumed that testosterone plays a role in

depressive symptoms [25]. Decreases in the HI occurred significantly less frequently than in patients with AUB, except patients with depressive states (Fig. 5).

Elevated C levels are encountered 2.5 times more frequently than reduced levels in adolescents with OM without comorbid psychopathology, although this did not reach statistical significance (Fig. 6). In the presence of comorbid neu-

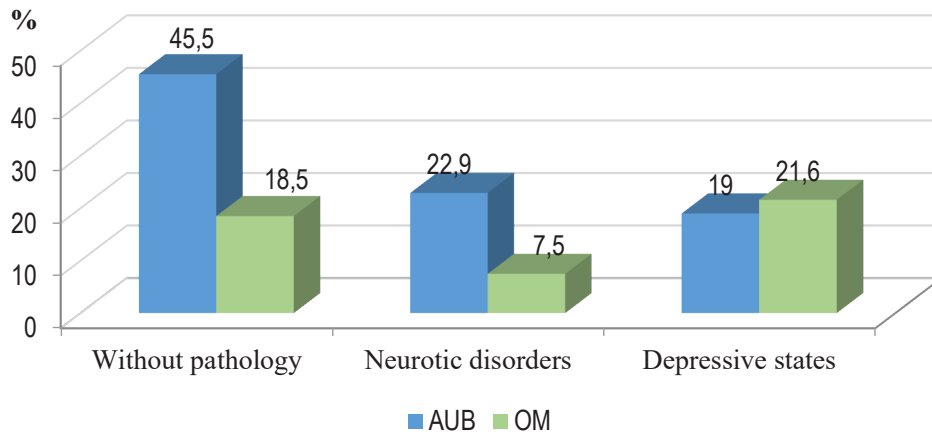


Figure 5. Percentage of girls with reduced HI based on psychopathology

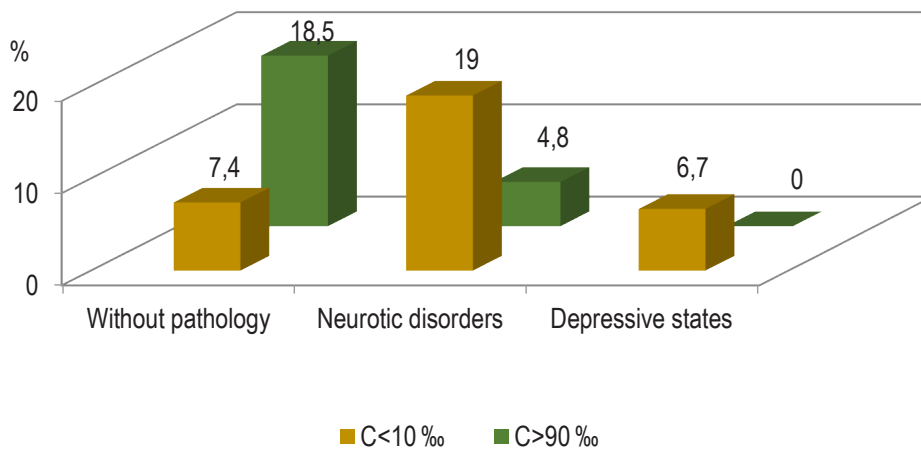


Figure 6. Percentage of patients with OM and C level abnormalities depending on psychopathology

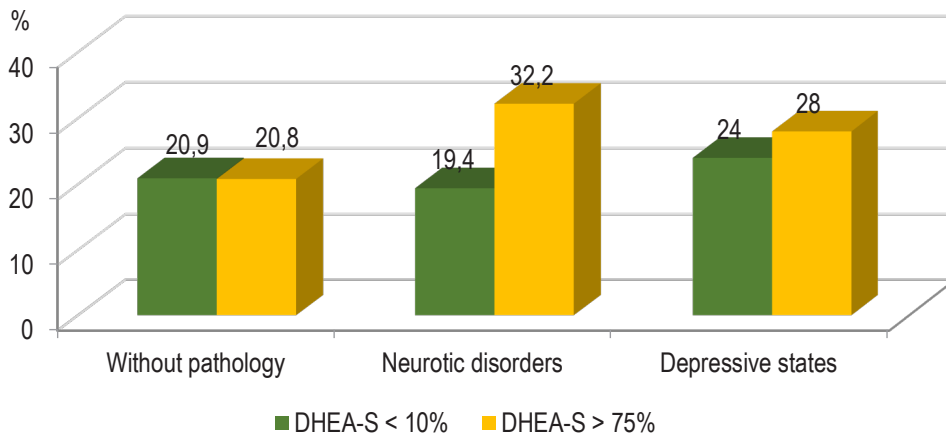


Figure 7. The percentage of patients with OM and deviations in DHEA-S levels depending on psychopathology

rotic disorders and depression, the number of girls with reduced C levels increased relative to those with elevated levels ($u_p = 2.11$; $p < 0.03$).

Menstrual function disorders in half of adolescents with OM are accompanied by deviations in the DHEA-S level. Changes in DHEA-S concentration in the patients with AUB mainly involved its reduction, in the patients with OM both increases and decreases in DHEA-S levels occurred evenly (Fig. 7).

Currently, menstrual function disorders are considered in terms of deviations in the coordinated activity of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal systems. DHEA and C are the most common adrenal gland hormones in fetuses and adult humans, released as the final products of a tightly coordinated endocrine response to stress. Together, they mediate short-term and long-term stress responses and provide the

physiological and behavioral adjustments necessary to maintain homeostasis.

The C/DHEA-S ratio indicates a balance in the secretion of C and DHEA-S. DHEA-S protects the body from the harmful effects of prolonged cortisol exposure. Therefore, high C to DHEA-S values suggests an imbalance that can predispose individuals to the development of psychopathology or various behavioral problems. Changes in this ratio were registered in more than half of the girls with OM. In contrast to patients with AUB, where an increase in C/DHEA-S ratio predominated, deviations in this ratio occurred equally in both directions in patients with OM, toward both increased and decreased values.

Comparing girls with menstrual cycle disorders with or without comorbid mental disorders showed that the C/DHEA-S ratio was significantly increased in patients without comorbid pathology compared (for AUB: $u_p = 1.74$; $p < 0.04$). In the case of OM this difference was not statistically significant. Thus, menstrual disorders themselves are a significant stressor for girls. This ratio slightly decreases when menstrual cycle disorders combined with neurotic and depressive states, which does not contradict the postulates of general adaptation syndrome.

Analyzing the duration of menstrual cycle disorders at the time of seeking medical help, it was found that girls with comorbid mental health problems were more likely to have menstrual disorders lasting 2 years or more. All of this indicates the existence of individual differences in the functioning of the hypothalamic-pituitary-adrenal system by Hans Selye.

Therefore, we have determined that AUB in one-third of the patients occurred against the backdrop of hypoestrogenemia. Hyperestrogenic forms of AUB were observed in 6-18% of adolescents, with a higher incidence in girls without psychopathology. In the majority of adolescents (90-95%), bleeding occurred with normal T levels. Increased T/E₂ ratio were sporadically observed, while its decrease occurred significantly more frequently, especially in girls without comorbid psychopathology ($u_p = 1.77$; $p_1 < 0.04$ compared to those with neurotic disorders; $u_p = 1.91$; $p_2 < 0.03$ compared to adolescents with depression).

Lower levels C predominated over higher levels, and this predominance gained statistical significance in cases of bleeding accompanied by depression ($u_p = 2.24$; $p < 0.01$).

The levels of DHEA-S, a major adrenal hormone involved in emotional regulation, were reduced in most girls. In contrast, the C/DHEA-S ratio was increased in the majority of cases, suggesting a link between the onset of uterine bleeding and stress.

OM in nearly half of the girls occurred against the backdrop of hypoestrogenemia and was significantly more prevalent than in cases with AUB ($u_p = 2.27$; $p < 0.01$). Hyperestrogenemia accompanied OM with the same frequency as AUB (from 6 to 13%). The T concentration remained within normal limits for 90% of the patients. An increased T/E₂ index was observed more frequently than in adolescents with AUB, and it reached statistical significance in patients with psychiatric disorders ($u_p = 2.36$; $p < 0.009$). The C concentration was more often reduced, and this reduction became statistically significant in cases of mental comorbidity ($u_p = 2.11$; $p < 0.02$). The adrenal hormone DHEA-S in most girls showed deviations in its level, both towards elevation and reduction, in contrast to patients

with AUB where a decrease in this hormone predominates. The C/DHEA-S ratio also displayed unique characteristics. Increased ratios were noted significantly less frequently than in AUB cases, while decreased ratios occurred somewhat more frequently than in AUB cases, suggesting a higher degree of coordinated synthesis and release of these hormones in cases with OM.

In summary, adolescents with AUB, especially with psychopathology, experienced more significant hormonal dysregulation than adolescents with OM, emphasizing the critical role of hormone interactions in the response to stressors.

CONCLUSIONS

1. Specific hormonal features in adolescent girls with menstrual function disorders were identified, dependent on the type of disorders and the presence of comorbid psychopathology.

2. Hypoestrogenic forms of menstrual disorders were significantly more likely to be observed in girls with OM. Importantly, the percentage of adolescents with hypoestrogenemia significantly increased in cases of comorbid depressive states, both in patients with AUB and OM. The T/E₂ ratio tended to increase in patients with OM and comorbid depression. In adolescents with AUB decreased T/E₂ ratio was significantly more likely to occur than in patients with OM ($p < 0.02$), with a significant reduction in those with depressive states.

3. Increased C/DHEA-S ratio reflecting the balance of the stress system, occurred significantly more often in cases of AUB. This suggests more pronounced stress manifestations compared to adolescents with OM and a higher adaptability of the girls' bodies with OM.

Conflict of interest

There is no conflict of interest.

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Objectives of the study: to investigate the peculiarities of the steroid hormone status in girls with menstrual function disorders, depending on comorbid psychopathology.
Materials and methods: A total of 174 girls with menstrual function disorders (78 with abnormal uterine bleedings (AUB) and 96 with oligomenorrhea (OM)) were examined. The diagnosis of psychopathology was determined based on the clinical presentation at the time of examination. The comparison group consisted of 35 girls with a normal menstrual cycle. The laboratory examination included the assessment of estradiol, testosterone, cortisol (C), and dehydroepiandrosterone sulfate (DHEA-S) levels. The C/DHEA-S ratio was calculated using the unprocessed raw values.
Results: Menstrual function disorders are often associated with hypoestrogenemia, a prevalent phenomenon. It was observed in almost a third of patients with AUB, whereas in girls with OM this number was significantly higher. Significant reduced values are found in girls with accompanying depressive states, especially in cases of AUB and OM. In instances of AUB and OM, the number of individuals with elevated levels of testosterone increased by 1.97–2.2 times in the presence of psychopathology. DHEA-S in patients with AUB was reduced in more than half of the girls, while in patients with OM it varies evenly in both directions, regardless of the presence or absence of psychopathology. A C level were more often reduced than increased, and achieves statistical significance when OM combined with neurotic disorders and AUB combined with depressive states. The C/DHEA-S ratio, as a stress indicator, was statistically significantly elevated in patients with AUB. This may suggest more pronounced manifestations of stress in patients with AUB than in girls with OM and a higher adaptability of the girls' bodies with OM.
Conclusions: Thus, the understanding of the role of reproductive steroids in the development of menstrual function disorders during adolescence has been deepened. Distinctive features of their interrelations in the presence of psychopathology have been identified. The impact of cortisol and DHEA-S, as well as C/DHEA-S ratio, on mental well-being in endocrine-related gynecological disorders in girls has been established
Keywords: reproductive hormones, cortisol, dehydroepiandrosterone sulfate, cortisol/DHEA-S ratio, adolescent girls, menstrual function disorders, mental deviations.

ОСОБЛИВОСТІ РІВНЯ СТЕРОЇДНИХ ГОРМОНІВ У ДІВЧАТ ІЗ ПОРУШЕННЯМИ МЕНСТРУАЛЬНОГО ЦИКЛУ ТА РОЗЛАДАМИ ПСИХІЧНОГО ЗДОРОВ'Я

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Мета дослідження: вивчення особливостей статусу стероїдних гормонів у дівчат із порушеннями менструальної функції залежно від психопатології.
Матеріали та методи. Обстежено 174 дівчинки з порушеннями менструальної функції (78 – з аномальними матковими кровотечами (АМК) і 96 – з олигоменореєю (ОМ)). До контрольної групи увійшли 35 дівчаток з нормальним менструальним циклом.

Діагноз психопатології визначався на підставі відповідності клінічної картини на момент обстеження. Комплексне лабораторне обстеження передбачало визначення рівня естрадіолу, тестостерону, кортизолу (К), дегідроепіандростерона сульфату (ДГЕА-С). Співвідношення К/ДГЕА-С розраховувалося з використанням необроблених вихідних значень.

Результати. Порушення менструальної функції часто супроводжуються гіпоестрогенією. При АМК цей розлад виявляє майже в третині хворих, а при ОМ – набагато частіше. Найбільший відсоток знижених показників був у підлітків з коморбідними депресивними станами. При АМК і ОМ частка дівчаток із високим рівнем тестостерону збільшувалася в 1,97–2,2 рази за наявності психопатології. Рівень ДГЕА-С при АМК у понад половини пацієнток був знижений, а при ОМ він рівномірно підвищувався або знижувався, незалежно від наявності чи відсутності психопатології. Вміст К частіше був знижений, ніж підвищений, а при поєднанні ОМ з невротичними розладами й АМК із депресивними станами це мало статистичну значущість. Співвідношення К/ДГЕА-С як ознака наявності стресу статистично значуще було вищим у хворих з АМК. Це може свідчити про більш виражені прояви стресу в пацієнток з АМК, ніж з ОМ, і більшу адаптованість організму дівчаток з ОМ.

Висновки. Проведене дослідження дозволило поглибити уявлення про роль репродуктивних стероїдних гормонів у розвитку порушень менструальної функції в підлітковому віці. Було виявлено особливості їх взаємодії за наявності психопатології. Доведено вплив К і ДГЕА-С та співвідношення К/ДГЕА-С на психічний стан при ендокринозалежних гінекологічних розладах у дівчат.

Ключові слова: репродуктивні гормони, кортизол, дегідроепіандростерона сульфат, співвідношення кортизол/ДГЕА-С, дівчата-підлітки, порушення менструальної функції, психічні відхилення.