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THE ROLE OF DEHYDROEPIANDROSTERONE IN THE FORMATION OF FUNCTIONAL HYPOANDROGENISM, ENDOMETRIOSIS AND WOMEN'S SEXUAL HEALTH DISORDERS

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The study aims to evaluate the role of the DHEA-S (dehydroepiandrosterone) as an indicator of female sexual dysfunction (FSD), in hypoandrogenism and endometriosis in women of reproductive age.

Materials and methods. Totally, 215 women of reproductive age were included in the study and were divided into 3 groups: Group A (n=114) – women with early pregnancy loss in the anamnesis with/without FSD; Group B (n=77) – women with FSD and hypoandrogenism with/without endometriosis; Group C (n=24, control) – healthy women. DHEA-S, free testosterone (fT), and estradiol levels were evaluated. The steroid hormones blood tests were conducted on the 5th to 7th day of the physiological or induced menstrual cycle.

Results. DHEA-S levels in group A women with FSD, corresponded to its deficit and were statistically significantly lower than those without FSD ($p < 0.001$). In women with FSD, estradiol levels were statistically significantly lower (deficiency) vs. without FSD (normal ranges), $p<0.001$. The median levels of fT in group A without FSD were at optimal ranges, while with FSD, they were at deficiency ranges, $p<0.001$. Levels of fT statistically significantly correlated with DHEA-S ($r=0.32$; $p=0.004$), which was also confirmed by linear regression ($adjR^2 = 0.087$; $p=0.005$). In Group B women with FSD +/- endometriosis, a significant difference in estradiol, fT, and DHEA-S values was not found: $p=0.24$, $p=0.05$, and $p=0.05$ respectively. In both subgroups, the average hormone values corresponded to: estradiol, fT – deficiency; DHEA-S – deficit.

Conclusions. The presence of FSD in isolated and combined forms with endometriosis is accompanied by a deficiency of estradiol, free testosterone and a deficiency of DHEA-S, which is clinically accompanied by a change in the structure of the mucous membranes, hypolubrication and dyspareunia. The diagnosis of androgen deficiency in women is of clinical importance, since the restoration of the physiological level of androgens is important for the prevention and treatment of miscarriage and disorders of a woman's sexual health.

Key words: dehydroepiandrosterone, testosterone, female sexual dysfunction, endometriosis.

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РОЛЬ ДЕГІДРОЕПІАНДРОСТЕРОНУ У ФОРМУВАННІ ФУНКЦІОНАЛЬНОЇ ГІПОАНДРОГЕНІЇ, ЕНДОМЕТРІОЗУ ТА ПОРУШЕННЯ СЕКСУАЛЬНОГО ЗДОРОВ'Я ЖІНОК

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Мета дослідження – оцінити роль дегідроепіандростерона (ДГЕА-С) як індикатора жіночої сексуальної дисфункції (ЖСД), при гіпоандрогенії, ендометриозі у жінок репродуктивного віку. Усього в дослідження було включено 215 жінок репродуктивного віку, які були розподілені на 3 групи: група А (n=114) – жінки з ранньою втратою вагітності в анамнезі з/без ЖСД; група В (n=77) – жінки з ЖСД гіпоандрогенією з/без ендометріозом; група С (n=24, контроль) – здорові жінки.

Результати. Рівень ДГЕА-С у жінок групи А з ЖСД відповідав його дефіциту та був нижчим порівняно з жінками без ЖСД ($p<0,001$). У жінок із ЖСД рівні естрадіолу були значуще нижчими (дефіцит) порівняно з жінками без ЖСД (нормальні діапазони), $p<0,001$. Середні рівні вільного тестостерону (вТ) у групі А без ЖСД були в оптимальних діапазонах, тоді як з ЖСД вони були в межах дефіциту, $p<0,001$.

Висновки. Діагностика андрогенної недостатності у жінок має клінічне значення, оскільки відновлення фізіологічного рівня андрогенів важливе для профілактики та лікування невиношування вагітності та розладів сексуального здоров'я жінки.

Ключові слова: дегідроепіандростерон, тестостерон, жіноча сексуальна дисфункція, ендометріоз.

Introduction. Testosterone is traditionally believed to be the hormone that determines fertile women's "reproductive health". This statement is not entirely accurate. Many authors suggest that dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most common steroids and play a crucial role in both men's and women's hormonal homeostasis as precursors of testosterone synthesis. To date, the physiological role of dehydroepiandrosterone (DHEA-S) has been poorly studied [1]. No specific high-affinity physiological DHEA receptor was identified [2].

Steroidogenesis in the human body is an enzyme-associated process [3] (Figure 1).

DHEA is secreted by the adrenal glands and metabolizes in the brain, liver, kidneys, and gonads, to 5-androstene-3β,17β-diol, 4-androstene-3,17-dione, testosterone, estrogen, and other biologically active steroids depending on the tissue [4]. DHEA is considered not only as a potential androgen but also a depo for all sex hormones [5].

The DHEA mostly circulates in the blood in the sulfated form (DHEA-S) and is freely interconverted by extra-adrenal sulfotransferase and sulfatase activity [6]. More than 30% of total androgen in men and more than 90% of estrogen in postmenopausal women are formed due to peripheral conversion of DHEA to DHEA-S [4].

In addition, in the brain, DHEA and/or its metabolites may act as neurosteroids through membrane receptors such as gamma-aminobutyric acid alpha and N-methyl-D aspartate receptors or are thought to interact with the peroxisome proliferator-activated receptor (PPARα), pregnane. The X receptor, androstanol, or estrogen receptor beta have central and metabolic effects [7; 8]. Studies have shown a role for DHEA in the immune system or in improving the immune response with aging, but no clinical outcome studies have been reported [9].

Levels of DHEA and DHEA-S in plasma depend on age, physiological status, and genetics [10; 11]. Secretion of DHEA and its sulfate progressively increases during adrenarche in children of both genders [6]. The leading role of DHEA in the development of adrenarche has been established It is responsible for the pubic and axillary hair growth, development and maintenance of immune competence and brain maturation [12]. Its maximum values are noted at the age of 20 to 30 years and significantly decrease to 20% at the age of 70 years and to 5% – at the age of 85–90 years [6].

Recently, interest in DHEA has been driven by its beneficial effects on women's health [6]. A decrease in the level of DHEA and DHEA-S in blood serum during aging leads to a decrease in the formation of powerful androgens and estrogens in peripheral tissues, which are believed to be involved in the pathogenesis of some age-related diseases [13; 14].

In our opinion, studies of the relationship between DHEA and mortality in disabled women of the older age group turned out to be interesting. The researchers investigated the relationship between serum DHEA-S levels and 5-year mortality in a cohort of 539 disabled women aged 65–100 who participated in the Women's Health and Aging I (WHAS I) study. The Cox proportional hazard model was used in the work, which made it possible to calculate mortality risks, adjusted for many parameters, for DHEA-S quartiles, and continuously for DHEA-S, considering the nonlinear relationship [14]. The researchers found a U-shaped relationship between the level of DHEA-S and mortality. After adjustment for multiple covariates, women in the upper and lower quartiles of the DHEA-S had more than 2-fold higher 5-year mortality than those in the middle quartiles (HR 2.15; 95% CI 1.17–3, 98 for the upper quartile and 2.05% CI, 1.27–3.32 for the lower quartile, each compared with the third quartile). Women with higher levels of DHEA-S tended to have higher mortality from cancer, while those with lower levels of DHEA-S tended to have higher mortality from cardiovascular disease [13; 15].

Considering such interesting and multifaceted effects of DHEA on the steroid environment of the human body, we

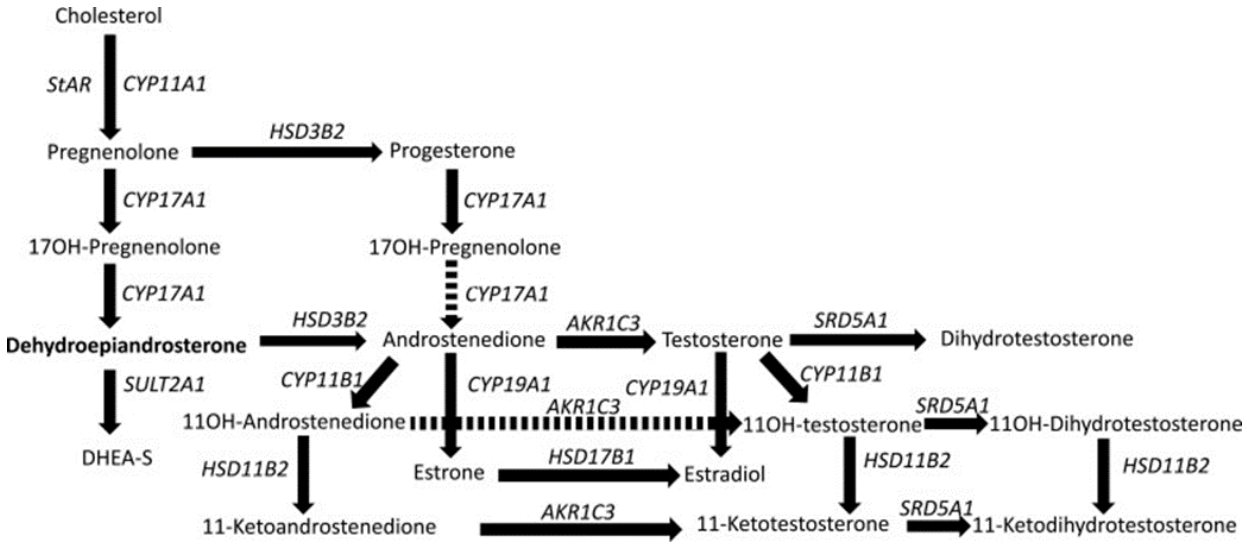

Fig. 1. Scheme of the stages of cholesterol metabolism in steroidogenesis: the main enzymes and stages of the conversion of cholesterol to DHEA-S and androstenedione to testosterone and estradiol in the adrenal gland; CYP (cytochrome 450); HSD (hydroxysteroid dehydrogenase), steroid 5a-reductase [3]

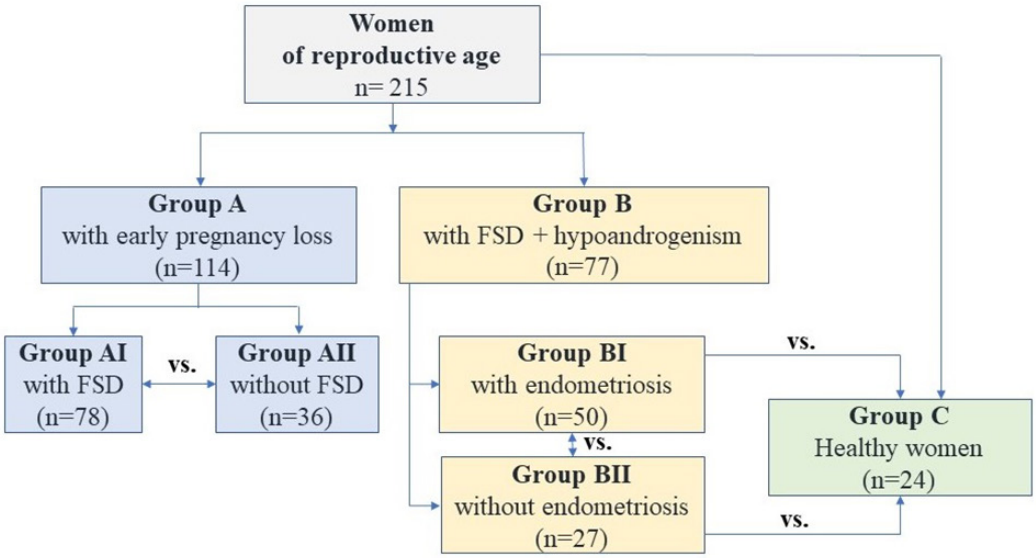

Fig. 2. Design of the study – patients grouping in the study (FSD – female sexual dysfunction)

Table 1

Referral levels of studied hormones

Parameter, U (CI)	Normal	Deficit	Deficiency	Optimal
DHEA-S, mg/dL	280–500	<150	150–280	-
fT, pg/mL	0.5 — 4.2	<0.5	0.5–1.5	1.5–3.8
Estradiol, pg/mL	19.5–144.2	19–30	30–70	80–110

Note! DHEA-S – Dehydroepiandrosterone sulfate; fT – free testosterone

monitored the indicators of DHEA-S in such conditions, which were clinically accompanied by hypolubrication, decreased libido, as the main markers of female sexual dysfunction in the fertile age.

The study aims to evaluate the role of the DHEA-S as an indicator of female sexual dysfunction (FSD), and hypoandrogenism in reproductive-age women.

Materials and methods.

Study Design and Population.

Study Design – a cohort prospective a single-center.

The study was performed in the Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of the Ministry of Health of Ukraine in 2021–2024.

Totally, 215 reproductive-age women were included in the study and were divided into 3 groups: Group A (n=114) – women with early pregnancy loss in the anamnesis (subgroup AI (n=78) – with FSD and subgroup AII (n=36) – without FSD); Group B (n=77) – women with FSD (subgroup BI (n=50) – hypoandrogenism with endometriosis, subgroup BII (n=27) – hypoandrogenism without endometriosis; Group C (n=24, control) – healthy women (Figure 2).

Inclusion criteria for Group A: women of reproductive age (18–45 years), early pregnancy loss in the anamnesis, FSD, hypoandrogenism (free testosterone < 1.5 pg/mL), informed consent.

Inclusion criteria for Group B: women of reproductive age (18–45 years), FSD, hypoandrogenism (free testosterone < 1.5 pg/mL), confirmed endometriosis, informed consent.

Non-Inclusion criteria: malignant oncogynecological pathology in anamnesis or at the moment of study, malignant extragynecological oncopathology in anamnesis or at the moment of the study, acute gynecological infections at the moment of study.

Exclusion criteria: refusal of the patient to participate in the study at any stage, the impossibility of follow-up.

The primary endpoints: levels of DHEA-S.

The secondary endpoints: levels of free testosterone (fT), estradiol.

Female Sexual Dysfunction Assessment.

Female Sexual Dysfunction was diagnosed with the Female Sexual Dysfunction Index (FSDI) Questionnaire Calculator – Female Sexual Dysfunction was present if FSDI Score was ≤ 26.55 (https://www.thecalculator.co/health/Female-Sexual-Function-Index-(FSFI)-Questionnaire-Calculator-949.html).

Biochemical Measurements.

The steroid hormones blood tests were conducted on the 5th to 7th day of the physiological or induced menstrual cycle. Hormone levels were measured by immunochemiluminescent assay (Access analyzer-Beckman Coulter, USA). Referral levels are in Table 1.

Statistical Analysis.

Statistical analysis was processed using a specialized package of statistical program SPSS 25.0 (StatSoft Inc., USA). Methods of non-parametric statistics were used for statistical processing of the obtained data, since the distribution of values of the majority of indicators differed from the normal one. Median with 25% and 75% (Me [QI; QIII]) was used to value a data set. The Mann-lWhitney U-test

was used to assess the statistical significance of the difference in the two independent groups. A statistically significant difference between the data was considered at a probability of validity of the null hypothesis of less than 5% ($p<0.05$). Kruskal-Wallis test with Bonferroni correction was used for multiple comparisons of independent samples. A statistically significant difference between them was considered at $p < 0.0085$. Spearman's coefficient was used for correlation analysis. A statistically significant difference between the data was considered as $p<0.05$.

Ethical standards. The study was approved by the Ethics Committee of the Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of the MoH of Ukraine (Protocol No. 19 from March 22nd, 2021). The study was performed following the principles of biomedical ethics – the European Convention on Human Rights, the European Convention "On the Protection of Human Rights and Dignity in Connection with the Use of Advances in Biology and Medicine", the Constitution of Ukraine, and the current Health Care legislation of Ukraine.

Results. The hormone levels in Group A women are presented in Table 2.

Evaluating the DHEA-S in women with FSD and early pregnancy loss in the anamnesis (Group AI) compared to women without FSD (Group AII), we revealed that this indicator had a statistically significant difference ($p <0.001$). In Group AI median values of DHEA-S corresponded to its deficit and in Group AII – to normal ranges.

Testing of the estradiol level in the studied A subgroups showed that in women with FSD and early pregnancy loss, its levels were statistically significantly lower (deficiency) vs. without FSD (normal ranges), $p<0.001$.

The median levels of fT in Group AII were at optimal ranges, while in Group AI, they were at deficiency ranges, $p<0.001$.

Further correlative analysis (Spearman's coefficient) showed that fT levels statistically significantly correlated with DHEA-S ($r=0.32$; $p=0.004$). A statistically significant correlation between estradiol levels and DHEA-S was not revealed ($r=0.14$; $p=0.209$).

Linear regression confirmed a statistically significant correlation between fT levels and DHEA-S ($adjR^2 = 0.087$; $p=0.005$), i.e. decreasing fT levels correlates with decreasing DHEA-S.

The hormone levels in groups B and Group C women are presented in Table 3.

Analyzing (Kruskal-lWallis test) results of hormones tests in groups B and C, a statistically significant difference was revealed between the groups in all parameters, $p<0.001$. However, a posteriori analysis (Mann-lWhitney test) showed no statistically significant difference in estradiol, fT, and DHEA-S values between subgroups B: $p=0.24$, $p=0.05$, and $p=0.05$ respectively. Moreover, in both subgroups, the average values of the studied indicators corresponded to: estradiol, fT – deficiency; DHEA-S – deficit. Whereas in the healthy women group, these indicators corresponded to the normal values and were statistically significantly higher vs. subgroups BI and BII (Mann-lWhitney test) – $p<0.001$, $p<0.001$, and $p<0.001$, respectively.

Correlation analysis didn't show a statistically significant correlation between DHEA-S levels and fT, estradiol in both groups B: Group BI – DHEA-S and fT $r=0.095$, $p=0.51$; DHEA-S and estradiol $r = -0.18$, $p=0.23$; Group BII – DHEA-S and fT $r=0.24$, $p=0.23$; DHEA-S and estradiol $r = -0.18$, $p=0.36$.

Discussion. There is a hypothesis of antagonism between cortisol (stress hormone) and DHEA-S. It is believed that DHEA counteracts the action of cortisol and produces a real anti-cortisol effect. The decrease in DHEA-S may be associated with depression, anxiety, and hypercortisolemia [10; 16].

The obtained data in our study may indicate that the presence of FSD in women with early pregnancy loss was associated with hypoandrogenism, first of all, caused by decreased levels of DHEA-S, which is a prehormone of testosterone. Thus, deficit or deficiency of DHEA-S can be one of the clinical factors of unfavorable gestational prognosis in women with early pregnancy loss and hypoandrogenism. Women with FSD associated with hypoandrogenism in our study had anxiety-depressive conditions which could be provoked by stress factors and may leaded to pregnancy fails. In our opinion, management of such category women should be directed to primary correction of DHEA-S levels. However, further research should be conducted to confirm such a causal correlation. Whereas for women with normal hormonal parameters and the absence of FSD, we suggest con-

Table 2

Average values of hormone levels in women of Group AI and Group AII

Parameter	Group AI (n=78)	Group AII (n=36)	p-value
DHEA-S	51.20 [37.35; 54.33]	342.15 [302.55; 397.35]	<0.001
fT	1.20 [0.70, 1.30]	3.40 [2.95, 3.90]	<0.001
Estradiol	33.85 [32.40; 36.80]	111.70 [98.23; 119.18]	<0.001

Note! Average values are presented as Me [QI; QIII]; groups were compared with Mann-Whitney U-test

Table 3

Average values of hormone levels in women of Groups B and Group C

Parameter	Group BI (n=50)	Group BII (n=27)	Group C (n=24)	p-value
DHEA-S	57.65 [52.2; 66.33]	45.9 [41.1; 65.9]	339.6 [294.7; 393.1]	<0.001
fT	1.1 [0.9; 1.4]	0.9 [0.9; 1.1]	3.1 [2.9;3.2]	<0.001
Estradiol	47.6 [45.3; 51.2]	46.9 [45.2; 48.9]	92.2 [89.5; 98.3]	<0.001

Note! Average values are presented as Me [QI; QIII]; groups were compared with Kruskal-lWallis test

tinuing the diagnostic search to identify the causes of early pregnancy loss with an emphasis on a hidden infectious factor. Moreover, despite the absence of a correlation between DHEA-S levels and fT, estradiol in women with FSD +/- endometriosis, a clinical manifestation of FSD was associated with hormonal disbalance caused by the deficiency of DHEA-S. Further research with a larger sample should be conducted to prove the hypothesis of DHEA-S deficit influence on FSD manifestation in reproductive-age women.

Therefore, we join the opinion of other researchers, who assign a prominent place in the steroid homeostasis of women precisely to the indicators of DHEA and its sulfate. Undoubtedly, the secretion of DHEA-S is mainly under the control of the hypothalamus/pituitary, stimulated by ACTH, but its secretion is modulated by other hormones such as estradiol, prolactin, and IGF-1 [17].

Conclusions

1. Hypoandrogenism with a deficiency of dehydroepiandrosterone and free testosterone contributes to disruption of the process of early gestation due to secondary estrogen deficiency.

2. The presence of FSD in isolated and combined forms with endometriosis is accompanied by a deficiency of estradiol, free testosterone and a deficiency of DHEA-S, which is clinically accompanied by a change in the structure of the mucous membranes, hypolubrication and dyspareunia.

3. The diagnosis of androgen deficiency in women is of clinical importance, since the restoration of the physiological level of androgens is important for the prevention and treatment of miscarriage and disorders of a woman's sexual health.

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Conflict of interest. The authors declare that they have no conflicts of interest.

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