

## 1. Introduction

Reproductive health is a state of complete physical, mental and social well-being, and not just the absence of diseases or ailments in all matters relating to the reproductive system and its functions and processes (United Nations, 1995). The concept of "reproductive health" includes sexual health - a condition that allows a person to fully experience sexual desire and realize it, while receiving satisfaction. Sexual disharmony increases the risk of gynecological diseases by 2–3 times, being one of the main pathogenetic links in the development of chronic inflammatory diseases of the female genital organs, infertility, chronic pelvic pain, tumors, pathological menopause and other disorders [1].

According to the Princeton Consensus [2], female sexual dysfunction can be a sign of androgen deficiency (AD) in women of reproductive age, which necessitates the inclusion of appropriate therapy in fertility rehabilitation protocols for patients with biochemically confirmed AD.

Hormonal changes inevitably affect the physiological regulation of metabolic processes in a woman's body, which, first, is manifested by changes in sexual behavior, menstrual irregularities and decreased fertility. A woman's menstrual cycle brings together processes of changes in the activity of tropic brain structures that control the ratio of gonadotropins and sex hormones, egg maturation and ovulation, and periodic preparation of the endometrium for embryo implantation [3]. The category of patients with ovarian dysfunction (OD) is not the same in composition and is divided into several groups depending on the etiology of the disease. Among the causes of ovarian dysfunction in women of reproductive age are the following: weight loss for weight loss, increased physical activity, stress, etc. [4]. Moreover, in women with an already formed menstrual cycle, more often than not classical (psycho-genic) amenorrhea is formed, but ovarian dysfunction, which is based on impaired folliculogenesis, ovulation, and functioning of

## INHIBIN B AS MARKER OF ANDROGEN INSUFFICIENCY IN WOMEN OF REPRODUCTIVE AGE WITH SEXUAL DYSFUNCTION

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**Abstract: Aim of the research.** The study of the value of inhibin B as a prognostic marker of fertility recovery in women with androgen deficiency and sexual dysfunction.

**Materials and methods.** The study design included 77 women of reproductive age of the main group with sexual dysfunction and androgen deficiency: 45 women with sexual dysfunction and the presence of thyroperoxidase Ak (I-a group), I-b group of 32 women with sexual dysfunction without antibodies to any organism tissues. Control group – 31 healthy women of reproductive age. Diagnostic laparoscopy was performed on an OLYMPUS device using a standard technique. Hormone testing was performed using a Johnson & Johnson Vitros automated system. Blood samples for the study were taken in the morning (8–11) on an empty stomach with venipuncture of the ulnar vein in the 1st phase of the menstrual cycle. Ultrasound test was performed on an Aloka Hitachi apparatus (Japan) with a sensor frequency of 7 MHz. Sexual dysfunction was determined by the Skindex-16V questionnaire. The diagnosis of the examined "Violation of female sexual desire/arousal" was done according to the classification DSM-5. Clinical manifestation of sexual dysfunction was >6 months.

**Results.** The average age of the examined main group was  $32.3 \pm 1.7$  years, in the control group –  $33.9 \pm 1.6$  years. The average age of menarche for women of both groups was 13–14 years (in the main  $13.3 \pm 0.34$ , in the control –  $13.0 \pm 0.23$  ( $p > 0.05$ )). The study of the hormonal background showed a pronounced, statistically significant in compare with healthy women, a decrease in the concentrations of not only estradiol, but also androgens, total testosterone, free testosterone, as well as dehydroepiandrosterone sulfate. Concentrations of sex steroids directly and statistically significantly correlated with the I-a group with concentrations of gonadotropins (luteinizing hormone (LH) and estradiol  $r = 0.67$ ; follicle-stimulating hormone (FSH) and estradiol  $r = 0.64$ ; LH and total testosterone  $r = 0.47$ ; FSH and total testosterone  $r = 0.42$ ; for all  $p < 0.001$ ). LH and DHEA-S  $p = 0.33$  ( $p = 0.02$ ), FSH and DHEA-S  $p = 0.27$  ( $p = 0.03$ ). In group I-b, LH correlation and total testosterone  $r = 0.58$   $p < 0.001$  were noted.

Diagnostic laparoscopy with ovarian biopsy was performed in 12 women of group I-a and group 23 of group I-b. At the same time, the presence of lymphoid infiltration, autoantibodies and complement on growing follicles was established, with primordial and primary follicles intact. Tissue fibrosis, the presence of activated B and T lymphocytes: CD8+, CD4+, natural killer cells (NK), polyclonal plasmocytes, macrophages of primordial and primary follicles were characteristic for group I-b.

**Conclusions.** The level of inhibin B can serve as an early marker of autoimmune ovarian damage in women of reproductive age with female sexual dysfunction. Therapy of androgen deficiency should be carried out taking into account the pathogenesis of the disease.

**Keywords:** androgen deficiency, sexual dysfunction, inhibin B.

the corpus luteum. The unifying for these conditions is absolute or relative progesterone deficiency and the resulting violations of the structural and receptive potential of the endometrium and mucous membranes of the genital tract of women, which leads to either acyclic uterine bleeding, or oligo-opsomenorrhea, sexual dysfunction [5].

Studying the restoration of hormonal support of the reproductive system of women of reproductive age with sexual dysfunction, we noted that even after 6 months of normal menstruation, biochemically in these women, various indicators of LH and FSH secretion were observed in relation to healthy women without sexual dysfunction. Some showed low (within the limits of reference norms) LH indices, while on the contrary, there was a clear tendency towards an increase in FSH and LH.

In women with high FSH and LH, a history of nonspecific inflammatory diseases of the appendages and external-internal endometriosis were observed more often.

Many authors point to the importance of the autoimmune process in the development of a decrease in tolerance to their tissue antigens due to depletion of regulatory T-cells and the activation of autoreactive T-cells as a result of molecular mimicry, leading to the production of antibodies to their own organs or body tissues. Induction of a persistent T-cell response against intrinsic antigens leads to tissue destruction and repeated stimulation of the B-cell response [6]. When analyzing the biopsy material of the ovaries (taken during diagnostic laparoscopy in women with OD and infertility in chronic lymphocytic thyroiditis), we noted the presence of lymphoid infiltration, autoantibodies and complement on growing follicles, with intact primordial and primary follicles, which explains the possibility of prolonged existence in some patients with autoimmune oophoritis lack of development of hypergonadotropic ovarian failure.

The authors [7] report that with hypofunction of the ovaries

of autoimmune genesis, an increase in inhibin B production occurs, in contrast to ovarian insufficiency of another etiology, which is due to selective damage to theca interna cells, while granulosa cells synthesizing inhibin B remain intact [8]. Ovarian failure can also develop due to the presence of chronic inflammatory and infectious diseases.

A study of the somatic history of patients with OD and sexual dysfunction revealed that women with low LH had autoimmune diseases: autoimmune thyroiditis, systemic lupus erythematosus, osteoarthritis, etc., which makes us think about the multifactorial nature of the problem in this category of patients.

**Aim of the research.** The study of the value of inhibin B as a prognostic marker of fertility recovery in women with androgen deficiency and sexual dysfunction.

## 2. Materials and methods.

The study was conducted at the Ukrainian Scientific and Practical Center for Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of the Ministry of Health of Ukraine during January-August 2019. The study was conducted after the approval of the Ethics Commission of the National Medical Academy of Postgraduate Education and in accordance with the Code of Ethics of the World Medical Association after obtaining information consent from patients.

The study design included 77 women of reproductive age of the main group with sexual dysfunction and androgen deficiency: 45 women with sexual dysfunction and the presence of thyroperoxidase Ak (I-a group), I-b group of 32 women with sexual dysfunction without antibodies to any organism tissues. Control group - 31 healthy women of reproductive age.

Diagnostic laparoscopy was performed on an OLYMPUS apparatus according to a standard technique according to Clifford R. Wiliss.

Hormone testing was performed using a Johnson & Johnson Vitros automated system. Blood samples for the study were taken in the morning (8-11) on an empty stomach with venipuncture of the ulnar vein. In the control group, the study of hormonal indicators was carried out in the 1st (follicular) phase of the menstrual cycle. Ultrasound investigation was performed on an Aloka Hitachi apparatus (Japan) with a sensor frequency of 7 MHz.

Sexual dysfunction was determined by the Skindex-16V questionnaire, which allows you to consider the state of the emotional background, the quality of the sexual life of women with vaginal dysfunction. The diagnosis of the examined "Violation of female sexual desire / arousal" was done according to the classification DSM-5. Clinical manifestation of sexual dysfunction was > 6 months.

Statistical processing of the results was carried out using the statistical program Statistica 8.0 for Windows 7.0 using the methods of variation statistics for nonparametric data. The results are presented as median (Me) and interquartile range [Q25; Q75]. For the correlation analysis, the Spearman method was used. To determine the reliability in independent groups, the Mann-Whitney U-test was used. The critical level of significance for statistical testing of hypotheses in this study was taken to be 0.05.

## 3. Results

The average age of the examined main group was  $32.3 \pm 1.7$  years, in the control group –  $33.9 \pm 1.6$  years. The average age of menarche for women of both groups was 13–14 years (in the main  $13.3 \pm 0.34$ , in the control –  $13.0 \pm 0.23$  ( $p > 0.05$ )).

The menstrual cycle in patients of the main group was anovulatory. Under ultrasound, the endometrium did not correspond to the phases of the cycle, cystic ovarian degeneration was detected.

A study of the hormonal background showed a pronounced, statistically significant in compare to healthy women decrease in the concentrations of not only estradiol ( $39$  [30; 55] and  $150$  [116; 218] pmol/L, respectively,  $p < 0.001$ ), but also of androgen: total testosterone ( $0.1$  [0.1; 0.2] and  $1.05$  [0.8; 1.4] nmol/L,  $p < 0.001$ ), free testosterone ( $1.4$  [0.6; 2.0] and  $10$  [7.0; 16.0] pmol/L,  $p < 0.001$ ), as well as dehydroepiandrosterone sulfate (DHEA-S) –  $128.3$  [73.3; 850] and  $559$  [403; 663] nmol/L,  $p < 0.001$ . FSH in the I-a group was  $5.3 \pm 1.12$  U/L, LH  $3.2 \pm 0.98$  U/L, in the I-b group it was  $11.3 \pm 3.12$  U/L, LH  $8.2 \pm 1.7$  U/L, in the control  $8.3 \pm 1.4$  U/L, LH  $7.2 \pm 1.2$  U/L. The Inhibin B index in the I-a group at 2–5 menstrual cycle day:  $39 \pm 1.23$  pg/ml [31; 67] and  $115 \pm 4.87$  [74; 218] pgr/ml (at a reference rate of 2.6–273 pg/ml). Concentrations of sex steroids directly and statistically significantly correlated in group I-a with concentrations of gonadotropins (luteinizing hormone (LH) and estradiol  $r = 0.67$ ; follicle-stimulating hormone (FSH) and estradiol  $r = 0.64$ ; LH and total testosterone  $r = 0.47$ ; FSH and total testosterone  $r = 0.42$ ; for all  $p < 0.001$ ). LH and DHEA-S  $r = 0.33$  ( $p = 0.02$ ), FSH and DHEA-S  $r = 0.27$  ( $p = 0.03$ ). In group I-b, LH correlation and total testosterone  $r = 0.58$  ( $p < 0.001$ ) were noted.

Diagnostic laparoscopy with ovarian biopsy was performed in 12 women of group I-a and 23 of group I-b. At the same time, the presence of lymphoid infiltration, autoantibodies and complement on growing follicles was established, with primordial and primary follicles intact. Tissue fibrosis, the presence of activated B and T lymphocytes: CD8+, CD4+, natural killer cells (NK), polyclonal plasmocytes, macrophages of primordial and primary follicles were characteristic for group I-b.

## 4. Discussion

The revealed biochemical changes in women with sexual dysfunction and androgen deficiency made it possible to clarify the cause of hormonal changes in the reproductive background in the examined patients. As we see in group I-b, the inhibin B index is closer to the lower limit of the norm – which may indicate ovarian hypofunction of autoimmune genesis, which is caused by selective damage to theca interna cells, while granulosa cells synthesizing inhibin B remain intact. Other researchers came to the same conclusions [9]. Thus, according to the obtained data, the level of inhibin B can be a marker of the depth of damage to the follicular reserve in women with sexual dysfunction.

The results of histological studies confirm the difference in the etiology of androgen deficiency in women with sexual dysfunction and androgen deficiency. These results are consistent with the data of researchers [10] that ovarian hypofunction of autoimmune origin is caused by selective damage to theca interna cells, while granulosa cells synthesizing inhibin B remain intact.

The knowledge of the revealed changes shows the ways to eliminate ovarian dysfunction in women of reproductive age with AD and female sexual dysfunction. The level of inhibin B can serve as an early marker of autoimmune ovarian damage in women of reproductive age with female sexual dysfunction. However, in comparison with a large database of studies of reproductive dysfunction and premature ovarian exhaustion syndrome, there are few studies of ovarian dysfunction in women with androgen deficiency and sexual dysfunctions in the literature. This makes it important and advisable to continue studying the markers of androgen deficiency in women with sexual dysfunctions and to develop methods for correcting androgen deficiency in women of reproductive age, taking into account the pathogenesis of the disease.

## Conflict of interests

No conflict of interest.

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