

CHARACTERISTICS OF THE FUNCTIONAL STATE OF THE HYPOTHALAMIC-PITUITARY-OVARIAN SYSTEM IN WOMEN OF REPRODUCTIVE AGE WITH OVARIAN EXHAUSTION SYNDROME

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Abstract. *The issue of estrogen deficiency remains a key area of focus in both scientific research and practical gynecological endocrinology. The negative impact of hypoestrogenism and possible ways of its correction have been thoroughly studied during the menopausal period, yet a significant decrease in the level of sex steroids can be observed at various stages of a woman's life: in juvenile and reproductive periods (Dedov I.I. et al., Ailamazyan E.K., 2007). Literature analysis indicates that ovarian exhaustion syndrome (OES), as a type of ovarian hypofunction, has been increasingly observed in recent years among relatively young individuals, aged 20–40 years (N.V. Barkalina, 2010). There are many conflicting opinions about the nature of this condition: some authors believe that it involves primary ovarian damage (Mal'tseva L.I. 2010), while others think that the primary damage occurs in the central structures of reproductive function (L.B. Butareva, M.A. Shakova, 2010). Finally, there is a viewpoint that excludes simultaneous damage to all structures of the reproductive system (N.A. Zhakhur, L.A. Marchenko, 2010). In this context, the aim of the current study was to investigate the pathogenetic mechanisms underlying menstrual function disorders by analyzing individual fluctuations in the levels of gonadotropins and ovarian steroid hormones and correlating them with the clinical characteristics of the examined patients.*

Keywords: *estrogen deficiency, gynecological endocrinology, menstrual dysfunction, secondary infertility, bacterioscopic study.*

Materials and Methods

Over the period from 2010 to 2013, we examined 115 women with menstrual dysfunction, secondary infertility, benign ovarian tumors, and inflammatory processes of the genitals at the City Maternity Hospital No. 6, the Gynecological Department of the MCH GTS in Tashkent, and the Republican Scientific and Practical Medical Center of Obstetrics and Gynecology of the Ministry of Health of the Republic of Uzbekistan. The average age of the women examined was 34.8 ± 0.83 years.

The examination included: clinical and laboratory studies (complete blood count, urine analysis, biochemical tests); a unified protocol for gynecological examination; bacterioscopic study; ultrasound of the genitals; hormonal studies (determination of the concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), progesterone (P), and testosterone (T) in the blood serum), as well as morphological examination of ovarian biopsy. To diagnose, all subjects underwent functional diagnostic tests; assessment of basal (rectal) temperature, determination of the karyopyknotic index, folliculometry, stretchability of cervical mucus, pupil sign, fern test, etc. The comparative analysis of functional diagnostic tests in women of the main group was significantly higher compared to control values. Based on these

tests, the diagnosis of OES was made. The content of gonadotropins and ovarian steroid hormones was studied in women with OES on days 21-23 of the menstrual cycle. The control group consisted of hormone levels determined in 30 essentially healthy women with normal reproductive function aged 31 - 40. Statistical processing of the clinical study data was carried out on a Hewlett Packard Pentium IV personal computer in the Windows 98 operating system using the Microsoft Excel 98 software package, including the use of built-in statistical processing functions.

Results and Discussion

The most frequent clinical symptoms of Ovarian Exhaustion Syndrome (OES) among the subjects were irregularities in the menstrual cycle in the form of oligomenorrhea, despite well-developed secondary sexual characteristics. In our studies, secondary amenorrhea was identified in 37 cases, dysfunctional uterine bleeding (DUB) in 21, secondary infertility in 18, miscarriage in 14, habitual spontaneous abortions in 9, benign ovarian formations in 39, regressing pregnancy in 7, and fibroids in 6. A sudden cessation of menstruation was noted in 7 patients. In 31 patients, since menopause was premature, the deficiency of sex hormones contributed to an earlier appearance of typical menopausal disorders in the form of vegetovascular and psycho-emotional disorders. A distinctive feature of the clinical picture of the disease among the examined cohort was the low frequency and absence of pronounced symptoms of osteoporosis and atrophy of the urogenital tract, which are characteristic of timely menopause.

After establishing the clinical fact of hormonal insufficiency of the ovaries, the levels of damage in the hypothalamic-pituitary-ovarian system were determined. Our studies showed that the hormonal status of patients with OES indicated a significant increase in the level of FSH to 94 ± 8.9 IU/L and LH to 78 ± 9.5 IU/L, which is 13 and 10 times respectively higher than the basal secretion of gonadotropins ($p < 0.001$). The level of prolactin in the main group of women was 369.3 ± 5.1 IU/L compared to $554.4 - 3.1$ IU/L in the control ($p < 0.001$), i.e., almost 1.5 times lower than in healthy women.

The estradiol level in the main group of patients averaged 70 ± 20.5 nmol/L compared to 208.1 ± 28.4 nmol/L in the control group ($p < 0.001$), which is significantly lower than its level in the early follicular phase in women with regular menstruations.

The study of ovarian steroid hormone content showed that the progesterone (P) concentration in the serum of peripheral blood in the main group was significantly low, amounting to 6.9 ± 0.23 nmol/L, versus 19.7 ± 0.5 nmol/L in the control group ($p < 0.001$).

Particular interest is the analysis of androgen secretion, both ovarian and adrenal in origin, in patients with OES. In this regard, significant differences were found between timely (physiological) and premature menopause. In patients with OES, a slight increase in serum peripheral blood testosterone was noted, which was 2.33 ± 0.12 nmol/L, compared to 1.98 ± 0.96 nmol/L in the control group ($p < 0.001$). The onset of physiological menopause did not significantly affect androgen production, unlike other sex steroids, which is why they were found in significant quantities in the blood.

Thus, with the onset of natural menopause, the majority of testosterone is produced through peripheral conversion from androstenedione and DHEA-S. Herein, unlike estrogens, its level does not decrease sharply but, on the contrary, can increase, especially in terms of its free fractions. On the other hand, due to the decrease in estradiol levels in the liver, the production of sex steroid-binding globulin (SSBG) decreases, and the level of free, biologically active testosterone fraction

in the blood increases. Therefore, a significant percentage of women undergoing timely menopause experience relative hyperandrogenism.

The results of hormone content analysis in 115 patients with OES and 30 essentially healthy women with regular menstrual function are reflected in Table № 1.

Table № 1:

Levels of Gonadotropins and Ovarian Steroid Hormones in Women of the Main and Control Groups (Mean ± Standard Error).

Hormone	Main Group (OES Patients)	Control Group (Healthy Women)
FSH (IU/L)	94 ± 8.9	(Baseline secretion reference)
LH (IU/L)	78 ± 9.5	(Baseline secretion reference)
Prolactin (IU/L)	369.3 ± 5.1	554.4 ± 3.1
Estradiol (nmol/L)	70 ± 20.5	208.1 ± 28.4
Progesterone (nmol/L)	6.9 ± 0.23	19.7 ± 0.5
Testosterone (nmol/L)	2.33 ± 0.12	1.98 ± 0.96

Note: "***" indicates a p-value of <0.001 compared to the control group.

Our research indicates that patients with Ovarian Exhaustion Syndrome (OES) exhibit a deficiency not only in estrogens but also in androgens, which is not characteristic of the physiological mechanisms of ovarian shutdown at the onset of timely menopause, as the adrenal glands partially assume the function of the ovaries in such cases.

Analyzing the levels of steroid hormones (estradiol, progesterone) and changes in basal temperature, it can be concluded that luteal phase insufficiency, characterized by decreased progesterone levels and relative hypoestrogenism, is the primary variant of dysfunction in the case of infectious ovarian damage.

Conclusions:

The assessment of ovarian steroidogenesis in the examined women revealed hormonal activity disturbances in all patients and consistent changes in the form of a significant decrease in estradiol levels; decreased progesterone; minor hyperandrogenism; high levels of FSH (up to 13 times); and increased LH (up to 10 times).

An FSH level in blood plasma above 20 IU/L and estradiol below 80 nmol/L confirms the diagnosis of OES.

In patients with hypergonadotropic ovarian insufficiency, high levels of gonadotropins, resulting in reduced estradiol and progesterone levels, are due to sclerotic and atrophic processes leading to irreversible pathological changes in the ovaries caused by previous inflammatory processes.

In OES, primary ovarian damage occurs due to disrupted folliculogenesis, accelerated apoptosis and follicular atresia, as well as depletion of the ovarian reserve, followed by secondary damage to the central structures of the hypothalamic-pituitary system.

Understanding the pathogenetic mechanisms of hormonal imbalance in women with premature ovarian exhaustion allows for effective treatment of OES and reduces the risk of recurrence and the potential for malignancy of the hormone-secreting ovarian cells.

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