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Features Of The Interrelationship Of Hormonal Autoimmune And Psychometric Parameters In Premature Ovarian Insufficiency

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Abstract: Premature ovarian insufficiency (POI) has not only medical but also socio-economic significance, extending far beyond the field of gynecology, and is associated with a risk of premature development of cardiovascular diseases and osteoporosis, as well as causing persistent impairment of quality of life and disability in women of early reproductive age. The aim of the study was to investigate the interrelationship of hormonal, autoimmune, and psychometric parameters in POI. Patients were divided into three groups: Group 1 (main group) included 50 women with POI; Group 2 (comparison group) consisted of 35 women with physiological menopause; Group 3 (control group) included women aged 18–40 years with a regular menstrual cycle (24–35 days) during the last 12 months. The study demonstrated that estrogen deficiency, increased follicle-stimulating hormone levels, decreased anti-Müllerian hormone levels, and the presence of autoimmune disorders exert a synergistic effect on bone metabolism, leading to the early development of osteopenia and an increased risk of osteoporosis in women of reproductive age. In addition, it was revealed that psychometric disorders in women with POI are closely associated with hormonal and metabolic changes, which emphasizes the systemic nature of the disease. Depression, anxiety, and sexual dysfunction accompany a decrease in bone mineral density, exacerbating the severity of clinical manifestations. The obtained data confirm the necessity of comprehensive rehabilitation and therapeutic programs, which will form the basis for the development of practical recommendations. In this regard, the management of women with POI requires not only correction of hormonal deficiency but also a comprehensive, multilevel approach that includes assessment of the psychoemotional state, diagnosis of autoimmune changes, and prevention of bone mass loss. Such an approach is capable of improving patients' quality of life, reducing the risk of long-term complications, and increasing the effectiveness of therapy. The foundation of further practical recommendations should be precisely the integration of endocrinological, psychological, immunological, and rehabilitative interventions.

Keywords: Premature ovarian insufficiency, autoimmune markers, thyroid gland changes, hormonal imbalance, psychometric disorders.

Introduction: Premature ovarian insufficiency (POI) is one of the most pressing problems of modern gynecology and reproductive endocrinology, affecting women during the most biologically, socially, and professionally active period of life. The clinical significance of POI extends far beyond gynecology and is associated with a risk of premature development of cardiovascular diseases and osteoporosis, as well as

causing persistent impairment of quality of life and disability in women of early reproductive age; therefore, it has not only medical but also socio-economic significance.

According to the latest clinical guidelines of the European Society of Human Reproduction and Embryology [9], POI is a clinical syndrome, the main manifestation of which is cessation of ovarian function before the age of 40 years, characterized by menstrual dysfunction (oligo-/amenorrhea), increased levels of gonadotropins (follicle-stimulating hormone and luteinizing hormone), and decreased estradiol concentration [1, 2, 6, 9, 14, 11].

The prevalence of premature ovarian insufficiency (POI), according to literature data, ranges from 1 to 10% of the female population [14]. However, the age-specific prevalence of the disease is as follows: under the age of 20 years – 1:10,000; by the age of 30 years – 1:1,000; by the age of 35 years – 1:250; by the age of 40 years – 1:100 [5]. According to Fakhrutdinova S.S. (2019), the prevalence of POI in Uzbekistan is 2.5%. The mean age of women with POI is 31.4±0.5 years [7].

In recent years, foreign researchers, as well as researchers in our country, have been studying in detail individual aspects of POI, including genetic and autoimmune mechanisms, characteristics of the hormonal profile, options for hormone replacement therapy, and reproductive prospects [13, 14, 3, 4]. However, an integrated assessment of the interrelationship between hormonal, autoimmune, and psychometric parameters and their impact on quality of life and bone mineral density, combined with the development of an organizational and practical model of medical care, remains insufficiently developed. This determines the necessity of conducting a comprehensive study and substantiates the choice of the topic of the present research.

The aim of the study was to investigate the interrelationship of hormonal, autoimmune, and psychometric parameters in premature ovarian insufficiency (POI).

METHODS

The study was designed as a single-center, comparative, controlled investigation with elements of retrospective and prospective analysis. The research was conducted from 2021 to 2025 on the basis of obstetric and gynecological departments and consultative and diagnostic services of the Shahrisabz District Medical Association, as well as clinical institutions involved in providing specialized care to women with reproductive function disorders.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki (2013) and was approved by the local ethics committee. Written informed voluntary consent for participation in the study and processing of personal data was obtained from all participants.

The study included women of reproductive age and women with physiological menopause who met the inclusion criteria and had no exclusion criteria. The total sample size comprised 120 women aged 18 to 40 years, which corresponds to current diagnostic criteria for POI and allows for comparison of clinical, hormonal, psychoemotional, and densitometric parameters in women of reproductive age. The patients were divided into three groups: Group 1 (main group) included 50 women with POI; the formation of the group of women with physiological menopause (Group 2) was aimed at comparing the manifestations of the hypoestrogenic state in POI and natural age-related loss of ovarian function; Group 3 (control group) included women aged 18–40 years with a regular menstrual cycle (24–35 days) during the last 12 months.

The inclusion criteria for the main group (women with POI) were as follows: age under 40 years; amenorrhea or oligoamenorrhea lasting at least 6 months; an elevated level of follicle-stimulating hormone (FSH) ≥ 25 IU/L confirmed by at least two measurements performed at intervals of no less than 4 weeks; a decreased estradiol level compared with the age-specific norm; absence of pregnancy; and absence of hormone replacement therapy at the time of inclusion in the study.

To achieve the aim and objectives of the study, clinical and anamnestic methods, hormonal and immunological analyses, and instrumental methods were applied, as well as statistical methods of data processing using parametric and nonparametric tests, correlation analysis, and assessment of the statistical significance of differences ($p < 0.05$).

RESULTS AND DISCUSSION

Analysis of the obtained data demonstrated that patients with POI had a significantly higher prevalence of infertility (36%) compared with the control group (8.6%; $p = 0.002$), which confirms the critical role of decreased ovarian reserve in the development of fertility disorders. In 24% of women with POI, cases of early menopause were reported among first-degree relatives, which is consistent with literature data on the hereditary nature of premature ovarian failure. Thyroid diseases were also more common in this group (30%) than in the control group (11.4%; $p = 0.047$), indicating a possible involvement of autoimmune processes in the pathogenesis of POI.

The severity of vasomotor, psychoemotional, and

urogenital symptoms in women with POI was significantly higher than in the control group ($p < 0.001$). The nature and frequency of symptoms in the POI group were comparable to those in the physiological menopause group, which confirms the presence of a pronounced hypoestrogenic state in women of reproductive age. Sleep disturbances, irritability, and dyspareunia were particularly significant, having a direct impact on FSFI and SF-36 scores.

The study assessed the levels of FSH, LH, estradiol, anti-Müllerian hormone (AMH), progesterone, testosterone, dehydroepiandrosterone sulfate (DHEA-S), thyroid-stimulating hormone (TSH), free T4, TPOAb, and TGAb (as markers of autoimmune thyroiditis) (Table 1).

Table 1

Levels of Reproductive Hormones in Women of the Studied Groups

Parameter	POI (n = 50)	Menopause (n = 35)	Control (n = 35)	p-value
FSH, IU/L	42,8 ± 11,5	63,4 ± 14,2	7,1 ± 2,3	<0,001
LH, IU/L	18,6 ± 4,9	29,1 ± 7,4	6,3 ± 1,8	<0,001
Estradiol (E2), pg/mL	38,5 ± 16,2	21,7 ± 9,8	96,4 ± 25,7	<0,001
AMH, ng/mL	0,45 ± 0,21	0,12 ± 0,09	2,87 ± 1,14	<0,001
Progesterone, ng/mL	0,48 ± 0,29	0,32 ± 0,27	1,78 ± 0,56	<0,001
Testosterone, ng/mL	0,33 ± 0,18	0,22 ± 0,14	0,42 ± 0,20	<0,05
DHEA-S, µg/dL	126 ± 41	98 ± 35	184 ± 52	<0,001

Women with premature ovarian insufficiency (POI) exhibited a pronounced imbalance of reproductive hormones characteristic of ovarian reserve depletion. A significant increase in follicle-stimulating hormone (FSH) levels (42.8 ± 11.5 IU/L), exceeding those of the control group by more than sixfold, indicates disruption of the negative feedback mechanism between the pituitary gland and the ovaries and reflects the absence of a fully functional follicular apparatus. At the same time, an elevation in luteinizing hormone (LH) was observed; however, the degree of its increase was less pronounced, which corresponds to the typical "dissociated" hypergonadotropic profile seen in POI. Estradiol concentrations in patients with POI were significantly reduced (38.5 ± 16.2 pg/mL) and were comparable to levels observed in women undergoing physiological menopause, confirming the presence of marked hypoestrogenism in patients of reproductive age.

One of the most sensitive markers of decreased ovarian reserve was anti-Müllerian hormone (AMH), the level of which in premature ovarian insufficiency (POI) was virtually depleted (0.45 ± 0.21 ng/mL), being sixfold lower than control values and corresponding to profound depletion of the primordial follicle pool. Low progesterone levels indicate the absence of ovulation, while reduced concentrations of testosterone and dehydroepiandrosterone sulfate (DHEA-S) underscore the presence of androgen deficiency, which plays a key role in the development of sexual dysfunction and decreased vitality.

Thus, the hormonal profile of women with POI demonstrates a comprehensive impairment of hormonal regulation involving the gonads, pituitary gland, and adrenal glands, which explains the diversity of clinical and psychoemotional manifestations of the disease.

The functional state of the thyroid gland is of significant importance in the pathogenesis of POI, as thyroid hormones participate in the regulation of gonadotropin secretion, steroidogenesis, and folliculogenesis. In the examined women with POI, a statistically significant increase in thyroid-stimulating hormone (TSH) levels was recorded compared with the control group (2.98 ± 1.12 vs. 2.21 ± 0.94 mIU/L; $p < 0.01$), which may indicate the presence of subclinical hypothyroidism. Even a slight elevation of TSH within the "upper normal" range is capable of impairing ovarian function

by altering follicular sensitivity to FSH and LH.

Of particular importance in the present study was the assessment of autoimmune markers, namely antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TGAb). In patients with premature ovarian insufficiency (POI), the prevalence of elevated TPOAb was 28%, and that of TGAb was 20%, which significantly exceeded the corresponding rates in the control group (11.4% and 5.7%, respectively). This suggests that autoimmune processes may represent one of the triggers of premature depletion of the follicular apparatus. The presence of elevated TPOAb was associated with lower AMH levels (as supported by contemporary data from ESHRE and ASRM), as well as with more pronounced manifestations of depression and anxiety, which is related to dysregulation of the thyroid–neurotransmitter system. In addition, women with increased antibody titers demonstrated a tendency toward reduced bone mineral density (lower Z-scores), which is consistent with international studies indicating the impact of chronic autoimmune inflammation on bone metabolism.

As was necessary to demonstrate, the combination of POI and latent autoimmune thyroiditis results in a more severe hormonal, psychoemotional, and metabolic profile in such patients, emphasizing the need for mandatory screening of thyroid function in all women with suspected POI.

Therefore, the hormonal profile of women with premature ovarian insufficiency (POI) is characterized by a pronounced hypergonadotropic state, a significant decrease in estradiol levels, almost complete depletion of ovarian reserve (AMH), androgen deficiency, and a high prevalence of clinically significant symptoms of hypoestrogenism. Additionally, elevated levels of thyroid antibodies and a tendency toward subclinical hypothyroidism were identified, which confirms the role of autoimmune mechanisms in the development of POI and diagnostically reinforces the observed differences. The combined reduction of steroid, gonadotropic, and thyroid hormones explains the severity of clinical manifestations, including decreased quality of life, sexual dysfunction, increased levels of depression and anxiety, as well as adverse effects on bone tissue.

The psychoemotional state of women with POI also depended on place of residence. Although differences in the prevalence of depression and anxiety according to PHQ-9 and GAD-7 did not reach statistical significance, rural women demonstrated a higher tendency toward moderate depressive states (68% versus 50%) and anxiety (59% versus 46%) (Table 2).

According to the SF-36 questionnaire, rural women had statistically significantly lower levels of vitality (VT)—42.1 versus 49.3 ($p = 0.032$), as well as a lower physical component summary (PCS)—52.3 versus 59.1 ($p = 0.049$). These differences reflect the impact of domestic workload, limited access to high-quality medical care, low levels of social support, and lower awareness of POI, which is consistent with data from global studies on women's health.

Table 2

Psychoemotional indicators in women with premature ovarian insufficiency (POI)

Indicator	Urban (n = 28)	Rural (n = 22)	p-value
PHQ-9 ≥10, n (%)	14 (50%)	15 (68%)	>0,05
Mean PHQ-9 score (points)	10,8 ± 4,5	12,1 ± 5,2	>0,05
GAD-7 ≥10, n (%)	13 (46%)	13 (59%)	>0,05
SF-36: VT (vitality)	49,3 ± 13,1	42,1 ± 12,8	0,032
SF-36: PCS (physical component summary)	59,1 ± 12,4	52,3 ± 11,8	0,049

In our study groups, place of residence influenced not only the hormonal and autoimmune profiles but also the psychoemotional well-being of patients with premature ovarian insufficiency (POI), thereby

increasing the severity of clinical manifestations.

Thus, analysis of the impact of place of residence demonstrated that women with POI living in rural areas have a lower ovarian reserve (AMH), a higher prevalence of autoimmune thyroiditis, and a more pronounced reduction in quality of life according to SF-36 data. These differences indicate the biopsychosocial nature of POI and emphasize the need to develop differentiated management approaches for patients in urban and rural settings.

To assess factors affecting bone tissue status in POI, a correlation analysis was performed between ultrasound densitometry parameters and hormonal indicators.

The obtained results reflect the complex influence of sex hormone deficiency, decreased ovarian reserve, and autoimmune disorders on bone mineral density.

1. Gonadotropins and BMD. A pronounced negative correlation was identified between FSH levels and T-scores ($r = -0.52$; $p < 0.001$), which confirms the role of a hypergonadotropic state in the acceleration of bone resorption. Elevated FSH, characteristic of POI, promotes osteoclast activation, reduces bone mineral density, and contributes to the progression of osteopenia.

2. Estradiol. Estradiol levels showed a positive correlation with SOS parameters ($r = +0.49$; $p < 0.001$), indicating the key role of estrogens in maintaining bone strength. Estrogen deficiency in POI leads to a reduction in trabecular density, deterioration of ultrasound bone characteristics, and an increased risk of fractures.

3. Anti-Müllerian hormone (AMH). A positive association was identified between AMH levels and the integral QUI index ($r = +0.58$; $p < 0.001$). Low AMH levels, reflecting depletion of the primordial follicle pool, were associated with reduced bone quality. This confirms that women with a pronounced decrease in ovarian reserve have the highest risk of developing osteopenia.

4. Autoimmune markers. Elevated levels of antibodies to thyroid peroxidase (TPOAb) were negatively correlated with Z-scores ($r = -0.31$; $p = 0.039$), indicating the impact of chronic autoimmune inflammation on bone metabolism. This confirms that the combination of POI and autoimmune disorders results in a more severe bone phenotype.

5. Psychoemotional factors. A weak but statistically significant correlation was identified between depression levels (PHQ-9) and decreased T-scores ($r = -0.28$; $p < 0.05$), which is consistent with current data on the effects of chronic stress on bone turnover through hypercortisolemia and behavioral changes.

CONCLUSIONS

1. The interrelationship between hormonal, autoimmune, and psychometric parameters confirms the multifactorial nature of reduced bone mineral density in premature ovarian insufficiency (POI). Estrogen deficiency, elevated follicle-stimulating hormone levels, decreased anti-Müllerian hormone concentrations, and the presence of autoimmune disorders exert a synergistic effect on bone metabolism, leading to the early development of osteopenia and an increased risk of osteoporosis in women of reproductive age.

2. In this regard, the management of women with POI requires not only correction of hormonal deficiency but also a comprehensive, multilevel approach that includes assessment of the psychoemotional state, diagnosis of autoimmune alterations, prevention of bone mass loss, correction of sexual dysfunction, and patient education on the principles of self-regulation and a healthy lifestyle. Such an approach is capable of improving patients' quality of life, reducing the risk of long-term complications, and increasing the effectiveness of therapy. The foundation of further practical recommendations should be precisely the integration of endocrinological, psychological, immunological, and rehabilitative interventions.

3. Psychometric disturbances in women with POI are closely associated with hormonal and metabolic changes, which underscores the systemic nature of the disease. Depression, anxiety, and sexual dysfunction accompany the reduction in bone mineral density, exacerbating the severity of clinical manifestations. The data obtained confirm the necessity of comprehensive rehabilitative and therapeutic programs, which will form the basis for the development of practical recommendations.

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