GALAXY INTERNATIONAL INTERDISCIPLINARY RESEARCH JOURNAL (GIIRJ)
ISSN (E): 2347-6915
Vol. 13, Issue 10 October (2025)

MODERN VIEWS ON CLINICAL AND DIAGNOSTIC CRITERIA FOR PREMATURE OVARIAN FAILURE (LITERATURE REVIEW)

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ABSTRACT

In recent times, postponing pregnancy to a later reproductive age has become a trend in the reproductive behavior of many women. The late reproductive period is considered to be the period from 40 to 45 years of age. Due to premature ovarian failure, a woman loses her reproductive potential by the age of 40, and this is a significant social problem. Women with this disease are at risk of a number of diseases associated with estrogen deficiency: impaired endothelial function, ischemic heart disease and its associated risks, a higher rate of bone fractures due to osteoporosis, decreased cognitive function, poorer quality of sexual life, and an increased risk of premature death. The purpose of this article is to systematize modern clinical diagnostic criteria for premature ovarian failure, their early detection and prevention of reproductive losses, as well as improve the quality of life of women. As a result of the analysis, the process of step-by-step diagnosis of pathology was described, the shortcomings of follicle-stimulating hormone, which is considered the main marker in assessing ovarian function, were identified and listed. The advantages of anti-mullerian hormone in the early detection of ovarian failure were also considered.

Keywords: Premature ovarian failure, ovarian reserve, diagnosis of premature ovarian failure, infertility, amenorrhea, anti-mullerian hormone, follicle-stimulating hormone.

INTRODUCTION

According to the latest clinical guidelines published by the European Society of Human Reproduction and Embryology (ESHRE, 2016), premature ovarian failure (POF) is a clinical syndrome characterized by the cessation of ovarian function in women under the age of 40. This condition is characterized by menstrual irregularities (oligo-/amenorrhea), increased levels of the gonadotropic hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and decreased levels of estradiol [1]. The term “POF” was first proposed by Fuller Albright in 1942. Later, this term was forgotten and, without sufficient justification, the symptom complex accompanied by amenorrhea, high gonadotropins and low sex hormone levels in women under 40 years of age was described in the literature as “premature menopause” or “premature ovarian failure” [2].

However, these terms do not fully reflect the variable nature of the condition and the incomplete cessation of ovarian function. Cases of spontaneous ovulation recovery and pregnancy in 5–10% of women against the background of long-term hypergonadotropic amenorrhea have been reported in the literature [3]. Despite many years of research, the exact

point at which hypergonadotropic amenorrhea becomes irreversible has not yet been determined [4].

Therefore, timely diagnosis, proper counseling and treatment of patients with a full understanding of the additional pathologies associated with estrogen-dependent disorders are of great importance. One of the most important steps is to prescribe hormone therapy in a timely manner to prevent menopausal symptoms and dangerous health consequences.

The vagueness of clinical signs and the lack of sufficient public awareness of this condition can lead to delays in diagnosis and treatment. Despite many years of research into the mechanisms involved in the development of premature ovarian failure, significant progress has not been made in recent decades - scientists are still struggling with the complex and heterogeneous nature of this phenomenon [5].

Etiology

Although there is a lot of information about the frequency of premature ovarian failure (POF), there is not enough clear evidence about its reliability. According to estimates by various authors, this figure varies from 1% to 13% [6, 7]. POF is a multifactorial disease, the causes of which include a sharp decrease in the follicular reserve, impaired folliculogenesis, increased apoptosis and atresia of follicles, and their insufficient formation during the fetal period.

The age of menopause and cessation of ovarian function depends on a number of factors, which are divided into two main groups: modifiable (medical, social and environmental factors) and non-modifiable (genetic) [8]. The etiological causes of the development of spontaneous TEY include: chromosomal and genetic abnormalities, infectious-toxic factors, environmental influences, autoimmune diseases, iatrogenic (caused by medical intervention) and idiopathic forms. Nevertheless, despite modern diagnostic capabilities, the idiopathic form prevails in the overall structure of the disease and occurs in more than 50% of cases [2].

The most important autoimmune diseases associated with TEY are autoimmune disease of the adrenal glands (Addison's disease), autoimmune lesions of the thyroid gland and pancreas. Addison's disease can occur even before the diagnosis of TEY or develop several years later. According to studies, antiadrenal antibodies are detected in half of women diagnosed with TEY after 8–14 years, and Addison's disease develops in 10% of cases.

The autoimmune reaction of the thyroid gland usually manifests itself in the form of hypothyroidism and occurs in 27% of women with idiopathic TEY. Type 1 diabetes mellitus is observed in 2.5% of women with autoimmune ovarian failure [9]. Therefore, after the diagnosis of TIE, annual screening of thyroid, adrenal and pancreatic functions is advisable.

Heredity and smoking are recognized risk factors for the development of premature ovarian failure [11]. Two X chromosomes are required for full ovarian function. The genetic integrity of both the short and long arms of the X chromosome is important. In particular, deletions in the terminal or proximal regions of these arms are associated with primary amenorrhea or premature ovarian failure.

One in 2500 girls is born with Shereshevsky-Turner syndrome (monosomy 45X). The majority of them have primary amenorrhea, but a mosaic karyotype is detected in a quarter of cases, and 3–5% of girls develop secondary sexual characteristics and menstruation. Premature ovarian failure develops in 4–5% of women with this syndrome [12].

Also, chromosomal defects associated with premature ovarian failure (POF) include trisomy and microdeletion of the X chromosome. Fragile X syndrome (Martin–Bell syndrome) is an X-linked dominant genetic disorder characterized by thinning of the ends of the X chromosome. This condition occurs as a result of an excessive increase in the nucleotide sequence "cytosine–guanine–guanine (CGG)". Normally, these repeats should not exceed 45 times, but in the syndrome they increase significantly.

As a result, there is a disruption in the activity of the FMR1 gene - this gene is responsible for the formation of neural connections, the development and differentiation of the nervous system. If the number of CGG repeats is from 55 to 199 times, this condition is called a premutation and is the cause of premature ovarian failure in 23% of cases [13]. In women of reproductive age, any surgical intervention performed in the pelvic area has a negative effect on the ovarian reserve. For example, the level of anti-Müllerian hormone (AMH) decreases rapidly after hysterectomy. Ovarian resection, removal of endometrioid cysts, electrocautery in polycystic ovary syndrome, and uterine artery embolization in the treatment of uterine fibroids increase the risk of developing TEE. In the case of bilateral oophorectomy (removal of both ovaries), the diagnosis is definitive [17–21].

Fertility preservation measures should be considered before any cancer therapy or planned surgical intervention for other diseases [15].

The role of infections is still controversial. In recent years, there has been evidence of an association between HIV infection, antiretroviral therapy, and the risk of premature ovarian failure [14].

Stress is also a common cause of ovarian failure. Chronic stress is one of the leading factors that negatively affect the endocrine glands. The individual response of a person to severe physical and mental stress can change the regulation of the immune system, affect the activity of the hypothalamic-pituitary-ovarian axis by increasing the level of corticosteroid hormones [16].

An important point is that combined oral contraceptives (COCs), drugs used in the treatment of infertility, and previously administered hormone replacement therapy (HRT) cannot cause ovarian reserve depletion. However, these agents can mask the clinical manifestations of premature ovarian failure (PFU) and temporarily alleviate the symptoms of the disease [19].

Clinical features. Women with premature ovarian failure (POF) usually present to primary health care providers with complaints of menstrual irregularities, infertility, and may suffer from symptoms of hypoestrogenism. They are at high risk of developing estrogen deficiency-related diseases: impaired endothelial function, ischemic heart disease and its complications, increased osteoporosis-related fractures, cognitive impairment, decreased quality of life, and an increased risk of premature death. More than 50% of such women consult an average of three different specialists before seeking medical attention [1, 6, 18]. Patients with POF (POF) differ from women who have entered physiological menopause in a number of ways. Since age-related changes in the hypothalamic and limbic structures have not yet developed, they do not exhibit severe climacteric disorders or signs of urogenital tract atrophy (except in cases after cancer treatment), since their urotherial aging mechanisms have not yet been activated [20].

If relative hyperandrogenism is observed during natural menopause, then a deficiency of male sex hormones is detected in 63% of women with PNY. Androgen deficiency is characterized by

a deterioration in general well-being, a dysphoric state (even up to depression), a constant feeling of unreasonable fatigue, sexual dysfunction (decreased libido), vasomotor disorders, a decrease in bone mass, weakening of muscle strength, cognitive functions and memory impairment [17, 18].

The clinical picture of ETY is not characterized by clear signs, and the degree of manifestation of symptoms varies significantly from woman to woman. In most cases, such women have a normal puberty period and a regular menstrual cycle. In most patients (85.5%) the disease begins in the form of a menstrual cycle disorder - opsomenorrhoea. Sudden cessation of menstruation is observed in 14.2% of cases.

Women may complain of the following complaints associated with a decrease in estrogen levels: vaginal dryness, decreased sexual desire, weight gain, deterioration of hair and nail condition, irritability, night sweats, increased blood pressure, etc. Disturbances in sleep and wakefulness lead to a significant decrease in the quality of life [9, 10, 11].

The European Society of Human Reproduction and Embryology (ESHRE) defines the following diagnostic criteria for the diagnosis of premature ovarian failure (POF):

— oligomenorrhea or absence of menstruation (amenorrhea) lasting at least 4 months;

— a follicle-stimulating hormone (FSH) level of more than 25 IU/ml, measured on two occasions at least 4 weeks apart [1].

At the same time, according to the International Menopause Society (IMS), the level of FSH in menopause should be more than 40 IU/ml [16]. Also, special attention should be paid to girls with primary amenorrhea (i.e., the absence of menstruation at all) after the age of 15, since usually 95–98% of adolescent girls begin menstruation by this age. An important point for the correct interpretation of the analysis is that the woman should not be taking hormonal contraceptives or hormone replacement therapy (HRT) at the time of the study. The drugs should be discontinued at least 6 weeks before measuring the hormone level.

Diagnosis

To identify women at high risk of premature ovarian failure (POF), the following factors should be considered: the age at which the mother began menopause, the presence of mental retardation in the family (especially among men), a history of recurrent pregnancy loss, and the presence of any autoimmune or genetic diseases in the woman or her close relatives [14].

The woman's menstrual function is assessed in detail from menarche: the age of onset of menstruation, its duration, regularity, character, and changes observed in the cycle are determined, as these signs may indicate the early stages of the disease. Also, surgical interventions in the pelvic area, hormonal or gonadotoxic drugs are determined, as they directly affect ovarian function and ovarian reserve [16]. Endocrine diseases — type 1 diabetes mellitus, hypothyroidism associated with Hashimoto's thyroiditis, Addison's disease, and other disorders — are important risk factors for the development of ETI, since in these cases ovarian function decreases earlier than usual [1, 15].

During a general examination, body mass index (BMI) is assessed — it is often increased. Attention is paid to the condition of the skin and hair: changes in skin pigmentation, dryness, early wrinkling, brittle nails, hair loss, and dullness are observed. Skin depigmentation or hyperpigmentation may indicate autoimmune diseases or thyroid pathologies. Certain

features of the external appearance indicate an underlying disease. For example, short stature, valgus deformity of the elbows (cubitus valgus), skin folds in the nape of the neck, or lymphostasis — all these are characteristic signs of Shereshevsky-Turner syndrome [16]. Gynecological examination may reveal mild atrophic changes in the external genitalia and vaginal walls, decreased vaginal discharge, and weakening of the pelvic floor muscles. Hypoestrogenism can lead to prolapse of the genitals or laxity of the vaginal walls. These conditions are associated with loss of elasticity of the collagen of the pelvic muscles and ligaments, leading to problems such as urinary incontinence [21]. When laboratory diagnostics are performed, other conditions associated with oligo-/amenorrhea and subfertility are also taken into account [12].

Differential diagnosis is carried out with the following diseases:

— pregnancy,
— hyperprolactinemia,
— hypothalamic (hypogonadotropin) amenorrhea,
— thyroid dysfunction,
— atypical forms of polycystic ovary syndrome (PCOS),
— congenital adrenal hyperplasia,
— uterine amenorrhea,
— psychological or physical exhaustion.

Therefore, laboratory tests include:

— pregnancy test,
— prolactin,
— thyroid hormones (TTG, free T4, AT-TPO),
— free testosterone fraction,
— 17-OH-progesterone (on days 3–5 of the menstrual cycle),
— morning cortisol,
— vitamin B12 and folic acid levels.

If there is a family history of genetic diseases or the woman is under 30 years of age, karyotyping and genotyping are recommended [37]. However, not all of these tests are mandatory - their necessity is determined individually, depending on each clinical situation. Each doctor independently determines the scope of the necessary examination, based on a complete collection of the patient's history, general and gynecological examination.

Reliable tests for confirming the diagnosis of premature ovarian failure (POF) include determination of FSH levels (>25 IU/ml, twice, with an interval of 4 weeks) and measurement of estradiol levels (<50 pg/ml). Currently, active research is being conducted on the early detection and prognosis of POF at the preclinical stage [18, 21].

In recent decades, much attention has been paid to **anti-Müllerian hormone (AMH)** as an important marker of ovarian reserve. Anti-Müllerian hormone (AMH) is a dimeric glycoprotein belonging to the transforming growth factor beta (TGF-ß) family, also known as Müllerian inhibitor [12, 13].

The strong correlation between AMG levels and the number of growing follicles suggests that its levels are elevated in ovarian tumors [14] and polycystic ovary syndrome (PCOS), but are

very low or undetectable in postmenopausal women or patients with Shereshevsky–Turner syndrome [8, 16].

1. Immunohistochemical analyses show that preantral and small antral follicles, 2–8 mm in size, produce the highest levels of AMG, making AMG the most sensitive marker of early ovarian follicle growth. AMG is not produced in FSH-dependent growth phase (follicles 8–10 mm in size) or atrophied follicles, but AMG secretion is restored in preovulatory follicles [14]. Recent data suggest that AMG levels begin to decline before the onset of menstrual cycle disruption and FSH elevation, thus being an early marker of ovarian decline. Serum AMG levels are directly proportional to the number of developing follicles in the ovaries, and AMG is therefore considered a marker of ovarian aging. In addition, AMG is of ovarian origin only, as it is not detectable in the blood of women 3–5 days after oophorectomy [17]. The advantage of AMG is that, unlike FSH, LH, estradiol, and inhibin-B, it does not change significantly during the menstrual cycle and can be measured on any day [19].

2. Thus, anti-Müllerian hormone (AMG) has been successfully used to predict the average age of menopause. This makes it the most reliable endocrine marker for predicting the decline in ovarian reserve in women [11].

3. Determination of AMG levels in the blood is used to predict ovarian failure that develops as a result of iatrogenic (medically induced) factors. AMG is a very sensitive marker of ovarian damage - it changes even after low-dose chemotherapy or radiotherapy. AMG levels not only reflect ovarian function before treatment, but also predict the likelihood of recovery of ovarian function after treatment [4].

4. Conclusion. As a result of the analysis of the literature, it can be said that the search for specific markers for early detection of premature ovarian failure (POF) is currently of great interest in scientific circles. However, despite the fact that anti-Müllerian hormone (AMH) is the most suitable indicator for early assessment of ovarian reserve, to date there is no unified data on its normal levels depending on age and population. In addition, the clinical application of AMH levels in the blood is limited, since the sensitivity of existing diagnostic systems is insufficient and technical difficulties remain. The above circumstances indicate the need for new studies, a deeper study of the diagnostic value of AMH, and the development of practical clinical protocols.

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