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EARLY DIAGNOSTIC APPROACHES TO OVARIAN RESERVE DECLINE BASED ON GENETIC RISK FACTORS IN PREMATURE OVARIAN FAILURE

Jurayev Islombek Izzatullo ugli – 1st Year Clinical Resident, Obstetrics and Gynecology
Toshmurodova Yorkinoy Rustam kizi – 2nd Year Clinical Resident, Obstetrics and Gynecology
Rakhmonova Mohigul Shodikulovna – 1st Year Clinical Resident, Obstetrics and Gynecology
Candidate of Medical Sciences, Professor Agababyan Larisa Rubenovna – Head of the Department of Postgraduate Education in Obstetrics and Gynecology
Candidate of Medical Sciences, Professor Khudoyarova Dildora Rakhimovna – Head of Department of Obstetrics and Gynecology No. 1
Samarkand State Medical University, Samarkand, Uzbekistan

Abstract: Premature ovarian failure (POF), also referred to as primary ovarian insufficiency (POI), is a complex reproductive disorder characterized by the loss of ovarian function before the age of 40 years. The condition is associated with hypoestrogenism, elevated gonadotropin levels, infertility, and long-term metabolic and cardiovascular consequences. Recent advances in reproductive medicine have highlighted the crucial role of genetic factors in the development of POF, as well as the importance of early identification of declining ovarian reserve. Modern diagnostic strategies combine genetic testing, hormonal assessment, and ultrasonographic evaluation to predict ovarian aging at an early stage. This review analyzes genetic predictors of premature ovarian failure, evaluates methods for early detection of reduced ovarian reserve, and summarizes clinical studies assessing diagnostic accuracy and prognostic value of current testing approaches. Early identification of women at risk allows timely reproductive counseling and fertility preservation strategies, significantly improving clinical outcomes.

Relevance

Premature ovarian failure represents a major medical and social problem in modern gynecology. According to epidemiological data, POF affects approximately 1% of women under 40 years of age, 0.1% under 30 years, and up to 0.01% under 20 years [1]. The increasing age of first pregnancy, environmental stressors, and improved diagnostic capabilities have contributed to a growing number of identified cases.

The condition has a profound impact on reproductive potential, psychological well-being, and overall quality of life. Women with POF face a significantly increased risk of infertility, osteoporosis, cardiovascular disease, and metabolic disorders [2]. In recent years, particular attention has been paid to genetic predictors and early markers of ovarian reserve decline, which allow identification of high-risk patients before irreversible ovarian damage occurs.

The relevance of this topic is further supported by the growing availability of genetic screening methods and ovarian reserve biomarkers, enabling personalized reproductive medicine approaches.

Key words: Premature ovarian failure; primary ovarian insufficiency; ovarian reserve; genetic predictors; AMH; fertility preservation.

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Introduction. Premature ovarian failure is defined as the cessation of ovarian activity before the age of 40, accompanied by menstrual disturbances (amenorrhea or oligomenorrhea), elevated follicle-stimulating hormone (FSH) levels (>25 IU/L), and reduced estrogen production [3]. Although traditionally considered a rare condition, recent studies indicate that subclinical forms of ovarian insufficiency may be considerably more prevalent.

The etiology of POF is multifactorial and includes genetic abnormalities, autoimmune disorders, iatrogenic factors, infections, and environmental influences. Among these, genetic factors account for up to 20–30% of cases, making them one of the most significant contributors to early ovarian failure [4]. Identification of genetic predisposition allows clinicians to predict ovarian reserve decline at an early stage, even before clinical symptoms become apparent.

Epidemiology and Clinical Significance of Premature Ovarian Failure

Large population-based studies have demonstrated that approximately 10–28% of women diagnosed with POF experience intermittent ovarian function, emphasizing the heterogeneous nature of the condition [5]. Despite temporary ovarian activity in some cases, spontaneous pregnancy rates remain low, estimated at 5–10% [6].

POF is associated with:

- infertility in over 90% of affected women,
- reduced bone mineral density in 50–60% of patients,
- increased cardiovascular risk due to prolonged hypoestrogenism [7].

These data highlight the importance of early diagnosis and intervention, particularly in women with genetic susceptibility.

Materials and Methods: Genetic Predictors of Premature Ovarian Failure:

Chromosomal Abnormalities.

Chromosomal defects are among the most well-established genetic causes of POF. Abnormalities involving the X chromosome are detected in approximately 10–15% of patients [8]. These include:

- Turner syndrome (45,X),
- mosaicism (45,X/46,XX),
- structural abnormalities of the X chromosome.

Women with X chromosome abnormalities often present with accelerated follicular depletion, leading to early decline in ovarian reserve.

FMR1 Gene Premutation

One of the most extensively studied genetic predictors of POF is the FMR1 gene premutation, characterized by 55–200 CGG repeats. Studies indicate that 15–25% of women carrying the FMR1 premutation develop POF, compared to less than 1% in the general population [9].

Carriers of the premutation demonstrate significantly lower anti-Müllerian hormone (AMH) levels and reduced antral follicle count (AFC) compared to age-matched controls, suggesting accelerated ovarian aging.

Genetic Mutations Associated with Ovarian Reserve Decline

Beyond chromosomal abnormalities and FMR1 premutation, a growing number of autosomal gene mutations have been implicated in the pathogenesis of premature ovarian failure. These genes are primarily involved in folliculogenesis, oocyte maturation, and regulation of ovarian apoptosis.

BMP15 and GDF9 Genes

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The BMP15 (Bone Morphogenetic Protein 15) and GDF9 (Growth Differentiation Factor 9) genes encode oocyte-derived growth factors that play a critical role in follicular development. Mutations in these genes impair granulosa cell proliferation and disrupt follicular maturation. Clinical studies have demonstrated that pathogenic variants of BMP15 are present in approximately 4–12% of women with idiopathic POF, while GDF9 mutations are detected in 2–6% of cases [10]. Women carrying these mutations often present with:

- reduced antral follicle count (AFC < 5),
- significantly decreased AMH levels (<0.8 ng/mL),
- earlier onset of menstrual irregularities.

A cohort study involving 312 women with unexplained infertility revealed that carriers of BMP15 mutations experienced a 35–40% faster decline in ovarian reserve compared to non-carriers [11].

FOXL2 and NOBOX Genes

The FOXL2 gene is essential for ovarian differentiation and maintenance of granulosa cell identity. Mutations in FOXL2 have been associated with accelerated follicular atresia and early ovarian insufficiency. Pathogenic variants are identified in approximately 2–5% of POF patients, particularly in familial cases [12].

Similarly, the NOBOX (Newborn Ovary Homeobox) gene regulates early follicle formation. Studies report NOBOX mutations in 3–6% of women with primary ovarian insufficiency, with a significantly increased risk of ovarian failure before the age of 35 [13].

Assessment of Ovarian Reserve: Diagnostic Markers and Their Predictive Value

Early prediction of ovarian reserve decline relies on a combination of hormonal, ultrasonographic, and genetic markers. Among these, anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and antral follicle count (AFC) are considered the most reliable.

Anti-Müllerian Hormone (AMH)

AMH is produced by granulosa cells of preantral and small antral follicles and reflects the remaining follicular pool. Numerous studies confirm that AMH is the most sensitive early marker of ovarian aging.

In women with genetically determined POF:

- AMH levels < 1.0 ng/mL are detected in 72–85% of cases,
- AMH < 0.5 ng/mL predicts ovarian failure within 3–5 years with a sensitivity of 82% and specificity of 88% [14].

Longitudinal studies involving more than 500 participants have shown that AMH decline precedes clinical symptoms by an average of 4–6 years, highlighting its value for early screening [15].

Follicle-Stimulating Hormone (FSH)

Elevated basal FSH levels (>25 IU/L) remain a diagnostic criterion for established POF. However, FSH demonstrates limited sensitivity in early-stage ovarian insufficiency.

Studies indicate that:

- only 30–40% of women with early ovarian reserve decline show elevated FSH,
- FSH levels often fluctuate, leading to delayed diagnosis [16].

As a result, FSH is considered more useful for confirmation rather than early prediction.

Antral Follicle Count (AFC)

Transvaginal ultrasound assessment of AFC provides a direct visualization of ovarian reserve. An AFC < 5 follicles is strongly associated with reduced reproductive potential.

Clinical data suggest that women with genetic mutations associated with POF demonstrate:

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• a 45–60% reduction in AFC compared to age-matched controls,
• significantly poorer response to ovarian stimulation protocols [17].

Genetic Testing Strategies in Clinical Practice

Advances in molecular diagnostics have enabled the implementation of genetic testing in women at risk for premature ovarian failure.

Karyotyping and CGG Repeat Analysis

Standard karyotyping remains the first-line genetic test and identifies chromosomal abnormalities in 10–15% of patients.

CGG repeat analysis of the FMR1 gene is recommended for all women with unexplained ovarian insufficiency, given its high diagnostic yield [18].

Next-Generation Sequencing (NGS)

Next-generation sequencing panels targeting ovarian function-related genes have significantly expanded diagnostic capabilities. Recent studies demonstrate that NGS identifies pathogenic variants in 20–35% of previously idiopathic POF cases [19].

In a multicenter study involving 428 women, the use of NGS increased diagnostic accuracy by 28% and allowed earlier reproductive counseling in more than 60% of patients [20].

Clinical Studies and Statistical Evidence

Multiple cohort and case-control studies confirm the strong association between genetic abnormalities and early ovarian reserve decline. A meta-analysis including over 3,000 women demonstrated that carriers of pathogenic genetic variants had a 2.5–3.8-fold increased risk of developing POF compared to non-carriers [21].

Furthermore, early identification of high-risk patients enabled timely fertility preservation strategies, resulting in:

• successful oocyte cryopreservation in 65–70% of cases,
• improved reproductive outcomes in assisted reproductive technologies [22].

Early Prediction Models for Ovarian Reserve Decline

The integration of genetic, hormonal, and ultrasonographic markers has led to the development of early prediction models aimed at identifying women at risk of premature ovarian failure before the onset of clinical manifestations.

Multivariate prediction models combining AMH levels, AFC, age, and genetic markers have demonstrated high diagnostic accuracy. According to recent studies, models incorporating AMH <1.0 ng/mL, AFC <5, and the presence of pathogenic genetic variants achieved a sensitivity of 85–90% and specificity of 80–88% for predicting ovarian reserve decline within five years [23].

A prospective cohort study including 612 asymptomatic women with a family history of POF revealed that combined screening identified high-risk individuals an average of 5.2 years earlier than conventional diagnostic approaches [24]. This early identification enabled timely reproductive counseling and personalized fertility planning.

Fertility Preservation Strategies and Clinical Outcomes

Early prediction of ovarian reserve decline plays a critical role in the selection of fertility preservation strategies. Oocyte and embryo cryopreservation are currently considered the most effective methods for preserving reproductive potential in women at risk of POF.

Clinical data indicate that:

• oocyte cryopreservation before AMH falls below 0.5 ng/mL results in a live birth rate of 40–55% per patient,

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• women undergoing fertility preservation prior to significant ovarian reserve depletion demonstrate a 2–3-fold higher success rate in assisted reproductive technologies compared to those diagnosed at later stages [25].

In a multicenter study involving 387 women with genetically confirmed risk of POF, fertility preservation was successfully performed in 72% of cases, with a mean retrieval of 8.4 ± 2.1 oocytes per cycle [26].

Psychological and Long-Term Health Implications

Beyond reproductive consequences, premature ovarian failure is associated with significant psychological distress. Studies report increased rates of anxiety and depressive disorders in 45–60% of affected women, emphasizing the importance of early diagnosis and counseling [27].

Long-term hypoestrogenism also contributes to:

• reduced bone mineral density in up to 60% of patients,

• increased cardiovascular risk by 30–40% compared to age-matched controls [28].

Early detection allows timely initiation of hormone replacement therapy, which has been shown to improve bone density and reduce cardiovascular risk markers when started before the age of 40.

Discussion

Premature ovarian failure represents a multifactorial condition in which genetic predisposition plays a central role. Advances in molecular genetics have significantly expanded our understanding of the mechanisms underlying early ovarian aging. Identification of mutations in genes such as FMR1, BMP15, GDF9, FOXL2, and NOBOX provides valuable insight into individual risk profiles and enables the implementation of personalized diagnostic strategies.

The combination of genetic testing with sensitive ovarian reserve markers, particularly AMH and AFC, allows clinicians to detect ovarian dysfunction at a preclinical stage. This approach not only improves diagnostic accuracy but also opens new opportunities for fertility preservation and long-term health management.

Despite significant progress, challenges remain regarding the accessibility and cost-effectiveness of genetic screening. Future research should focus on refining prediction models, expanding genetic panels, and establishing standardized screening protocols for high-risk populations.

Conclusion: Premature ovarian failure is a significant gynecological condition with profound reproductive and systemic consequences. Genetic factors contribute substantially to the development of POF and play a crucial role in the early decline of ovarian reserve. Modern diagnostic strategies integrating genetic testing, hormonal assessment, and ultrasonographic evaluation provide high predictive accuracy and enable early identification of women at risk.

Early prediction of ovarian reserve decline allows timely reproductive counseling, fertility preservation, and preventive interventions, ultimately improving reproductive outcomes and quality of life. Continued research and implementation of personalized diagnostic approaches are essential for optimizing the management of premature ovarian failure in modern gynecological practice.

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