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MODERN CONCEPTS OF PATHOGENETIC MECHANISMS OF OVARIAN DYSFUNCTION (LITERATURE REVIEW)

Azizova Z. Sh.[1],
Musakhodzhaeva D.A.[1],
Mukhamedov R. S.[2],
Ruzimuradov N. F.[1],
Rustamova N. B.[1],
Mannopjonov P. B.[1]
[1]Institute of Immunology and Human Genomics,
Academy of Sciences of the Republic of Uzbekistan
[2]Hayot Technology LLC

Abstract
Ovarian dysfunction is a complex functional disorder driven by interactions among neuroendocrine, immune, metabolic, and genetic factors. This review article presents contemporary concepts of the pathogenetic mechanisms underlying ovarian dysfunction, emphasizing the role of cytokines, disturbances in hypothalamic-pituitary-ovarian axis regulation, and immune and genetic determinants. Special attention is given to diagnostic approaches and interdisciplinary aspects of patient management. The review is based on the analysis of recent data from authoritative international sources.

Aim: To conduct a comprehensive analysis of modern insights into the pathogenetic mechanisms of ovarian dysfunction, its clinical manifestations, and diagnostic approaches, as well as to examine the characteristics and prognosis of this condition in various gynecological and endocrine disorders.

Methods of literature selection: The sources include up-to-date information from international peer-reviewed scientific journals and major bibliographic databases such as PubMed, Scopus, Web of Science, eLibrary, and CyberLeninka.

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Keywords: ovarian dysfunction, pathogenesis, immune mechanisms, neuroendocrine regulation, cytokines, polycystic ovary syndrome, ovarian reserve, diagnostics, inflammation, reproductive function.

Introduction

Ovarian dysfunction is a complex clinical and functional condition characterized by impaired ovulatory, hormonal, and reproductive functions of the ovaries while preserving the anatomical integrity of the gonads. Unlike ovarian insufficiency associated with the depletion of ovarian reserve, ovarian dysfunction is often reversible and may result from primary regulatory disorders within the hypothalamic-pituitary-ovarian axis or secondary metabolic, inflammatory, or immune factors [1, 2].

According to the World Health Organization, approximately 30–40% of all female infertility cases are attributed to anovulation, predominantly associated with chronic ovarian dysfunction [3]. This condition is commonly accompanied by hyperandrogenism, insulin resistance, chronic anovulation, and metabolic profile alterations, increasing the risk not only of infertility but also cardiovascular diseases, type 2 diabetes, and endometrial cancer.

The pathogenesis of ovarian dysfunction is multifactorial, encompassing neuroendocrine, immunological, metabolic, and genetic mechanisms. Recent studies indicate that cytokines, synthesized both systemically and locally within ovarian tissues, act as mediators that disrupt folliculogenesis and steroidogenesis [4, 5].

The relevance of systematizing recent literature lies in the need for a comprehensive analysis of mechanisms underlying ovarian dysfunction and the clinical, laboratory, and instrumental markers contributing to early diagnosis, risk stratification, and individualized therapeutic approaches.

The objective of this review is to conduct a comprehensive analysis of modern concepts regarding the pathogenetic mechanisms of ovarian dysfunction, its clinical manifestations, and diagnostic approaches, as well as to examine the course and prognosis of this condition in various gynecological and endocrine diseases. Special attention is given to interdisciplinary aspects, including the

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involvement of metabolic, immune, and neuroendocrine factors, to form an integrated understanding of the problem and substantiate personalized patient management strategies.

Methods of literature selection

To achieve the objectives of this review, targeted selection and analysis of scientific publications covering key aspects of pathogenesis, clinical manifestations, diagnostic criteria, and comorbidities associated with ovarian dysfunction in gynecological and endocrine disorders were conducted. The sources included current data published in international peer-reviewed journals and major bibliographic databases such as PubMed, Scopus, Web of Science, eLibrary, and CyberLeninka.

Publication selection was based on thematic relevance, with priority given to studies published within the last ten years. Particular emphasis was placed on systematic reviews, meta-analyses, and multicenter cohort studies that provide high levels of evidence. National and international clinical guidelines from leading reproductive, endocrine, and gynecological associations (ESHRE, ASRM, Endocrine Society, RARCH, and others) were also taken into account. This approach enabled the formation of an integrated and modern perspective on ovarian dysfunction and its systemic associations.

Classification and Forms of Ovarian Dysfunction

Table 1. Classification of ovarian dysfunction according to ICD-10 and ICD-11

Clinical-Diagnostic Form	Description	ICD-10	ICD-11
Central (Hypothalamic-Pituitary)	Anovulation, hypoestrogenism	N91.1 / E28.8	GA30.2 / GA34.Z
Ovarian	Decreased ovarian reserve, resistant ovaries	E28.3	GA34.1
Target-dependent	Steroid resistance	E28.8	GA34.Z
Metabolic	PCOS with IR and hyperandrogenism	E28.1 / N97.0	GA34.0 / 5A53.1
Immune-dependent	Autoimmune oophoritis, thyroiditis	E28.2	GA34.Z
Iatrogenic	Post-surgery, chemotherapy/radiation	E28.8 / N91.2	GA34.1
Mixed	Combined forms (PCOS + AIT, etc.)	E28.1 + E28.2	GA34.0 + GA34.Z

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Ovarian dysfunction represents a heterogeneous functional disorder resulting from disrupted regulation of the ovarian cycle, accompanied by anovulation, impaired steroidogenesis, altered hormonal profiles, and, in some cases, infertility. Modern understanding of the pathogenesis and clinical forms of ovarian dysfunction allows for the identification of several key variants differing in etiology, formation mechanisms, and clinical manifestation.

One of the most common forms is hypothalamic-pituitary, or central dysfunction, caused by disturbances in the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus or decreased production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland. Such conditions are observed in functional hypothalamic amenorrhea due to chronic stress, significant weight loss, anorexia, or excessive physical activity. According to Warren & Fried et al., these cases present with normal ovarian anatomy but significant gonadotropin deficiency, leading to hypoestrogenism and secondary amenorrhea [6]. Another common variant, identified by Gillam et al., is hyperprolactinemia, often associated with pituitary prolactinomas, which inhibits GnRH secretion and disrupts ovarian cyclicity [7].

The ovarian form of dysfunction, in which the receptor and steroidogenic mechanisms within the ovaries are primarily affected, is another significant clinical-pathogenetic type. Polycystic ovary syndrome (PCOS), one of the most frequent causes of anovulatory infertility in reproductive-age women, is the most prominent example. According to epidemiological data by Teede et al. and Lizneva et al., PCOS occurs in 6–13% of women [8, 9], and in certain ethnic populations, up to 20%. The syndrome is characterized by chronic anovulation, hyperandrogenism, polycystic ovarian morphology, and pronounced metabolic disorders, including insulin resistance and obesity. Nelson et al. also identified resistant ovary syndrome, where follicles are present but insensitive to gonadotropins despite normal or elevated hormone levels, as an ovarian form [10].

Receptor-related disorders also play a critical role in the pathogenesis of ovarian dysfunction. This target-dependent form maintains normal hypothalamic-pituitary function and ovarian morphology but disrupts hormonal action at the

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cellular level. As noted by Ehrmann et al., such conditions include congenital steroidogenesis enzyme dysfunction, impaired LH and FSH sensitivity, and genetic forms of hyperandrogenism [11]. These may manifest with hyperandrogenic symptoms and anovulation despite normal gonadotropin levels.
Metabolic ovarian dysfunction is another distinct category that develops against the background of insulin resistance, hyperinsulinemia, obesity, and metabolic syndrome. Studies have shown that insulin exerts a direct stimulatory effect on ovarian theca cells, enhancing androgen production, and indirectly disrupts FSH/LH balance, inhibiting ovulation [12]. This mechanism underlies PCOS pathogenesis and aggravates clinical manifestations, increasing the risk of metabolic and cardiovascular complications.
The immune-dependent form of ovarian dysfunction is associated with autoimmune damage to ovarian tissue, as seen in autoimmune oophoritis. These processes may occur in isolation or as part of autoimmune polyglandular syndrome. Characteristic features include ovarian autoantibodies, follicular inflammatory infiltration, and gradual depletion of ovarian reserve [13]. Dysfunction may also be observed in systemic autoimmune diseases such as systemic lupus erythematosus, Addison's disease, and autoimmune thyroiditis.
Iatrogenic and postoperative ovarian dysfunction, which often results from surgical interventions involving the ovaries, particularly resection or endometrioma removal, as well as chemotherapy and radiation therapy, is clinically significant. In such cases, ovarian tissue may partially retain functionality, yet ovulation disorders and reduced fertility are common. Wallace et al. demonstrated that even unilateral ovarian resection significantly reduces ovarian reserve, especially in women over 30 years old [14].
In some instances, mixed forms of ovarian dysfunction arise, where multiple pathogenetic mechanisms coexist. According to Azziz et al., PCOS exemplifies this category, involving neuroendocrine, metabolic, inflammatory, and immune components [15].
Thus, this classification of ovarian dysfunction enhances patient stratification based on pathogenesis and presumed etiology, which is crucial for selecting optimal diagnostic and therapeutic strategies. Future attention should focus on

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interdisciplinary analysis, including immunological, neuroendocrine, and metabolic aspects, particularly relevant in the context of personalized reproductive medicine.

Pathogenesis of Ovarian Dysfunction

The pathogenesis of ovarian dysfunction is a multifactorial and complex process involving the interplay of neuroendocrine, metabolic, immune, and genetic mechanisms. It includes dysregulation of the hypothalamic-pituitary-ovarian axis, altered expression of receptors for gonadotropins and sex steroids, follicular apparatus dysfunction, local inflammation, and the influence of external and iatrogenic factors.

A central link in the pathogenesis of most forms of ovarian dysfunction is associated with hypothalamic-pituitary system dysregulation. Insufficient or erratic GnRH secretion leads to impaired pulsatile stimulation of the pituitary, disrupting the LH/FSH ratio and consequently impairing folliculogenesis. According to Warren & Fried, this is especially pronounced in functional hypothalamic amenorrhea developing against a background of chronic stress, low body weight, and hypercatabolic states [6]. In hyperprolactinemia, GnRH suppression occurs via dopaminergic mechanisms, reducing gonadotropin stimulation and leading to hypoestrogenism [7].

Insulin resistance plays a significant role in the pathogenesis of ovarian dysfunction and, according to numerous studies, contributes to anovulation even with preserved ovarian structure. Elevated insulin levels enhance androgen production in ovarian theca cells, inhibit sex hormone-binding globulin (SHBG) synthesis, and reduce follicular sensitivity to FSH [12]. Diamanti-Kandarakis & Dunaif have established that this process is characteristic primarily of women with PCOS, where insulin resistance represents both a metabolic and reproductive disorder.

The immune-inflammatory component also plays a crucial role in the pathogenesis of ovarian dysfunction. Studies by Bednarska & Siejka, and Pizzo et al., indicate that elevated expression of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β may impair local folliculogenesis and luteinization

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regulation, trigger granulosa cell apoptosis, and create a microenvironment unfavorable for follicle maturation [5, 4]. Furthermore, chronic subclinical inflammation typical of metabolic syndrome and PCOS has additional adverse effects on ovarian tissue, promoting fibrosis and reducing gonadotropin sensitivity.

Autoimmune mechanisms are also significant, especially in cases of coexisting autoimmune diseases (e.g., Hashimoto's thyroiditis, systemic lupus erythematosus, Addison's disease). Eisenbarth & Gottlieb's research found ovarian antibodies, stromal lymphocytic infiltration, elevated HLA-DR expression, and other immune activation markers, supporting the role of autoimmunity in ovarian dysfunction development [13]. These cases may involve progressive follicular apparatus destruction and reduced hormonal production.

Genetic and epigenetic mechanisms are increasingly recognized. Genes regulating folliculogenesis (e.g., FSHR), steroid metabolism (CYP11A1, CYP19A1), and polymorphisms associated with insulin resistance and inflammation regulation (INR, TNF, IL-6) are implicated. Additionally, studies by Kevenaar et al. and La Marca et al. identified mutations and polymorphisms in AMH and AMHR2 genes, potentially linked to impaired follicular recruitment and decreased ovarian reserve [17, 18].

Iatrogenic factors, including ovarian surgeries (especially endometrioma resection), chemotherapy, and radiation therapy, cause direct damage to the follicular apparatus, decrease AMH levels, and increase FSH, which clinically manifests as dysfunction and, in some cases, progresses to premature ovarian insufficiency [14].

Thus, the pathogenesis of ovarian dysfunction involves a complex interplay between regulatory, metabolic, and immunological factors. Comprehensive understanding of these mechanisms allows for more precise diagnosis of dysfunction forms and the development of personalized therapeutic strategies targeting pathogenetic links.

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Clinical Manifestations and Forms of Ovarian Dysfunction

The clinical presentation of ovarian dysfunction is highly polymorphic and depends on the predominant pathogenetic mechanism, patient age, duration of the pathological process, and associated conditions. Nevertheless, several characteristic syndromes and phenotypic manifestations allow clinicians to suspect ovarian dysfunction even during initial consultation.

One of the most common manifestations is anovulation — the absence of ovulation despite preserved or irregular menstruation. Anovulation may remain latent and only be revealed during infertility evaluation. Clinically, it often presents as oligomenorrhea (menstrual intervals longer than 35 days), sporadic menstruation, or secondary amenorrhea. Some patients may exhibit hypomenorrhea — scant and short menstrual periods indicative of low estrogen levels and impaired endometrial transformation.

A second key symptom is hormonal imbalance, primarily hyperandrogenism, which manifests clinically as seborrhea, acne, hirsutism, and male-pattern alopecia. Hyperandrogenic signs are most typical in PCOS and metabolic syndrome patients, where both ovarian and adrenal sources contribute to androgen excess [4]. Biochemical hyperandrogenism may be detected by elevated serum testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEA-S) levels, along with reduced SHBG levels, increasing free testosterone proportion [3].

Some patients, especially those with central forms of ovarian dysfunction, develop hypoestrogenism, which manifests as vaginal dryness, decreased libido, mood lability, sleep disturbances, and vasomotor symptoms. As Nelson describes, prolonged hypoestrogenism, particularly in hypogonadotropic amenorrhea or post-iatrogenic cases, may lead to bone mass loss, osteopenia, and osteoporosis [10].

Reproductive dysfunction plays a substantial role in the clinical picture, including infertility, recurrent pregnancy loss, and failed assisted reproductive technology (ART) attempts. According to Norman et al., up to 40% of women attending reproductive clinics have some form of ovarian dysfunction [16]. These patients

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often experience impaired follicular maturation, untimely ovulation, luteal phase deficiency, and abnormal responses to gonadotropin stimulation.

Ultrasound findings also vary. In PCOS, a typical polycystic ovarian morphology is noted, characterized by increased ovarian volume, >12 follicles (2–9 mm) per ovary, and enhanced stromal echogenicity [17]. Conversely, women with ovarian hypofunction (e.g., post-surgery or autoimmune forms) may show reduced ovarian volume, sparse follicles, or follicular absence.

Additional clinical features include abdominal obesity, insulin resistance, acanthosis nigricans, arterial hypertension, and dyslipidemia — all common in metabolic forms of ovarian dysfunction and necessitating a multidisciplinary approach [18].

Given the heterogeneity of clinical manifestations, comprehensive clinical, laboratory, and instrumental diagnostics are crucial. These include menstrual history analysis, hormonal profiling, pelvic ultrasound, ovarian reserve assessment, and, when necessary, immunological and genetic testing.

Ovarian Dysfunction in Gynecological and Endocrine Disorders

Ovarian dysfunction may occur as an independent pathological condition or as a secondary manifestation of various gynecological and endocrine disorders. In such cases, it arises against the background of hormonal, immune, and metabolic dysregulation, leading to menstrual irregularities, impaired ovulation, and reduced fertility.

Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy in reproductive-aged women, affecting between 6% and 13% of the female population, and up to 20% in certain ethnic groups [9, 8]. PCOS is a polyetiological condition involving hormonal, metabolic, and immune disturbances, resulting in persistent ovarian dysfunction. The pathogenesis of PCOS includes chronic anovulation linked to elevated LH secretion, an LH/FSH imbalance, hyperandrogenism, and insulin resistance. Androgen overproduction by theca cells impairs follicular maturation and ovulation, while hyperinsulinemia reduces SHBG synthesis, increasing free testosterone levels and exacerbating hyperandrogenic symptoms.

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Inflammatory factors also play a role in PCOS pathogenesis. Elevated IL-6, TNF-α, and CRP levels correlate with the severity of metabolic and reproductive disturbances [19]. Thus, PCOS should be considered not only a local ovarian disorder but also a systemic condition involving immune and metabolic pathways, requiring an interdisciplinary approach.

Hyperprolactinemia, characterized by chronically elevated prolactin levels, disrupts the hypothalamic-pituitary-ovarian axis and affects 10–20% of women with menstrual irregularities and infertility [7]. Causes include prolactinomas, hypothyroidism, chronic stress, and certain medications. Prolactin suppresses GnRH secretion, reducing LH and FSH production and leading to hypoestrogenism. This state is accompanied by oligomenorrhea or amenorrhea, anovulation, decreased libido, vaginal dryness, and sometimes galactorrhea. Timely diagnosis and pharmacological treatment, especially dopamine agonists (cabergoline, bromocriptine), often restore hormonal balance and reproductive function.

Endometriosis, a chronic inflammatory disorder characterized by endometrial cell implantation outside the uterus, frequently involves the ovaries. Ovarian endometriomas are associated with reduced ovarian reserve. The pathogenesis includes direct tissue damage, impaired blood supply, fibrosis, and chronic inflammation with elevated cytokines and growth factors [19]. Surgical removal of endometriomas risks healthy tissue resection and AMH decline. Bilateral cystectomy notably reduces ovarian reserve even in young women [17]. Managing endometriosis requires balancing surgical intervention with fertility preservation.

Autoimmune thyroid disorders (e.g., Hashimoto's thyroiditis), particularly with hypothyroidism, influence female reproductive health. Thyroid hormones modulate gonadotropin sensitivity and SHBG synthesis. Hypothyroidism impairs GnRH pulsatility, reduces ovarian stimulation, and contributes to anovulation. Elevated prolactin further exacerbates ovulatory dysfunction. Anti-TPO and anti-TG antibodies may also impact ovarian function [20]. Women with Hashimoto's thyroiditis face increased infertility risks, requiring TSH monitoring and hypothyroidism correction during preconception planning.

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Metabolic syndrome (MS) and abdominal obesity are key modifiable risk factors for ovarian dysfunction. Insulin resistance and hyperinsulinemia activate theca cells and enhance androgen synthesis. Adipose tissue secretes pro-inflammatory cytokines (IL-6, TNF-α) and adipokines (leptin, resistin), disrupting ovarian homeostasis [21]. MS patients often show oligomenorrhea, anovulation, low AMH, and poor ART outcomes. Weight loss, insulin sensitizers, and lifestyle modification significantly improve ovulatory function and fertility.

Modern Diagnostic Methods and Principles

Diagnosing ovarian dysfunction requires a comprehensive evaluation of hormonal profiles, ovarian function, gonadal morphology, and related metabolic and immune factors. Early detection is critical for preventing infertility.

Hormonal analysis remains central. FSH and LH levels (measured on cycle days 2–5) assess hypothalamic-pituitary-ovarian axis function. An elevated LH/FSH ratio (>2) often indicates PCOS. Estradiol, prolactin, testosterone, androstenedione, DHEA-S, TSH, and free thyroxine levels are also assessed. Hormonal shifts, particularly elevated androgens and prolactin, play key roles in anovulation [15].

Ovarian reserve assessment has gained importance. AMH reflects pre-antral and antral follicle counts and correlates with fertility potential and ovulation response. La Marca & Sunkara showed that AMH <1.1 ng/mL indicates diminished reserve [22]. Antral follicle count (AFC) <5 per ovary also indicates low reserve. Combining AMH and AFC enhances assessment accuracy, particularly for ART planning [23].

Ultrasound remains essential. PCOS is characterized by enlarged ovaries, ≥12 follicles (2–9 mm), and increased stromal echogenicity [17]. Advanced imaging (3D ultrasound, automated folliculometry) improves measurement precision [21].

Given the link with metabolic disorders, glucose, HbA1c, insulin levels, HOMA-IR, and lipid profiles are routinely assessed. Inflammatory biomarkers such as IL-6, TNF-α, and hsCRP indicate chronic subclinical inflammation [5, 24].

Immunological testing, including anti-TPO and anti-TG antibodies, is critical in suspected autoimmune ovarian dysfunction, especially with Hashimoto's

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thyroiditis. Anti-ovarian and anti-21-hydroxylase antibodies may be present in autoimmune syndromes. Research highlights altered Th17/Treg balance and elevated IL-17 in ovarian dysfunction, suggesting future potential for immunomodulatory therapies [25].

Genetic testing is recommended for young women with early menstrual irregularities and family history. FMR1 premutation analysis, linked to fragile X syndrome, assesses early ovarian insufficiency risk [16]. Polymorphisms in FSHR, AMH, AMHR2, and CYP19A1 genes may also affect ovarian sensitivity. NGS technology now enables comprehensive gene panel analysis.

In summary, modern diagnostics integrate clinical, hormonal, ultrasound, metabolic, immune, and genetic data to accurately identify dysfunction forms and guide personalized management strategies. Ovarian dysfunction reflects complex endocrine, immune, and genetic interactions. Immunoinflammatory and autoimmune contributions are increasingly recognized. Emerging evidence on cytokines (IL-6, TNF-α, IL-17A), Th17/Treg imbalance, microRNAs, and oxidative stress suggests new therapeutic targets.

NGS genetic testing enables early identification of premature ovarian insufficiency risk, essential for individualized IVF and fertility management. Guidelines (ESHRE, ASRM, Russian Ministry of Health, RARCH) emphasize a multilayered approach incorporating hormonal, ultrasound, immune, and genetic screening.

Unresolved challenges remain, including standardizing cytokine reference levels, immune marker panels, and evaluating environmental factors like xenobiotics and microparticles (e.g., microplastics) potentially contributing to chronic ovarian inflammation.

Conclusion

Ovarian dysfunction is a heterogeneous and multi-level condition that requires an interdisciplinary approach to diagnosis and treatment. Modern methods enable the classification of clinico-pathogenetic forms of the disease, facilitating more precise risk stratification and the personalization of patient management strategies. Immunological and genetic research, including the assessment of

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cytokines, autoantibodies, FSHR, AMH, AMHR2 polymorphisms, and the use of next-generation sequencing (NGS), play an increasingly important role.

To enhance reproductive care and prevent infertility, unified diagnostic algorithms should be implemented, screening programs expanded, and new molecular therapeutic targets investigated, with particular emphasis on the individual pathogenetic profile. Special attention should be paid to patients with metabolic syndrome, autoimmune disorders, and a family history of reproductive dysfunction.

The presented analysis highlights ovarian dysfunction as a result of complex interactions between endocrine, immune, and genetic factors. The growing recognition of immunoinflammatory responses and autoimmune processes has expanded the understanding of its pathogenesis. Advances in research on cytokines (IL-6, TNF-α, IL-17A), Th17/Treg imbalances, microRNAs, and oxidative stress offer promising avenues for immunomodulatory and antioxidant therapies.

Genetic diagnostics, particularly using NGS, now enable the identification of predispositions to premature ovarian insufficiency, which is critical for individualized IVF planning and fertility management. According to leading clinical guidelines (ESHRE, ASRM, Russian Ministry of Health, RARCH), a multi-level diagnostic approach — spanning hormonal, ultrasound, immune, and genetic assessments — is essential.

Nevertheless, unresolved challenges remain. Reference ranges for cytokines in reproductive practice have not been standardized, validated immune marker panels are still lacking, and the impact of environmental factors, such as xenobiotics and microparticles like microplastics, on chronic ovarian inflammation remains insufficiently studied.

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