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CURRENT IDEAS ABOUT THE ROLE OF THE IMMUNE SYSTEM IN THE DEVELOPMENT OF OVARIAN DYSFUNCTION IN WOMEN OF REPRODUCTIVE AGE (LITERATURE REVIEW)

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Abstract

Topicality. Ovarian dysfunction is one of the leading causes of female infertility, manifesting itself in the form of anovulation, premature ovarian exhaustion (POI), polycystic ovary syndrome (PCOS), and reduced response to gonadotropic stimulation. Modern research increasingly indicates the involvement of the immune system in the pathogenesis of these conditions, which requires systematic analysis and generalization of data.

Purpose. To review the current scientific data reflecting the mechanisms of immune dysregulation in various forms of ovarian dysfunction in women of reproductive age.

Materials and methods. The review includes publications from the last decades, selected from the international databases PubMed, Scopus, Web of Science and Google Scholar. The inclusion criteria were: clinical and experimental studies concerning the role of immune cells, cytokines, autoantibodies and immune regulation molecules (IL-6, TNF-α, IL-10, FOXP3, HLA-G, etc.) in PCOS, POI and other forms of ovarian dysfunction. Particular attention is paid to multiplex diagnostic methods and immunological predictors reproductive prognosis.

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Key words: ovarian dysfunction, immune system, cytokines, autoantibodies, polycystic ovary syndrome, premature ovarian failure, FOXP3, HLA-G.

Introduction

Ovarian dysfunction is a heterogeneous group of ovarian dysfunction that includes anovulation, oligomenorrhea, primary ovarian insufficiency (POI), gonadotropin resistance, and decreased ovarian reserve. It is one of the leading pathogenetic mechanisms of female infertility [71]. According to the World Health Organization (WHO), infertility is the inability to achieve clinical pregnancy within 12 months of regular sexual activity without the use of contraception [65].

According to the WHO, about 1 in 6 people in the world experience infertility during their lifetime, which is about 17.5% of the adult population [66]. The female factor associated with ovulatory disorders contributes to about 25–30% of all infertility cases [43; 60;]. Among all forms of reproductive dysfunction, polycystic ovary syndrome (PCOS), POI, and chronic anovulation are of the greatest clinical significance.

In general, ovarian dysfunction is a multifactorial condition that develops against the background of neuroendocrine, metabolic, immunological, and inflammatory disorders [52]. Of particular interest is the role of the immune system, which regulates the most important processes such as folliculogenesis, ovulation, atresia, angiogenesis, and luteinization [7]. Immune cells (T-lymphocytes, macrophages, NK cells), as well as pro-inflammatory and anti-inflammatory cytokines, are actively involved in the regulation of the ovarian microenvironment [36].

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Table 1. Prevalence of female infertility associated with ovarian dysfunction: international data and sources

Country	Female infertility rate (%)	Type of predominant infertility	Source (authors, year)	Database / Organization
United States	**12.1%** (≈ 7.4 million women with fertile dysfunction)	Primary and secondary	CDC National Health Statistics Report, 2024	CDC NSFG 2015–2019
Russia (Western Siberia)	**16.7%** (3.8% primary, 12.9% secondary)	Predominantly secondary	Tomsk Study (WHO Methodology), 2000	WHO-Centric Demographic Survey
Nigeria	**17 %**	Both types	Abebe et al., 2020	DHS / WHO Global Health Observatory
Ethiopia	**18 %**	Both types	Abebe et al., 2020	DHS / WHO
China (Henan)	**24.6%** (6.5% primary, 18.1% secondary)	Both types (ovulation disorder)	Wang et al., 2021	Regional Survey of the People's Republic of China (Henan)

In recent years, there has been growing evidence of the involvement of immune imbalances—in particular, chronic subclinical inflammation, decreased regulatory activity of Treg cells, and activation of the Th1/Th17 response—in the pathogenesis of various forms of ovarian dysfunction [16; 31]. However, systemic generalizations of data on specific immune markers remain limited.

The purpose of the review article is to conduct a generalized analysis of current data on the role of key immune markers (including cytokines, cells of innate and adaptive immune response, autoantibodies) in the development of ovarian dysfunction in women of reproductive age, as well as to assess their potential diagnostic and prognostic significance.

Methods of Selection of Literary Sources. To achieve the goal, a targeted selection and analytical processing of scientific publications containing information on the immunological aspects of pathogenesis, clinical manifestations and diagnostic approaches in various forms of ovarian dysfunction

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was carried out. The review includes data from peer-reviewed international and national journals indexed in the PubMed, Scopus, Web of Science, eLibrary and CyberLeninka databases.

Publications were selected with priority in favor of works of the last 10 years, with special attention paid to systematic reviews, meta-analyses, and large cohort studies, as well as original articles with a high evidence base. In addition, current clinical guidelines and consensus documents of organizations such as ESHRE, ASRM, Endocrine Society and RAHR were analyzed. This made it possible to integrate fundamental and clinical data into a single pathogenetic context and form a holistic view of the immunological mechanisms of ovarian dysfunction within the framework of personalized medicine.

Physiological role of the immune system in the ovaries

The immune system plays a key role in regulating reproductive function, providing immunological control over processes such as folliculogenesis, ovulation and luteolysis. These processes are accompanied by local activation of an innate and adaptive immune response, involving macrophages, T lymphocytes, NK cells, and a wide range of pro-inflammatory and anti-inflammatory cytokines.

Table 2. **Phase-dependent immune activity in the ovarian cycle in women**

Cycle phase	**Key immune cells**	**Key cytokines and mediators**	**Main functions**	**Source (authors, year)**
Folliculogenesis	Macrophages, dendritic cells, Th2, Treg	IL-4, IL-10, TGF-β, VEGF	Follicle maturation, angiogenesis, immune tolerance	*Basini et al., 2023; Vasilyeva et al., 2020*
Ovulation	ILC1, ILC3, NK cells, neutrophils, Th1	TNF-α, IL-1β, IL-22, MMP-2/9, IFN-γ	Follicular wall destruction, lysis, neutrophil recruitment	*Jiang et al., 2022; Liu et al., 2021*
Luteolysis	CD8+ T cells, NK cells, macrophages	FasL, TRAIL, TNF-α, IL-17A	Apoptosis of luteal cells, regression of the corpus luteum	*Bukovsky et al., 2021; Danilova et al., 2022*

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1. **Folliculogenesis** is a multi-step process of follicle maturation regulated by both hormonal and immune signals. In the early stages of follicle development, resident macrophages and dendritic cells play a key role, providing the production of IL-6, IL-1β, and TNF-α, which modulate granulosa cell proliferation and steroidogenesis [56; 67]. An important role is also played by Th2 and Treg cells, which synthesize IL-4, IL-10, and TGF-β, which contribute to immune tolerance and maintenance angiogenesis [2].

At the stage of preovulatory growth, the synthesis of chemokines (MCP-1, IL-8, and CCL2) is activated, which contribute to the attraction of monocytes and neutrophils to follicular tissue, increasing the expression of growth factors, including VEGF, and ensuring angiogenesis in the growing follicle [55; 20]. Insufficient expression of MCP-1 and IL-6 is accompanied by impaired growth of the dominant follicle [40].

Normally, there is a close interaction between Th2 cytokines (IL-4, IL-13) and local antigen-presenting cells, which promotes immune tolerance and oocyte maturation. Disruption of this balance can lead to increased activity of NK cells and activation of the Th1 response associated with follicular atresia [18; 37].

2. **Ovulation** is a localized sterile inflammatory process induced by a peak release of luteinizing hormone (LH). This hormonal signal stimulates a sharp release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in the follicular fluid and tissue, which initiates degradation of the basement membrane and rupture of the follicular wall [1; 27].

TNF-α and IL-1β activate the expression of matrix metalloproteinases (MMP-2, MMP-9) and prostaglandins (PGE2), which contribute to the destruction of the connective tissue framework of the follicle and local vascular remodeling [73]. Recruitment of neutrophils and macrophages enhances the inflammatory response and provides immune control over tissue damage [49].

In vivo studies have shown that TNF-α deficiency is accompanied by anovulation and follicle rupture defects [37]. Overexpression of IL-6 is associated with a premature luteinizing effect and impaired oocytic maturity [22].

A special role in the ovulatory peak is played by the cells of innate immunity. According to [28; 29], ILC1 and ILC3 subtypes are expressed in ovarian tissue

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and follicular fluid, modulating the synthesis of TNF-α, IL-22, and angiogenic factors (VEGF, Ang-1), promoting MMP expression and follicular wall remodeling. Impaired activity of ILC cells is associated with anovulation and deficiency of LH peaks.

Natural killer cells (NK cells) with cytotoxic potential perform a regulatory function during the ovulatory phase: they promote follicular membrane lysis, corpus luteum formation, and vascularization through the production of IFN-γ and TNF-α [35; 64]. Increased activity of CD56dim NK cells and decreased expression of NKG2D receptors are associated with chronic ovulatory failure and implantation disorders [13; 14].

3. **Luteolysis** is the process of reverse development of the corpus luteum in the absence of implantation. It is accompanied by a decrease in progesterone production and the induction of apoptosis. The most important mediators are FasL, TRAIL and TNF-α produced by macrophages and CD8+ T-lymphocytes [3; 4; 7; 8].

Cytotoxic signals cause apoptosis of luteal cells, capillary degradation, and an influx of CD68+ macrophages phagocytizing cell residues [11; 69]. IFN-γ enhances the expression of Fas receptors and promotes regression of the corpus luteum [9], while a decrease in IL-10 weakens anti-inflammatory defenses, contributing to the completion of luteolysis [33].

Thus, the immune system has a multi-level effect on the reproductive function of the ovaries, participating in follicle maturation, ovulation and regression of the corpus luteum. Disruption of these mechanisms underlies ovarian dysfunction and can serve as an early marker of infertility risk.

Cytokine imbalance in ovarian dysfunction

Ovarian function in women of reproductive age is provided by the subtle interaction of hormonal and immune regulators. One of the central mechanisms that support fertility is immune homeostasis, based on the balanced interaction of pro-inflammatory and anti-inflammatory cytokines. Disruption of this balance leads to the formation of a pathological immune microenvironment that

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contributes to the death of follicular cells, impaired angiogenesis, chronicity of inflammation, and a decrease in ovarian reserve [38; 17;].

Cytokines are low-molecular signaling molecules produced by cells of innate and adaptive immunity. They play a key role in coordinating folliculogenesis, ovulation, corpus luteum function, and cell death processes in ovarian tissue. Normally, their production is under the control of hormonal and local cellular factors. However, in pathological conditions, a persistent cytokine imbalance develops, accompanied by subclinical inflammation, impaired follicle maturation and a progressive decrease in ovarian reserve.

Pro-inflammatory cytokines. Interleukin-1β (IL-1β) is one of the early mediators of inflammation, secreted by macrophages and dendritic cells in response to tissue damage. In studies by Basini et al. (2023), as well as Fedorova et al. (2022) showed that IL-1β induces cyclooxygenase-2 (COX-2) expression, metalloproteinase activation (MMP-2/9), and prostaglandin synthesis, promoting ovulatory follicle rupture. At the same time, chronic overexpression of IL-1β disrupts the expression of FSH receptors and accelerates atresia processes [2; 19; 20].

Interleukin-6 (IL-6) produced by macrophages and granulosa cells regulates angiogenesis, enhances VEGF expression, and affects immune infiltration. According to Kianmehr et al. (2021), as well as research conducted by Vasilyeva et al. (2020), the level of IL-6 is significantly increased in plasma and follicular fluid in patients with PCOS and PON, which correlates with anovulation and hormonal resistance [31; 64].

Tumor necrosis factor-alpha (TNF-α), actively secreted by macrophages and T-lymphocytes, has a dual effect. It is involved in the rupture of the mature follicle during ovulation, but in chronic overexpression it induces apoptosis of granulosa cells, suppresses the expression of steroidogenic enzymes and reduces ovarian reserve. In studies by Duleba and Dokras (2012), as well as Melnik et al. (2021), TNF-α has been considered as a key mediator of immunometabolic disorders in women with PCOS, especially in combination with obesity and insulin resistance [15; 45].

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Interleukin-8 (IL-8, CXCL8) and the chemoattractant MCP-1 (CCL2) provide neutrophil and monocyte chemotaxis to the ovarian stroma, especially during ovulation. In a study by Zhou et al. (2023) found that overexpression of these molecules is accompanied by an increase in local inflammatory infiltration and oxidative stress, and may also impair follicle receptivity [74]. Similar data are provided by Fedorova et al. (2022), which showed the participation of IL-8 and MCP-1 in the formation of a subclinical inflammatory microenvironment [19].

Interleukin-17A (IL-17A), produced by Th17 cells, has a cytotoxic effect on the cells of the granulosa layer, enhances angiopathic processes and the expression of pro-inflammatory genes. According to the results of Liu et al. (2022) and Danilova et al. (2022), elevated IL-17A levels are detected in women with autoimmune forms of POI, accompanied by pronounced impaired angiogenesis and early follicle degradation [37; 11].

Interferon-gamma (IFN-γ), a key cytokine of the Th1 response, induces the expression of major histocompatibility complex class I molecules and Fas receptors, activates NK cells and cytotoxic CD8+ T lymphocytes. In the studies of Chudaeva et al. (2019) and El-Kabarity et al. (2023) described its role in implantation window disruption, premature regression of the corpus luteum, and immune mediation of oocyte apoptosis [9; 10; 18].

GM-CSF (granulocyte-macrophage colony-stimulating factor) promotes monocyte activation, increases the expression of adhesion molecules, and enhances ovarian infiltration by dendritic cells. According to Huang et al. (2021), an increase in GM-CSF levels is observed in inflammatory forms of anovulation and impaired morphofunctional maturity of follicles [26].

Among the recently studied markers, CXCL12 (SDF-1) and IL-18 are of particular interest. CXCL12/SDF-1, which belongs to the chemokine family, plays an important role in stem cell migration, vascular remodeling and follicular environment regulation. Normally, it promotes chemotaxis of progenitor cells, supports angiogenesis and provides optimal conditions for the growth of the dominant follicle. However, in women with polycystic ovary syndrome (PCOS) and resistance to stimulation, there is a decrease in the expression of CXCL12 in

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the follicular fluid, which correlates with impaired follicle growth and a decrease in oocyte quality [40; 35].

Interleukin-18 (IL-18), a member of the IL-1 family, has the ability to induce IFN-γ production and enhance the Th1 response. Elevated levels of IL-18 are associated with chronic inflammation in the ovaries, activation of cytotoxic cells, and angiogenic imbalance. According to Danilova et al. (2022) and El-Kabarity et al. (2023), IL-18 overexpression is detected in autoimmune forms of premature ovarian insufficiency and may contribute to a decrease in ovarian reserve [14; 17]. Thus, CXCL12 and IL-18 represent promising immune markers that reflect the depth of reproductive disorders and are potentially applicable for patient stratification and monitoring therapy efficacy.

Anti-inflammatory cytokines and regulatory mediators. Among the anti-inflammatory mediators, IL-10, a key cytokine synthesized by Treg cells and macrophages of alternative activation, occupies a central place. In studies by El-Kabarity et al. (2023) and Makarova et al. (2020) showed a significant decrease in IL-10 in patients with POI and PCOS, which is associated with a loss of anti-inflammatory control and an increase in the Th1 response [16; 41].

TGF-β1/β2 has an immunosuppressive effect, promotes tissue remodeling, stimulates Treg differentiation, and inhibits the synthesis of pro-inflammatory cytokines. Its decrease is associated with impaired vascular stability of the follicle and increased apoptotic activity [25; 39].

Cytokines of the Th2 profile, including IL-4 and IL-13, regulate humoral immunity and contribute to the maintenance of immune tolerance in the follicular environment. In the studies of Liu et al. (2022) described an imbalance between IL-4 and IFN-γ as a predictor of cell-mediated immune shift in PCOS, accompanied by impaired granulosa cell proliferation and increased local inflammation [35].

Of particular importance in the mechanisms of luteolysis is occupied by the Fas ligand (FasL) and TRAIL, expressed by activated CD8+ T cells and NK cells. These molecules bind to death receptors on luteal cells, activating the caspase cascade and induction of apoptosis. According to Bukovsky et al. (2021) and

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Danilova et al. (2022), their overexpression is associated with premature regression of the corpus luteum and shortening of the luteal phase [6; 8; 11].

Thus, in various forms of ovarian dysfunction, including PCOS, POI, and resistance to stimulation, a persistent cytokine shift towards a pro-inflammatory profile is revealed, which contributes to a decrease in ovarian reserve and impaired fertility. Immunological assessment of IL-1β, IL-6, TNF-α, IL-17A, IFN-γ levels, along with a decrease in IL-10 and TGF-β, can be used as a diagnostic and prognostic tool in a personalized patient management strategy.

Imbalance of T-cell immunity. Immune homeostasis in ovarian tissue is largely ensured by the functional balance between different subpopulations of $CD4^+$ T lymphocytes (Th1, Th2, Th17) and regulatory T cells (Treg). These cells coordinate local immune responses, interact with granulosa cells, vascular and endothelial elements, and also affect the expression of immunomodulatory cytokines and major histocompatibility complex (MHC) molecules.

In ovarian dysfunction, there is a shift in the immune balance towards Th1 and Th17 responses, accompanied by overproduction of IFN-γ, IL-2 and IL-17A, as well as a decrease in the secretion of anti-inflammatory cytokines – IL-4, IL-10 and TGF-β. In the studies of Liu et al. (2022) and Danilova et al. (2022) showed that in patients with polycystic ovary syndrome and premature ovarian insufficiency, Th17/Treg imbalance predominates, contributing to autoimmune destruction of the follicular apparatus and impaired angiogenesis [37; 24]. Decreased expression of FOXP3, a key transcription factor in Treg cells, indicates a deficiency in immunoregulatory mechanisms and increased autoaggression in ovarian tissue [66].

A central role in maintaining immune tolerance is played by T-regulatory cells expressing FOXP3 and CD25. They limit the activity of Th1/Th17 effector cells, preventing the development of autoimmune reactions in the follicular niche. A decrease in the number or suppressive activity of Treg cells is associated with autoimmune forms of ovarian insufficiency and impaired endometrial implantation capacity [29; 16]. In this regard, $FOXP3^+/CD25^+$ Treg cells are considered as promising biomarkers and targets of therapy, including low-dose administration of IL-2 for selective stimulation of their activity [53].

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Of particular interest is HLA-G, a non-polymorphic MHC class Ib antigen expressed in follicular epithelium and corpus luteum cells. In both membrane and soluble form (sHLA-G), it has immunosuppressive effects by modulating the activity of NK cells and T lymphocytes by interacting with ILT2 and KIR2DL4 receptors. A decrease in the level of sHLA-G in the follicular fluid is associated with a deterioration in the quality of oocytes and a reduced pregnancy rate during IVF [50; 61]. In addition, in autoimmune forms of ovarian insufficiency, insufficient expression of HLA-G contributes to the activation of cytotoxic lymphocytes, increasing damage to ovarian tissue [16].

Thus, the predominance of the Th1/Th17 profile against the background of Treg cell deficiency and HLA-G expression forms a proautoimmune microenvironment that contributes to the development of ovarian dysfunction. These immune components are important diagnostic and therapeutic targets for the assessment and correction of immune disorders in reproductive pathology.

Autoimmune mechanisms of ovarian dysfunction

One of the pathogenetic mechanisms of ovarian dysfunction, especially in case of premature depletion of ovarian reserve, are autoimmune processes mediated by the production of organ-specific and systemic autoantibodies.

Antiovary autoantibodies (AOAs) and antinuclear antibodies (ANAs) are key immunological markers indicating the presence of autoimmune disorders involving both ovarian tissue and systemic immune homeostasis. AOAs are organ-specific autoantibodies directed against follicular and luteal tissue antigens, including follicle-stimulating hormone (FSH) receptors, inhibin B, steroidogenesis enzymes, and granulosa cell proteins. ANAs, in contrast, are nonspecific markers of systemic autoimmune dysregulation, and their presence is indicative of a loss of immunological tolerance in general.

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Table 2. Immune markers of autoimmune ovarian dysfunction

Category	Immune marker	Diagnostic value	Источники
Cytokines	IL-6	A marker of chronic inflammation, correlates with a decrease in ovarian reserve	Kianmehr et al., 2021; Vasilyeva et al., 2020
Cytokines	TNF-α	Increased in PCOS, impairs receptor sensitivity, and is associated with FSH resistance	Melnik et al., 2021; Duleba & Dokras, 2012
Cytokines	IL-10	A marker of immune tolerance; Low Levels - POI Predictor	El-Kabarity et al., 2023; Makarova et al., 2020
Cytokines	IFN-γ	Th1 response indicator; participates in impaired angiogenesis and folliculogenesis	Zhou et al., 2023; Danilova et al., 2022
Cytokines	IL-17A	Key mediator of the Th17 response; promotes ovarian atresia	Zhou et al., 2023; El-Kabarity et al., 2023
Autoantibodies	Antiovary autoantibodies (AOA)	Organ-specific marker of autoimmune aggression; detected at POI	Silva et al., 2019; Klimova et al., 2021
Autoantibodies	Antibodies to FSH receptors	Blocks the binding of FSH to receptors and is associated with hormonal resistance	Silva et al., 2019; Hoek et al., 2022
Autoantibodies	Inhibin B antibodies	Associated with an accelerated decrease in ovarian reserve and low AMH	Gleicher et al., 2015; Broer et al., 2020
Autoantibodies	AHA (antinuclear)	Reflect systemic autoimmune activity, often in AIT and celiac disease	Melo et al., 2019; Danilova et al., 2022
Autoantibodies	Antibodies to HSP70	A marker of cellular stress, increased in autoimmune aggression to follicular cells	Tani et al., 2020; Silva et al., 2021
Tolerance	TGF β	Immunomodulator involved in the creation of a tolerance microenvironment	Zhou et al., 2023
Tolerance	sCD25	The IL-2 solina receptor; Treg activation and functional immune control indicator	Danilova et al., 2022

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One of the pathogenetically significant mechanisms of POI is the activation of autoimmune responses accompanied by the synthesis of AOA. In a study, *Silva et al.* (2019) showed that AOAs are found in 24–40% of women with POIs, especially in the idiopathic form [57]. Their presence is associated with blockade of FSH receptors, decreased sensitivity of granulosa cells, and impaired steroidogenesis, which is manifested by a decrease in estradiol levels and impaired ovulation.

According to *Hoek et al.* (2022), AOAs initiate complement-dependent cytolysis and apoptosis of follicular cells through activation of the caspase cascade, which accelerates follicular atresia and progressive decline in ovarian reserve [24].

In a study , *Gleicher et al.* (2015) demonstrated that antibodies to inhibin B, a regulator of folliculogenesis, are associated with a faster decrease in ovarian reserve and hormonal imbalance [21]. Similar results were obtained by *Broer et al.* (2020), which confirmed the association of these antibodies with a reduced efficiency of gonadotropic stimulation [5].

The clinical significance of AOA in the context of reproductive function is confirmed by *Klimova et al.* (2021), which found that women with AOA positive status require higher doses of FSH, have a reduced ovarian response to stimulation, and receive fewer mature oocytes in assisted reproductive technology (ART) programs [34].

The pathogenesis of autoimmune ovarian insufficiency is often not limited to isolated ovarian involvement. A study by *Nelson* (2009) showed that 20–30% of patients with POI simultaneously have autoantibodies to other organs, primarily to the thyroid gland and adrenal glands. *Silva et al.* et al. (2021) expanded these data to indicate the combination of AOA with diseases such as autoimmune thyroiditis (AIT), Addison's disease, and autoimmune blepharoconjunctivitis (AE), which confirms the systemic nature of immune dysregulation [51; 58].

Antinuclear antibodies (ANAs), despite their non-specificity to the ovaries, are detected in 25–50% of women with POI, especially in combination with AIT, celiac disease, and autoimmune polyglandular syndrome [47; 13]. Their presence is associated with subclinical inflammation, impaired angiogenesis in the

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follicles, increased apoptotic activity, and shortening of the luteal phase of the cycle.

In some cases, AOA and ANA can be detected simultaneously, which correlates with a more severe clinical course, in particular, with ovarian resistant syndrome, in which functionally active ovarian tissue does not respond to stimulation due to a blockage of the receptor apparatus.

Genetic studies indicate the association of AOA and ANA with certain HLA haplotypes (HLA-DR3, DR4, DQ2), which indicates a hereditary predisposition to autoimmune ovarian pathology [59]. Within the framework of autoimmune polyglandular syndromes type I and II, AOA can be combined with antibodies to the thyroid gland, adrenal glands, and pancreas, forming a multi-organ autoimmune phenotype.

Thus, accumulating data indicate that AOA, ANA, and antibodies to FSH receptors and inhibin B are not only markers of autoimmune aggression, but also prognostically significant biomarkers of decreased ovarian reserve and ineffectiveness of hormonal stimulation. Their inclusion in immunological screening in women with POI, infertility, primary or secondary amenorrhea, especially in the presence of an autoimmune history, contributes to a more accurate diagnosis, risk stratification, and individualization of therapeutic tactics.

Discussion

The immune system plays a key role in the regulation of ovarian function, participating both in the maintenance of folliculogenesis and ovulation, and in pathological processes leading to ovarian dysfunction. Current research emphasizes that in conditions such as PCOS, POI, and resistance to gonadotropic stimulation, characteristic changes in the immune profile are observed, encompassing both cytokine regulation and autoimmune components.

One of the central links in the pathogenesis of ovarian dysfunction is chronic subclinical inflammation mediated by an increase in the levels of pro-inflammatory cytokines IL-6, TNF-α, IL-17A and IFN-γ. These mediators not only reflect the systemic inflammatory background, but are also directly involved in the suppression of granulosa cell activity, impaired angiogenesis and the

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initiation of follicular atresia. Increased concentrations of IL-6 and TNF-α in follicular fluid correlate with low mature oocyte counts, reduced AMH levels, and ineffective controlled ovarian stimulation. Thus, the pro-inflammatory cytokine signature can be considered as a pathogenetic and prognostic marker of reproductive disorders.

Along with pro-inflammatory factors, a deficiency of immunoregulatory mechanisms is important. Decreased levels of IL-10 and TGF-β, FOXP3 expression, and HLA-G antigen are indicative of impaired immune tolerance in ovarian tissue. An imbalance between Treg and Th17 cells with a predominance of the Th17 response contributes to an increase in autoaggression and the destruction of the follicular apparatus. Against this background, a decrease in the number of $FOXP3^+/CD25^+$ Treg cells indicates the depletion of protective immune mechanisms and can be used as a criterion for the autoimmune component of the disease.

No less significant is the involvement of autoantibodies, primarily AOA, ANA, as well as antibodies to FSH receptors and inhibin B. These markers reflect the involvement of adaptive immunity in the pathogenesis of ovarian dysfunction. AOAs disrupt the interaction of hormones with target cells, activate complement-dependent apoptosis, exacerbating the functional depletion of ovarian reserve. ANAs, although nonspecific, serve as an indicator of generalized autoimmune pathology and are associated with a poor reproductive prognosis at POI. The identification of these autoantibodies, especially in combination with autoimmune diseases of the thyroid gland or adrenal glands, confirms the multi-organ nature of immune dysregulation.

Thus, the totality of literature data allows us to identify three main immunopathogenetic axes of ovarian dysfunction: chronic inflammation, immune tolerance deficiency, and autoimmune aggression. The identified immune disorders can serve not only as biomarkers of reproductive risk, but also as potential targets for immunomodulatory therapy. The inclusion of immunological indicators in the algorithms for the diagnosis and stratification of patients with ovarian dysfunction opens up prospects for the introduction of personalized approaches in reproductive medicine.

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Conclusion

Modern ideas about the pathogenesis of ovarian dysfunction emphasize the key role of the immune system in impaired reproductive function in women of childbearing age. Against the background of neuroendocrine and metabolic dysregulation, a persistent immune imbalance is revealed, including the activation of IL-6, TNF-α, IL-17A, IFN-γ, a decrease in the levels of immunoregulatory IL-10, TGF-β, FOXP3, as well as the production of antiovarian and antinuclear autoantibodies. These changes contribute to the chronicity of subclinical inflammation, autoaggression and impaired immune tolerance in the ovarian microenvironment.

Immunomediated damage to the follicular apparatus, blockade of FSH receptors, suppression of angiogenesis and activation of apoptosis of granulosa cells cause a decrease in ovarian reserve, disruption of the ovulatory cycle and a decrease in the effectiveness of assisted reproductive technologies. The imbalance between effector Th1/Th17 and regulatory Treg cells confirms the autoimmune nature of many forms of POI and PCOS.

Thus, immunological markers are not only pathogenetically significant links, but also potentially informative diagnostic and prognostic biomarkers that can be integrated into a personalized approach to the management of women with ovarian dysfunction. Further research in this direction is needed to validate biomarkers and develop targeted immunomodulatory therapies.

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