Received: 28 February 2025 / Accepted: 14 July 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.021

UDC 616-008:618.11

METABOLIC SYNDROME AND ITS ASSOCIATION WITH OVARIAN DYSFUNCTION. LITERATURE REVIEW

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Abstract

Introduction. Metabolic syndrome (MS) – a cluster of conditions like central obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia – increases the risk of cardiovascular disease and type 2 diabetes in women of reproductive age. Its prevalence is rising globally due to poor diets and reduced physical activity. Additionally, ovarian dysfunction conditions such as PCOS, diminished ovarian reserve (DOR), and premature ovarian insufficiency (POI) are increasingly linked to metabolic disturbances. Understanding the connection between MS and ovarian dysfunction is critical to improving reproductive outcomes and reducing long-term health risks.

Aim. This review aims to summarize and critically analyze the current understanding (2020–2025) of the relationship between MS and ovarian dysfunction, emphasizing shared mechanisms, clinical implications, and future research directions.

Material's and method. A targeted literature review was performed using PubMed, ScienceDirect, and PMC databases. Studies published between January 2020 and June 2025, peer-reviewed, and focused on MS and ovarian dysfunction (PCOS, DOR, POI) were included.

Results and Conclusions. Recent research reveals that MS and ovarian dysfunction share common pathophysiological mechanisms, including hyperinsulinemia, adipokine imbalance, chronic inflammation, oxidative stress, and altered hepatic metabolism. Insulin resistance is present even in lean PCOS phenotypes. Mendelian randomization studies suggest a bidirectional causal link between MS and ovarian dysfunction. The coexistence of these conditions impairs fertility, increases pregnancy complications, and elevates long-term cardiometabolic risk. Interventions like lifestyle changes, insulin-sensitizing drugs, and integrated reproductive-metabolic care show promise.

Key words: *metabolic syndrome, polycystic ovary syndrome, diminished ovarian reserve, premature ovarian insufficiency, insulin resistance*

For citation:

Serikbayeva A.T., Khamidullina Z.G. Metabolic syndrome and its association with ovarian dysfunction. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 166-173. *doi 10.34689/SH.2025.27.4.021*

Резюме

МЕТАБОЛИЧЕСКИЙ СИНДРОМ И ЕГО ВЗАИМОСВЯЗЬ С НАРУШЕНИЕМ ФУНКЦИИ ЯИЧНИКОВ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Метаболический синдром (МС) — сочетание таких состояний, как центральное ожирение, инсулинорезистентность, гипертония, дислипидемия и гипергликемия — повышает риск сердечно-сосудистых заболеваний и диабета 2 типа у женщин репродуктивного возраста. Его распространенность растет в мире из-за неправильного питания и снижения физической активности. Кроме того, состояния овариальной дисфункции, такие как синдром поликистозных яичников (СПЯ), сниженный овариальный резерв (СОР) и преждевременная овариальная недостаточность (ПНЯ), все чаще связаны с метаболическими нарушениями. Понимание связи между МС и овариальной дисфункцией крайне важно для улучшения репродуктивных исходов и снижения долгосрочных рисков для здоровья.

Цель исслендования. Целью данного обзора является обобщение и критический анализ современного понимания (2020–2025) связи между МС и овариальной дисфункцией, с акцентом на общие механизмы, клинические последствия и направления будущих исследований.

Методы. Был проведен целенаправленный обзор литературы с использованием баз данных PubMed, ScienceDirect и PMC. Включены исследования, опубликованные с января 2020 года по июнь 2025 года, рецензируемые и фокусирующиеся на МС и овариальной дисфункции (СПЯ, СОР, ПНЯ).

Результаты и выводы. Последние исследования показывают, что МС и овариальная дисфункция имеют общие патофизиологические механизмы, включая гиперинсулинемию, дисбаланс адипокинов, хроническое воспаление, оксидативный стресс и нарушенный метаболизм в печени. Инсулинорезистентность наблюдается даже у женщин с "тонкими" фенотипами СПКЯ. Исследования Менделевской рандомизации предполагают двустороннюю причинно-следственную связь между МС и овариальной дисфункцией. Совместное существование этих состояний ухудшает

фертильность, увеличивает количество осложнений при беременности и повышает долгосрочные кардиометаболические риски. Обещающие методы вмешательства включают изменение образа жизни, препараты, повышающие чувствительность к инсулину, а также интегрированное репродуктивно-метаболическое лечение.

Ключевые слова: *метаболический синдром, синдром поликистозных яичников, сниженный овариальный резерв, преждевременная овариальная недостаточность, инсулинорезистентность.*

Для цитирования:

Серикбаева А.Т., Хамидуллина З.Г. Метаболический синдром и его взаимосвязь с нарушением функции яичников. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С. 166-173. *doi 10.34689/SH.2025.27.4.021*

Түйіндеме

МЕТАБОЛИКАЛЫҚ СИНДРОМ ЖӘНЕ ОНЫҢ ОВАРИАЛДЫ ДИСФУНКЦИЯМЕН БАЙЛАНЫСЫ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Метаболикалық синдром (МС) - орталық семіздік, инсулинге төзімділік, гипертензия, дислипидемия және гипергликемия сияқты жағдайлардың жиынтығы - репродуктивті жастағы әйелдерде жүрек-қан тамырлары аурулары мен 2 типті қант диабетінің даму қаупін арттырады. Оның таралуы әлемде дұрыс тамақтанбау мен физикалық белсенділіктің азаюына байланысты өсіп келеді. Сонымен қатар, овариальды дисфункция жағдайлары, мысалы, аналық безінің поликситоздылық синдромы (АПС), аналық без резервінің төмендеуі (АРТ) және ерте аналық без жеткіліксіздігі (ЕАЖ) метаболикалық бұзылыстармен жиі байланысты. МС және овариальды дисфункция арасындағы байланысты түсіну репродуктивті нәтижелерді жақсарту және ұзақ мерзімді денсаулық қаупін азайту үшін маңызды.

Зерттеу мақсаты. Бұл шолу мақсаты МС пен овариальды дисфункция арасындағы байланыс туралы қазіргі түсініктерді (2020–2025) жинақтап, сыни түрде талдау жасау, жалпы механизмдер, клиникалық салдарлар және болашақ зерттеулердің бағыттарына назар аудару.

Әдістер. PubMed, ScienceDirect және PMC дерекқорларын пайдаланып мақсатты әдебиет шолуы жүргізілді. 2020 жылдың қаңтарынан 2025 жылдың маусымына дейін жарияланған, рецензияланған және МС пен овариальды дисфункцияға (аналық бездің поликистозды синдромы, аналық бездің резистенттілік синдромы, аналық бәзінің біріншілік жетіспеушілігі) бағытталған зерттеулер енгізілді.

Нәтижелер мен қорытындылар. Соңғы зерттеулер МС пен овариальды дисфункцияның ортақ патофизиологиялық механизмдері бар екенін көрсетеді, оған гиперинсулинемия, адипокиндер дисбалансы, созылмалы қабыну, оксидативті стресс және бауыр метаболизмінің бұзылуы кіреді. Инсулинге төзімділік тіпті «жіңішке» поликистозды аналық без синдромы фенотиптері бар әйелдерде де байқалады. Менделевтік рандомизация зерттеулері МС мен овариальды дисфункция арасындағы өзара байланыстың болатынын көрсетеді. Бұл жағдайлардың бірлесіп болуы ұрпақ өрбіту қабілетіне зиян келтіреді, жүктілік кезіндегі асқынуларды арттырады және ұзақ мерзімді кардиометаболикалық қауіптерді жоғарылатады. Өмір салтын өзгерту, инсулинге сезімталдықты арттыруға арналған дәрілер және интеграцияланған репродуктивті-метаболикалық емдеу сияқты араласу әдістері болашағы бар.

Түйінді сөздер: *метаболикалық синдром, поликистозды аналық бездер синдромы, аналық бездердің төмен резерві, ерте аналық без жеткіліксіздігі, инсулинге төзімділік*

Дәйексөз үшін:

Серикбаева А.Т., Хамидуллина З.Г. Метаболикалық синдром және оның овариалды дисфункциямен байланысы. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 166-173. *doi 10.34689/SH.2025.27.4.021*

Introduction

The global prevalence of metabolic syndrome (MS) is estimated at 20–30% and continues to rise, particularly in low- and middle-income countries, where changing lifestyles contribute to increasing rates of obesity, insulin resistance (IR), and other metabolic disturbances. Among women of reproductive age, this growing metabolic burden is mirrored by a higher incidence of ovarian dysfunction, most notably polycystic ovary syndrome (PCOS), which affects 5–21% of women worldwide. While PCOS has long been recognized as a key reproductive manifestation of MS, emerging evidence highlights important links between MS and other forms of ovarian pathology, including diminished ovarian reserve (DOR) and premature ovarian insufficiency (POI) [1]. This intersection underscores the need for integrated approaches that address both metabolic health and reproductive function, as metabolic management strategies may represent an underutilized opportunity to protect ovarian reserve, extend reproductive lifespan, and improve overall health outcomes in affected women [2].

MS is considered a combination of disorders, the complex of which is associated with an increased risk of cardiovascular disease and diabetes mellitus [3]. Currently, several definitions of MS are used by specialists, including the World Health Organization (WHO), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP

III), and the International Diabetes Federation (IDF). Although there are slight variations between these definitions, they share common components.

By NCEP ATP III criteria (2001, updated 2005) metabolic syndrome is diagnosed when three or more of the following risk factors are present:

- Waist circumference: >102 cm (40 in) in men; >88 cm (35 in) in women (population-specific cutoffs may apply)
- Triglycerides (TG): ≥150 mg/dL (1.7 mmol/L) or on treatment for elevated TG
- HDL cholesterol: <40 mg/dL (1.03 mmol/L) in men; <50 mg/dL (1.29 mmol/L) in women or on treatment for low HDL
- Blood pressure: ≥130/85 mmHg or on antihypertensive treatment
- Fasting plasma glucose: ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes [4].

According to IDF, central obesity (defined by waist circumference with ethnicity-specific values) is a required criterion plus any two of the following:

- Triglycerides: ≥150 mg/dL (1.7 mmol/L) or specific treatment
- HDL cholesterol: <40 mg/dL (1.03 mmol/L) in men; <50 mg/dL (1.29 mmol/L) in women or specific treatment
- Blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg or treatment of previously diagnosed hypertension
- Fasting plasma glucose: ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes [5].

The WHO criteria (1999) place greater emphasis on insulin resistance, requiring evidence of insulin resistance (e.g., impaired glucose tolerance, impaired fasting glucose, type 2 diabetes, or elevated insulin levels) plus at least two of the following: obesity (BMI >30 kg/m² or high waist-hip ratio), dyslipidemia, hypertension, or microalbuminuria [6].

Despite slight differences among criteria, the core components of MS remain consistent: abdominal obesity, dyslipidemia, elevated blood pressure, and impaired glucose metabolism [7]. Early identification using standardized diagnostic criteria allows timely lifestyle and pharmacological interventions to reduce the risk of future cardiovascular and metabolic disease [8].

Ovarian Dysfunction

PCOS is the most prevalent cause of anovulatory infertility and metabolic disturbances in women of reproductive age [9]. According to the Rotterdam criteria (2003), PCOS is diagnosed when at least two of the following three features are present, after exclusion of other etiologies (such as thyroid disease, hyperprolactinemia, or congenital adrenal hyperplasia):

- Oligo- or anovulation: Infrequent or absent ovulation, typically manifesting as irregular menstrual cycles.
- Clinical and/or biochemical signs of hyperandrogenism: This includes hirsutism, acne, alopecia, and/or elevated serum androgen levels.
- Polycystic ovarian morphology on ultrasound: Presence of ≥12 antral follicles (2–9 mm) in each ovary and/or increased ovarian volume (>10 mL) [10].

PCOS is a heterogeneous condition, with phenotypes that may or may not exhibit all features, making thorough clinical and laboratory assessment critical [11].

DOR refers to a reduction in the quantity and often quality of oocytes available in the ovaries, leading to reduced fertility potential. Diagnostic markers include low levels of Anti-Müllerian hormone (AMH), elevated levels of Follicle-stimulating hormone (FSH) and low Antral follicle count (AFC) on transvaginal ultrasound (typically <5–7 follicles in total) which are indicative of a decreased follicular pool. DOR may be age-related or occur prematurely due to genetic factors, surgery, chemotherapy, or autoimmune conditions [12].

POI is characterized by early loss of ovarian function before the age of 40, leading to hypoestrogenism and infertility. Diagnostic criteria include elevated gonadotropins (FSH ≥25–40 IU/L on at least two occasions, typically 4 weeks apart), low estradiol levels reflecting ovarian failure to produce estrogen, and amenorrhea or oligomenorrhea (absence of menstruation or irregular cycles for at least 4–6 months). POI may have genetic, autoimmune, or idiopathic causes, and is distinct from natural menopause in its earlier onset and potential for intermittent ovarian activity [13]. PCOS, DOR, and POI represent key forms of ovarian dysfunction, each with unique diagnostic features and clinical implications [14]. Early and accurate diagnosis using validated criteria is crucial for personalized management aimed at preserving fertility, preventing long-term complications, and improving quality of life [15].

Pathophysiological Mechanisms

Insulin resistance, a core feature in up to 80% of PCOS cases, affects both obese and lean women [16]. Compensatory hyperinsulinemia stimulates ovarian theca cells to produce excess androgens and suppresses Sex Hormone-Binding Globulin (SHBG) synthesis, leading to hyperandrogenism and disrupted folliculogenesis [17]. Insulin resistance is defined as the diminished ability of cells in peripheral tissues - such as skeletal muscle, liver, and adipose tissue - to respond effectively to insulin. This leads to compensatory hyperinsulinemia as pancreatic β-cells increase insulin secretion to maintain normoglycemia [18]. In women with MS, IR is not only a driver of hyperglycemia and dyslipidemia, but also a critical factor in disrupting ovarian function. Even in the absence of overt obesity, IR is prevalent among women with PCOS and contributes to the characteristic features of the syndrome [16].

Hyperinsulinemia exerts direct and indirect effects on ovarian steroidogenesis by synergizing with LH on theca cells to stimulate excessive androgen production via upregulation of androgen biosynthesis enzymes, suppressing hepatic SHBG synthesis and thereby increasing free androgens, and impairing granulosa cell function and follicular maturation, which leads to anovulation and accumulation of small antral follicles characteristic of PCOS [19].

While the role of IR is well established in PCOS, emerging evidence suggests its involvement in DOR and POI. Chronic hyperinsulinemia and metabolic stress contribute to oxidative stress and low-grade inflammation, accelerating follicular atresia. Disrupted intraovarian insulin signaling may impair oocyte quality and the survival of primordial follicles, potentially shortening reproductive lifespan. Additionally, IR-associated endothelial dysfunction can impair ovarian blood flow, further compromising follicular health. Although further research is needed, IR

and its metabolic consequences are increasingly recognized as significant factors in early ovarian aging [20].

The coexistence of insulin resistance, hyperinsulinemia, and ovarian dysfunction places women at risk for infertility, pregnancy complications (e.g., gestational diabetes, preeclampsia), and long-term cardiometabolic disease. Early detection and management of insulin resistance are crucial [21, 22].

Interventions targeting insulin sensitivity, including lifestyle modification (weight loss, dietary changes, physical activity) and pharmacotherapy (e.g., metformin), have shown efficacy in improving ovulatory function, reducing androgen levels, and enhancing fertility outcomes, particularly in PCOS [20].

Insulin resistance and compensatory hyperinsulinemia are key pathophysiological mechanisms linking metabolic syndrome and ovarian dysfunction. Understanding these mechanisms is essential for developing effective strategies to preserve reproductive function and prevent long-term metabolic complications in women.

Adipokines play a critical role in the pathophysiology of ovarian dysfunction associated with metabolic syndrome. Leptin, secreted by adipocytes, regulates energy balance and reproductive function, but in obesity and MS, hyperleptinemia and leptin resistance impair the hypothalamic-pituitary-gonadal axis, disrupt granulosa cell steroidogenesis, and reduce oocyte quality [23]. Adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, is reduced in MS, contributing to systemic and ovarian insulin resistance, androgen excess, and anovulation in PCOS. Elevated resistin and visfatin levels in obesity further promote insulin resistance, inflammation, and disrupted ovarian steroidogenesis, while the precise role of visfatin in follicular development remains under study. Additionally, pro-inflammatory cytokines like TNF-α and IL-6 produced by adipose tissue impair insulin signaling, contribute to ovarian stromal fibrosis, and disturb the follicular microenvironment and endometrial receptivity, exacerbating reproductive dysfunction [24].

Studies show that even modest weight loss (5–10% of body weight) in overweight or obese women with PCOS improves menstrual regularity, ovulation, and fertility potential. Adiposity and altered adipokine secretion form a critical mechanistic link between metabolic syndrome and ovarian dysfunction. Recognizing the endocrine role of adipose tissue highlights the importance of comprehensive metabolic management in women with reproductive disorders to optimize both reproductive and long-term health outcomes [25].

Abnormal lipid profiles in MS increase oxidative stress and endothelial dysfunction, potentially reducing ovarian blood flow and follicular health. Additionally, dysregulated liver metabolism - notably nonalcoholic fatty liver disease - is prevalent in PCOS and may exacerbate systemic metabolic disturbances [26]. Dyslipidemia is a common feature of MS, typically characterized by elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol. **This abnormal lipid profile contributes to:**

- **Lipotoxicity**, where excessive circulating free fatty acids accumulate in non-adipose tissues, including the ovaries, leading to cellular dysfunction and apoptosis.
- **Disruption of steroidogenesis**, as altered lipid availability impairs the synthesis of sex steroids essential for normal follicular development.
- **Endothelial dysfunction**, reducing ovarian blood flow and impairing the follicular environment, further compromising oocyte quality and ovulation [27].

Dyslipidemia, a common component of metabolic syndrome, is typically characterized by elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol, and it plays a significant role in ovarian dysfunction. The abnormal lipid profile contributes to lipotoxicity, where excess free fatty acids accumulate in the ovaries, leading to cellular dysfunction and apoptosis. It also disrupts steroidogenesis by impairing the synthesis of sex steroids necessary for normal follicular development, and causes endothelial dysfunction, which reduces ovarian blood flow and compromises the follicular environment, ultimately impairing oocyte quality and ovulation [28].

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. Women with MS exhibit elevated oxidative stress due to chronic inflammation, hyperglycemia, and dyslipidemia.

Key consequences for ovarian function include:

- **Damage to oocytes and granulosa cells**, leading to impaired folliculogenesis and anovulation.
- **Acceleration of follicular atresia**, contributing to diminished ovarian reserve and potentially earlier onset of POI.
- **Altered endometrial receptivity**, reducing fertility potential even if ovulation occurs [29].

Studies in women with PCOS have consistently shown increased markers of oxidative stress, which correlate with hyperandrogenism and insulin resistance, further perpetuating ovarian dysfunction [30].

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is elevated in women with metabolic syndrome due to chronic inflammation, hyperglycemia, and dyslipidemia, and it has significant consequences for ovarian function. This stress damages oocytes and granulosa cells, impairing folliculogenesis and leading to anovulation, accelerates follicular atresia, contributing to diminished ovarian reserve and potentially earlier onset of premature ovarian insufficiency (POI), and alters endometrial receptivity, thereby reducing fertility potential even when ovulation occurs. Studies in women with PCOS consistently demonstrate increased oxidative stress markers that correlate with hyperandrogenism and insulin resistance, creating a vicious cycle that exacerbates ovarian dysfunction [31].

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of MS and is frequently observed in women with PCOS and other forms of ovarian dysfunction.

- **Altered hepatic metabolism of sex hormones:** The liver is essential for the clearance and binding of sex steroids. NAFLD is associated with reduced SHBG production, increasing free androgens and exacerbating hyperandrogenic states in PCOS.
- **Contribution to systemic insulin resistance:** Liver dysfunction aggravates insulin resistance, further impacting ovarian function.

- **Pro-inflammatory cytokine production:** The fatty liver contributes to systemic low-grade inflammation, amplifying oxidative stress and ovarian damage [32].

Non-alcoholic fatty liver disease (NAFLD), often considered the hepatic manifestation of metabolic syndrome, is frequently observed in women with PCOS and other forms of ovarian dysfunction and contributes to reproductive disturbances through several mechanisms. Altered hepatic metabolism of sex hormones in NAFLD leads to reduced production of sex hormone-binding globulin (SHBG), increasing levels of free androgens and worsening hyperandrogenic states characteristic of PCOS. Additionally, liver dysfunction exacerbates systemic insulin resistance, further impairing ovarian function, while the fatty liver's production of pro-inflammatory cytokines amplifies low-grade inflammation, oxidative stress, and subsequent ovarian damage [33].

The interplay of dyslipidemia, oxidative stress, and liver dysfunction not only contributes to infertility through impaired oocyte development and ovulatory dysfunction but also increases the risk of pregnancy complications (e.g., gestational diabetes, preeclampsia) and long-term cardiovascular disease [34]. Management strategies targeting lipid abnormalities, reducing oxidative stress through antioxidant supplementation, and improving liver health (via lifestyle change or pharmacotherapy) have shown promise in improving reproductive outcomes in affected women [35].

Dyslipidemia, oxidative stress, and liver dysfunction are central components linking MS to ovarian dysfunction. Their combined effects disrupt steroidogenesis, folliculogenesis, and oocyte quality, highlighting the need for integrated metabolic and reproductive care in women at risk [36]. Early intervention targeting these mechanisms is essential for preserving fertility and preventing long-term complications.

MS associates with elevated pro-inflammatory cytokines (e.g., CRP, IL-6, TNF-α, CXCL12, MIF, Serpin E1) that disrupt insulin signaling and ovarian steroidogenesis [37].

MS is characterized by a state of persistent low-grade systemic inflammation. Adipose tissue, especially visceral fat, plays a key role in this process by:

- Producing pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1).
- Recruiting and activating immune cells (e.g., macrophages) that amplify inflammatory signaling.
- Promoting oxidative stress and endothelial dysfunction, contributing to metabolic and vascular complications [38].

This inflammatory milieu is closely tied to the progression of insulin resistance and other metabolic abnormalities characteristic of MS.

Chronic inflammation adversely affects ovarian physiology through multiple mechanisms:

- **Disruption of folliculogenesis:** Pro-inflammatory cytokines impair granulosa and theca cell function, inhibiting normal follicular development and promoting atresia.
- **Promotion of hyperandrogenism:** TNF-α and IL-6 can enhance androgen production by theca cells, contributing to the hyperandrogenic state observed in PCOS.
- **Oocyte damage:** Elevated levels of inflammatory mediators and associated oxidative stress compromise oocyte quality, leading to reduced fertility potential.
- **Endometrial effects:** Systemic inflammation alters endometrial receptivity, increasing the risk of implantation failure and pregnancy loss [39].

Chronic inflammation adversely affects ovarian physiology by disrupting folliculogenesis through impaired granulosa and theca cell function [40], promoting hyperandrogenism via increased androgen production by theca cells [41], compromising oocyte quality through elevated inflammatory mediators and oxidative stress [42], and altering endometrial receptivity, which increases the risk of implantation failure and pregnancy loss [43].

In women with PCOS, markers of chronic inflammation—including elevated C-reactive protein (CRP), TNF-α, and IL-6—are consistently reported and correlate with disease severity, insulin resistance, and hyperandrogenism [44].

Role in DOR and POI

Emerging evidence suggests that chronic inflammation may contribute to the accelerated loss of ovarian follicles, leading to diminished ovarian reserve and premature ovarian insufficiency [45].

- Persistent low-grade inflammation can damage ovarian stromal and follicular tissue, accelerating follicular apoptosis [46].
- Autoimmune mechanisms, often linked to inflammatory pathways, are implicated in some cases of POI [47].

Although the exact causal relationships require further study, inflammation appears to be a common thread connecting metabolic dysfunction and early ovarian aging [46].

Emerging evidence suggests that chronic inflammation plays a role in the accelerated loss of ovarian follicles, contributing to diminished ovarian reserve (DOR) and premature ovarian insufficiency (POI). Persistent low-grade inflammation can damage ovarian stromal and follicular tissue, promoting follicular apoptosis and reducing the ovarian follicular pool, while autoimmune mechanisms linked to inflammatory pathways are implicated in certain cases of POI [1]. Although the precise causal relationships remain to be fully clarified, inflammation appears to be a unifying factor that connects metabolic dysfunction with early ovarian aging.

Genetic and Epigenetic Factors

Bidirectional Mendelian randomization studies (2024) support a causal interplay between MS components- waist circumference, triglycerides, HDL, insulin resistance-and ovarian dysfunction [48]. Epigenetic changes in glucose transporters (e.g., GLUT4) and steroidogenic enzymes further link systemic metabolism to ovarian pathology [1].

Genetic susceptibility underlies both metabolic and reproductive traits, and certain genes appear to influence both MS and ovarian dysfunction [49].

- **PCOS and MS shared loci:** Genome-wide association studies (GWAS) have identified genetic variants in loci such as DENND1A, THADA, FSHR, and INSR that are implicated in both PCOS and metabolic traits, including insulin resistance and obesity [50].
- **Genes regulating insulin signaling:** Mutations and polymorphisms in genes involved in insulin receptor function and post-receptor pathways (e.g., INSR, IRS-1, IRS-2) are linked to both MS and ovarian hyperandrogenism [51].
- **Lipid metabolism genes:** Variants in genes involved in lipid handling (e.g., APOE, CETP) may contribute to the

dyslipidemia seen in MS and its association with ovarian dysfunction [1].

While genetic factors do not act in isolation, they set the foundation upon which environmental influences exert their effects, shaping individual susceptibility to both metabolic and reproductive disorders [53].

Genetic factors play a significant role in linking metabolic syndrome (MS) and ovarian dysfunction, as certain genes influence both metabolic and reproductive traits. Genome-wide association studies (GWAS) have identified shared genetic loci such as DENND1A, THADA, FSHR, and INSR, which are implicated in both PCOS and metabolic abnormalities like insulin resistance and obesity. Mutations in genes regulating insulin signaling (e.g., INSR, IRS-1, IRS-2) contribute to both MS and ovarian hyperandrogenism, while variants in lipid metabolism genes (e.g., APOE, CETP) may underlie dyslipidemia and its reproductive consequences [54]. Although these genetic predispositions do not act alone, they provide the basis upon which environmental factors influence individual susceptibility to both metabolic and ovarian dysfunction [55].

Women with DOR exhibit higher rates of hypertension, dyslipidemia, elevated TyG index, and serum homocysteine compared to those with normal reserve. Narrative reviews also highlight adipose dysfunction in POI, including hyperlipidemia and insulin resistance, and underline the potentiating effect of DNA repair gene variants (e.g., BRCA1, MCM8/9) in reproductive age [54].

Ovarian reserve refers to the quantity and quality of a woman's remaining follicles and oocytes, which determine reproductive potential. Key biomarkers of ovarian reserve include serum levels of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and the antral follicle count (AFC) assessed via ultrasound [55]. In women with MS, these markers are increasingly being studied, with evidence suggesting that metabolic dysfunction may accelerate ovarian aging and deplete the follicular pool [54].

Ovarian reserve, reflecting the quantity and quality of a woman's remaining follicles, is increasingly recognized as vulnerable to the effects of MS, with studies showing that women with MS often have lower AMH levels, higher FSH, and reduced antral follicle count independent of age and BMI [56]. MS contributes to diminished ovarian reserve through insulin resistance and hyperinsulinemia that disrupt folliculogenesis and promote early atresia, chronic inflammation and oxidative stress that damage ovarian tissue, dyslipidemia causing lipotoxicity and mitochondrial dysfunction, and adipokine imbalances that impair oocyte competence [1]. These same mechanisms, along with endothelial dysfunction and epigenetic alterations, may accelerate ovarian aging and contribute to POI, while women with POI often display features of MS, suggesting a bidirectional link. Clinically, these associations underscore the need for early metabolic screening and lifestyle interventions in women with menstrual irregularities or subfertility to protect ovarian reserve and delay ovarian aging. An integrated approach addressing both reproductive and metabolic health is essential to optimize long-term outcomes in this population [57].

Conclusion

Advances in biomarker development, including genetic, epigenetic, metabolomic, proteomic, and imaging markers, offer great potential for early identification and monitoring of metabolic syndrome (MS)-associated ovarian dysfunction, enabling personalized risk assessment and more precise diagnostics. There is an urgent need for large longitudinal and interventional studies to elucidate the natural history of MS-related reproductive disorders and to evaluate the long-term impact of lifestyle, pharmacologic, and reproductive therapies on both fertility and cardiometabolic outcomes. Mechanistic and genetic research focusing on insulin signaling, oxidative stress, adipokines, and androgen pathways, as well as Mendelian randomization and polygenic risk analyses, will help clarify causal links and inform targeted prevention. Finally, integrated care models - combining multidisciplinary teams, digital health tools, and personalized management strategies—are essential to address the complex interplay between reproductive and metabolic health and to optimize outcomes for affected women.

Future progress in addressing MS-associated ovarian dysfunction requires integration of biomarker discovery, rigorous clinical research, and innovative care delivery models. Such strategies will enable earlier detection, better prevention, and more effective treatment of this complex intersection of reproductive and metabolic health.

The evidence points to a robust, bidirectional relationship between metabolic syndrome and ovarian dysfunction, spanning PCOS, DOR, and POI. Underlying mechanisms include insulin resistance, adipokine dysregulation, inflammation, oxidative stress, liver metabolism, and genetic/epigenetic drivers. Clinically, this interplay exacerbates infertility and long-term metabolic risk. Effective care requires integrated metabolic and reproductive strategies emphasizing lifestyle change, targeted pharmacotherapy, fertility monitoring, and cardiovascular risk management. Future discovery hinges on refined biomarkers, targeted interventions, and integrated clinical care pathways.

Contributors. *All the authors equally participated in the selection, assessment, and analysis of the selected studies. All of them have approved the final article.*

Conflict of interest. *The authors declared no potential conflicts of interest with respect to the authorship, research, and publication of this article.*

Funding. *The authors received no financial support for the authorship, research, and publication of this article*

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