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Metabolic syndrome in women with polycystic ovary syndrome (PCOS): Pathogenesis, clinical consequences, and therapeutic strategies

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Abstract
Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age, with an estimated global prevalence of 8–20%, depending on diagnostic criteria. Beyond its reproductive manifestations, including menstrual irregularities, hyperandrogenism, and infertility, PCOS is increasingly recognized as a complex metabolic disorder closely associated with obesity, insulin resistance, chronic low-grade inflammation, dyslipidemia, and metabolic syndrome. Metabolic syndrome significantly increases the lifetime risk of type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and premature mortality. Among the multiple pathogenic mechanisms involved in PCOS, obesity, insulin resistance, and inflammation form an interconnected triad that drives disease progression and metabolic complications. Excess visceral adiposity promotes adipokine imbalance and inflammatory cytokine release, while insulin resistance exacerbates ovarian androgen production, further worsening metabolic dysfunction. Chronic inflammation amplifies oxidative stress and endothelial dysfunction, contributing to long-term cardiometabolic risks. This review discusses the pathophysiological links between PCOS and metabolic syndrome, emphasizing the central roles of obesity, insulin resistance, and inflammation. Current evidence regarding molecular mechanisms, clinical implications, diagnostic strategies, and therapeutic interventions—including lifestyle modification, pharmacotherapy, and emerging anti-inflammatory approaches—is also summarized. Understanding these interconnected pathways is essential for early diagnosis, individualized management, and prevention of long-term metabolic complications in women with PCOS.

Keywords: Polycystic ovary syndrome, metabolic syndrome, obesity, insulin resistance, chronic inflammation, hyperandrogenism, cardiovascular disease, Type 2 diabetes

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders among women of reproductive age, affecting approximately one in every ten women worldwide (Neven *et al*., 2024) [43]. Although traditionally regarded as a reproductive disorder characterized by ovulatory dysfunction and hyperandrogenism, PCOS is now recognized as a lifelong metabolic disease with significant implications for cardiovascular and endocrine health (Neven *et al*., 2024 [43]; Yu *et al*., 2026). Women with PCOS frequently exhibit obesity, insulin resistance, dyslipidemia, hypertension, and impaired glucose tolerance, placing them at considerably higher risk of developing metabolic syndrome (Prosperi, 2025) [48].

Metabolic syndrome represents a cluster of metabolic abnormalities that include central obesity, hyperglycemia, hypertension, elevated triglycerides, and reduced high-density lipoprotein (HDL) cholesterol (Moini, 2014; Shruthi, 2024) [39, 60]. The coexistence of PCOS and metabolic syndrome substantially increases the risk of type 2 diabetes mellitus, cardiovascular disease, stroke, and non-alcoholic fatty liver disease (Prosperi, 2025) [48]. Depending on ethnicity and diagnostic criteria, metabolic syndrome affects approximately 30–50% of women with PCOS (Shruthi, 2024) [60].

The pathogenesis linking PCOS and metabolic syndrome is multifactorial and involves complex interactions among genetic predisposition, environmental influences, hormonal disturbances, adipose tissue dysfunction, insulin resistance, and chronic low-grade inflammation. Obesity, particularly visceral obesity, accelerates insulin resistance and inflammatory responses, creating a vicious cycle that perpetuates hyperandrogenism and metabolic dysfunction (Shruthi, 2024) [60]. Consequently, obesity, insulin resistance, and inflammation have emerged as the three central pathological mechanisms connecting PCOS with metabolic syndrome (Shruthi, 2024) [60].

Pathophysiology of PCOS

The pathophysiology of Polycystic Ovary Syndrome (PCOS) is complex and multifactorial, involving intricate interactions among genetic susceptibility, environmental influences, neuroendocrine dysregulation, and metabolic abnormalities (Emanuel *et al*., 2022) [20]. Although the precise etiology remains incompletely understood, accumulating evidence suggests that genetic predisposition, coupled with lifestyle factors such as sedentary behavior, unhealthy dietary patterns, obesity, and environmental endocrine-disrupting chemicals, contributes significantly to disease onset and progression (Barraza-Ortega, 2026; Xu, 2026) [5]. Central to the disorder is the dysregulation of the hypothalamic–pituitary–ovarian (HPO) axis, characterized by increased pulsatile secretion of gonadotropin-releasing hormone (GnRH), elevated luteinizing hormone (LH) levels relative to follicle-stimulating hormone (FSH), and excessive ovarian androgen production (Rambaran, 2024) [53]. Hyperandrogenism disrupts normal follicular

maturation, resulting in follicular arrest, chronic anovulation, menstrual irregularities, and the characteristic polycystic ovarian morphology observed on ultrasonography (Rambaran, 2024; Qu & Donnelly, 2020) [50, 53]. Concurrently, insulin resistance—present in a majority of women with PCOS regardless of obesity—leads to compensatory hyperinsulinemia, which further stimulates ovarian theca cells to produce androgens while suppressing hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing circulating free androgen concentrations (Ding *et al*., 2021; Tűű *et al*., 2024) [18, 71].

In addition to endocrine disturbances, chronic low-grade inflammation, oxidative stress, and adipose tissue dysfunction play crucial roles in disease progression (Qu & Donnelly, 2020) [50]. Excess visceral adipose tissue secretes pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), along with altered adipokines such as decreased adiponectin and increased leptin, promoting systemic inflammation and worsening insulin resistance (Ding *et al*., 2021; Qu & Donnelly, 2020) [18, 50]. Increased oxidative stress resulting from excessive production of reactive oxygen species further impairs insulin signaling, damages ovarian tissue, and contributes to endothelial dysfunction (Ding *et al*., 2021; Emanuel *et al*., 2022) [18, 20]. These interconnected mechanisms establish a self-perpetuating cycle of hyperandrogenism, insulin resistance, inflammation, and metabolic dysfunction, ultimately increasing the risk of infertility, obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease in women with PCOS (Emanuel *et al*., 2022; Qu & Donnelly, 2020) [20, 50].

Hyperinsulinemia stimulates ovarian theca cells to increase androgen synthesis while suppressing hepatic production of sex hormone-binding globulin (SHBG), thereby increasing circulating free testosterone (Ding *et al*., 2021) [18]. Elevated androgen levels impair normal follicular development, leading to anovulation and infertility (Rambaran, 2024) [53].

Obesity: The Major Driver of Metabolic Dysfunction

Obesity affects nearly 50–80% of women with PCOS, although lean PCOS also exists. Central (visceral) obesity is particularly detrimental because visceral adipose tissue functions as an active endocrine organ.

Mechanisms Linking Obesity to PCOS

1. Visceral Fat Accumulation

Visceral fat accumulation is one of the primary mechanisms linking obesity to the development and progression of Polycystic Ovary Syndrome (PCOS) (Rojas *et al*., 2014; Zhao *et al*., 2023) [55, 75]. Unlike subcutaneous adipose tissue, visceral adipose tissue is highly metabolically active and functions as an endocrine organ by secreting a variety of bioactive molecules known as adipokines, along with inflammatory mediators (Elena, 2026; Gusev, 2024) [19, 23]. In women with PCOS, excessive visceral fat releases increased amounts of free fatty acids (FFAs), leptin, resistin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), while simultaneously reducing the production of the insulin-sensitizing adipokine adiponectin (Elena, 2026; Niu *et al*., 2014) [19, 44]. Elevated circulating FFAs impair insulin signaling in skeletal muscle and liver, promoting insulin resistance and compensatory hyperinsulinemia (Prosperi, 2025; Niu *et al*., 2014) [44, 48]. Increased leptin levels and leptin resistance disrupt appetite regulation, energy homeostasis, and reproductive hormone secretion, whereas TNF-α and IL-6 activate inflammatory pathways that further inhibit insulin receptor signaling and contribute to chronic low-grade inflammation (Gusev, 2024; Rahman *et al*., 2024) [23, 51].

Resistin also plays a role in worsening glucose intolerance and reducing insulin sensitivity (Rahman *et al*., 2024) [51]. Conversely, decreased adiponectin removes its protective anti-inflammatory, anti-atherogenic, and insulin-sensitizing effects, thereby exacerbating metabolic dysfunction (Gusev, 2024) [23]. The combined effects of adipokine imbalance, inflammation, and impaired insulin action create a vicious cycle that promotes hyperandrogenism, ovarian dysfunction, and the development of metabolic syndrome, making visceral obesity a central pathogenic factor in PCOS (Baranowska-Bik, 2022; Rojas *et al*., 2014) [4, 55].

2. Adipokine Dysregulation

Adipokine dysregulation is a hallmark of obesity-associated Polycystic Ovary Syndrome (PCOS) and plays a critical role in the development of insulin resistance, chronic inflammation, and metabolic syndrome (Koleva-Tyutyundzhieva, 2024; Schüler-Toprak *et al*., 2022) [32, 59]. Adipose tissue functions as an active endocrine organ that secretes numerous adipokines involved in regulating energy balance, glucose metabolism, immune responses, and reproductive function (Bongrani *et al*., 2019; Chen *et al*., 2022) [8, 14]. In obese women with PCOS, this endocrine function becomes disrupted, resulting in increased leptin resistance, reduced adiponectin levels, elevated resistin, and increased visfatin concentrations (Chen *et al*., 2022; Koleva-Tyutyundzhieva, 2024) [14, 32]. Hyperleptinemia accompanied by leptin resistance impairs appetite regulation and energy expenditure while contributing to neuroendocrine dysfunction and ovarian abnormalities (Bongrani *et al*., 2019; Koleva-Tyutyundzhieva, 2024) [8, 32]. Reduced adiponectin, an adipokine with potent anti-inflammatory and insulin-sensitizing properties, diminishes peripheral glucose uptake, enhances hepatic glucose production, and increases the risk of insulin resistance and dyslipidemia (Al-Mayoofee *et al*., 2024; Chen *et al*., 2022; Fernando, 2026) [1, 14, 21].

Elevated resistin further impairs insulin signaling by promoting inflammatory cytokine production and interfering with glucose metabolism, thereby contributing to hyperinsulinemia (Al-Mayoofee *et al*., 2024; Koleva-Tyutyundzhieva, 2024) [1, 32]. Similarly, increased circulating visfatin has been associated with obesity, visceral adiposity, and systemic inflammation, and may further exacerbate insulin resistance through activation of pro-inflammatory pathways (Kowalska *et al*., 2007; Koleva-Tyutyundzhieva, 2024) [32, 33]. Collectively, these alterations in adipokine secretion establish a pro-inflammatory and insulin-resistant metabolic environment that aggravates hyperandrogenism, disrupts ovarian function, and accelerates the progression of metabolic syndrome and cardiovascular complications in women with PCOS (Koleva-Tyutyundzhieva, 2024; Schüler-Toprak *et al*., 2022) [32, 59].

3. Lipotoxicity

Lipotoxicity is a critical mechanism through which obesity contributes to the pathogenesis of Polycystic Ovary Syndrome (PCOS) and its associated metabolic complications (Connolly *et al*., 2018) [16]. In obese individuals, particularly those with excessive visceral

adiposity, adipose tissue loses its capacity to safely store triglycerides, leading to increased release of circulating free fatty acids (FFAs) (Brennan *et al*., 2019) [9]. These FFAs accumulate ectopically in non-adipose tissues, including skeletal muscle, liver, pancreas, and ovaries, where they exert toxic effects on cellular metabolism (Brennan *et al*., 2019; Connolly *et al*., 2018) [9, 16]. In skeletal muscle, excess lipid metabolites interfere with insulin receptor signaling pathways by inhibiting insulin receptor substrate (IRS) activity and glucose transporter type 4 (GLUT4) translocation, thereby reducing glucose uptake and promoting insulin resistance (Calcaterra *et al*., 2021; Li, 2026) [5, 18]. In the liver, excessive FFA deposition stimulates triglyceride accumulation, leading to hepatic steatosis (non-alcoholic fatty liver disease) and increased hepatic glucose production, which further aggravates hyperglycemia and hyperinsulinemia (Brennan *et al*., 2019; Li, 2026) [5, 9]. Within pancreatic -cells, chronic exposure to elevated FFAs induces endoplasmic reticulum stress, mitochondrial dysfunction, and apoptosis, ultimately impairing insulin secretion and accelerating -cell dysfunction (Brennan *et al*., 2019) [9].

Furthermore, intracellular lipid accumulation increases the generation of reactive oxygen species (ROS), resulting in oxidative stress, lipid peroxidation, DNA damage, and activation of inflammatory signaling pathways (Brennan *et al*., 2019; Raviv *et al*., 2020) [9, 54]. In the ovaries, lipotoxicity disrupts granulosa cell function, follicular development, and steroid hormone synthesis, contributing to hyperandrogenism and ovulatory dysfunction (Connolly *et al*., 2018; Raviv *et al*., 2020) [16, 54]. Thus, lipotoxicity serves as a crucial link between obesity, insulin resistance, oxidative stress, and reproductive dysfunction, playing a central role in the progression of PCOS and increasing the risk of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease (Brennan *et al*., 2019; Connolly *et al*., 2018) [9, 16].

Insulin Resistance: The Metabolic Core of PCOS

Insulin resistance is considered the central metabolic abnormality in Polycystic Ovary Syndrome (PCOS) and plays a pivotal role in the development of both reproductive and metabolic complications (Chen, 2025) [15]. It is present in approximately 70–90% of obese women with PCOS and 30–50% of lean women, indicating that insulin resistance is an intrinsic feature of the disorder and not solely a consequence of obesity (Mitkova Orbetzova, 2020; Toosy *et al*., 2018) [38, 67]. Insulin resistance is characterized by a diminished biological response of peripheral tissues, particularly skeletal muscle, adipose tissue, and the liver, to normal circulating concentrations of insulin (Toosy *et al*., 2018) [67]. As a result, the pancreas compensates by secreting larger amounts of insulin, leading to chronic hyperinsulinemia (Sun, 2025) [63].

Elevated insulin levels not only impair glucose homeostasis but also stimulate ovarian androgen production, suppress hepatic synthesis of sex hormone-binding globulin (SHBG), and exacerbate hyperandrogenism, thereby contributing to menstrual irregularities, anovulation, and infertility (Chen, 2025;Toosy *et al*., 2018) [15, 67]. Moreover, persistent insulin resistance increases the risk of impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease, making it a key therapeutic target in the management of PCOS (Chen, 2025; Prosperi, 2025) [15].

1. Impaired Insulin Signaling

The molecular basis of insulin resistance in PCOS involves multiple defects within the insulin receptor signaling cascade (Houston & Templeman, 2025; Zhao *et al*., 2023) [25, 75]. Under normal physiological conditions, insulin binds to its receptor and activates insulin receptor substrate-1 (IRS-1), which subsequently stimulates phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt), ultimately promoting the translocation of glucose transporter type 4 (GLUT4) to the cell membrane for efficient glucose uptake (Houston & Templeman, 2025; Sun, 2026) [19, 25]. In women with PCOS, this signaling pathway is significantly disrupted due to increased serine phosphorylation of the insulin receptor and IRS-1, which inhibits their normal tyrosine phosphorylation and reduces downstream signaling efficiency (Arora, 2012; Woo, 2024) [2, 71].

Consequently, IRS-1 activation is impaired, PI3K activity decreases, and GLUT4 translocation to the plasma membrane is diminished, resulting in reduced glucose uptake by skeletal muscle and adipose tissue (Kisiała, 2025; Sun, 2026) [31, 62]. These defects lead to persistent hyperglycemia and compensatory hyperinsulinemia, which further amplify ovarian androgen production and metabolic dysfunction (Houston & Templeman, 2025; Zhao *et al*., 2023) [25, 75]. Additionally, inflammatory cytokines, oxidative stress, elevated free fatty acids, and adipokine imbalance further impair insulin signaling, establishing a vicious cycle that perpetuates insulin resistance, chronic inflammation, and the progression of PCOS-associated metabolic syndrome (Arora, 2012; Woo, 2024) [2, 71].

2. Effects of Hyperinsulinemia

Hyperinsulinemia, a compensatory response to insulin resistance, is a key pathogenic factor linking the reproductive and metabolic manifestations of Polycystic Ovary Syndrome (PCOS) (Houston & Templeman, 2025) [25]. As peripheral tissues become less responsive to insulin, pancreatic -cells increase insulin secretion to maintain normal blood glucose levels, resulting in chronically elevated circulating insulin concentrations (Houston & Templeman, 2025; Sakumoto *et al*., 2010) [25, 58]. Excess insulin acts synergistically with luteinizing hormone (LH) to stimulate ovarian theca cells, markedly increasing the synthesis of androgens such as testosterone and androstenedione (Sakumoto *et al*., 2010) [58]. Simultaneously, insulin suppresses hepatic production of sex hormone-binding globulin (SHBG), leading to higher levels of biologically active free testosterone in the circulation (Ding *et al*., 2021; Pateguana & Janes, 2019; Qu & Donnelly, 2020) [18, 47, 50].

Elevated androgen concentrations disrupt normal follicular development, causing follicular arrest, chronic anovulation, menstrual irregularities, and infertility (Sakumoto *et al*., 2010) [58]. Hyperinsulinemia also contributes to adipose tissue expansion by promoting lipogenesis and inhibiting lipolysis, thereby exacerbating obesity, particularly visceral adiposity (Sakumoto *et al*., 2010) [58]. Furthermore, excess insulin adversely affects lipid metabolism by increasing hepatic very-low-density lipoprotein (VLDL) production, elevating triglyceride levels, reducing high-density lipoprotein (HDL) cholesterol, and promoting the formation of small dense low-density lipoprotein (LDL) particles, all

of which contribute to dyslipidemia and increased cardiovascular risk (Ding *et al*., 2021) [18].

These metabolic disturbances are further intensified by chronic inflammation and oxidative stress, creating a self-perpetuating cycle in which insulin resistance, hyperinsulinemia, hyperandrogenism, obesity, and dyslipidemia reinforce one another (Ding *et al*., 2021; Houston & Templeman, 2025) [18, 25]. Consequently, hyperinsulinemia represents a central mechanism through which insulin resistance drives both the reproductive dysfunction and long-term metabolic complications associated with PCOS, including metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease (Ding *et al*., 2021; Houston & Templeman, 2025) [18, 25].

Chronic Inflammation: The Missing Link

Chronic low-grade systemic inflammation is increasingly recognized as a fundamental mechanism linking the reproductive and metabolic abnormalities of Polycystic Ovary Syndrome (PCOS) (Guan *et al*., 2022) [22]. Although obesity amplifies inflammatory responses, numerous studies have demonstrated that women with PCOS exhibit persistent systemic inflammation even in the absence of excess body weight, indicating that inflammation is an intrinsic feature of the disorder (Rudnicka *et al*., 2021) [56].

This inflammatory state arises from a complex interplay among hyperandrogenism, insulin resistance, adipose tissue dysfunction, oxidative stress, and genetic susceptibility (Bullock *et al*., 2012) [10]. Dysfunctional adipose tissue, particularly visceral fat, secretes excessive amounts of pro-inflammatory cytokines and chemokines that activate immune cells and inflammatory signaling pathways (Steinbach *et al*., 2024) [61]. In addition, hyperglycemia, elevated circulating free fatty acids, and oxidative stress further stimulate inflammatory cascades, perpetuating insulin resistance and endocrine dysfunction (Bullock *et al*., 2012; Guan *et al*., 2022) [2, 22].

Chronic inflammation not only disrupts metabolic homeostasis but also contributes to endothelial dysfunction, impaired ovarian folliculogenesis, and increased long-term cardiovascular risk in women with PCOS (Rudnicka *et al*., 2021) [56].

1. Major Inflammatory Biomarkers

Several inflammatory biomarkers are consistently elevated in women with PCOS and serve as indicators of chronic low-grade inflammation. High-sensitivity C-reactive protein (hs-CRP), an acute-phase protein synthesized by the liver, is one of the most widely studied markers and is strongly associated with insulin resistance and cardiovascular risk (Guan *et al*., 2022) [22]. Pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin- (IL-), and tumor necrosis factor- (TNF-) are secreted by activated macrophages and dysfunctional adipose tissue, where they interfere with insulin receptor signaling by promoting inhibitory serine phosphorylation of insulin receptor substrate proteins (Bullock *et al*., 2012) [10].

Monocyte chemoattractant protein-1 (MCP-1) recruits inflammatory monocytes and macrophages into adipose tissue, further amplifying local and systemic inflammation (Steinbach *et al*., 2024) [61]. In parallel, activation of the nuclear factor-kappa B (NF- B) signaling pathway serves as a central regulator of inflammatory gene expression, promoting the production of numerous cytokines, chemokines, and adhesion molecules that sustain chronic inflammation (Bullock *et al*., 2012) [10].

Collectively, these inflammatory mediators impair insulin sensitivity, reduce endothelial nitric oxide bioavailability, promote vascular endothelial dysfunction, and accelerate the development of atherosclerosis (Rudnicka *et al*., 2021) [56]. The resulting inflammatory milieu reinforces the cycle of insulin resistance, hyperandrogenism, oxidative stress, and metabolic dysfunction, thereby contributing to the increased prevalence of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease among women with PCOS (Guan *et al*., 2022; Rudnicka *et al*., 2021) [22, 56].

Interaction Among Obesity, Insulin Resistance, and Inflammation

These three pathological processes reinforce one another in a self-perpetuating cycle:

Obesity → Adipose inflammation → Insulin resistance → Hyperinsulinemia → Hyperandrogenism → Further obesity and inflammation

This vicious cycle explains the progressive nature of metabolic complications in PCOS.

Metabolic Syndrome in PCOS

Metabolic syndrome is diagnosed when at least three of the following abnormalities are present:

Component	Diagnostic Feature
Central obesity	Increased waist circumference
Hyperglycemia	Elevated fasting glucose
Hypertension	≥130/85 mmHg
High triglycerides	≥150 mg/dL
Low HDL cholesterol	<50 mg/dL (women)

Women with PCOS are approximately two to four times more likely to develop metabolic syndrome than women without PCOS.

Cardiometabolic Consequences

The long-term cardiometabolic consequences of Polycystic Ovary Syndrome (PCOS) extend far beyond reproductive dysfunction, making the disorder a significant public health concern (Cooper *et al*., 2024) [17]. Persistent insulin resistance, hyperinsulinemia, obesity, dyslipidemia, chronic low-grade inflammation, oxidative stress, and endothelial dysfunction collectively contribute to a markedly increased risk of metabolic and cardiovascular diseases throughout a woman's lifetime (Cooper *et al*., 2024; Cardinal *et al*., 2010) [13, 17]. Women with untreated or poorly controlled PCOS are substantially more likely to develop prediabetes and type 2 diabetes mellitus due to progressive deterioration of insulin sensitivity and pancreatic -cell function (Cooper *et al*., 2024; Moran *et al*., 2010) [17, 41].

The coexistence of hypertension, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and central obesity further predisposes these women to metabolic syndrome and accelerates the development of cardiovascular disease, including coronary artery disease, myocardial infarction, and stroke (Cardinal *et al*., 2010) [13].

Chronic metabolic disturbances also promote the accumulation of fat within hepatocytes, increasing the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), which may progress to metabolic dysfunction-associated steatohepatitis

(MASH, formerly NASH), fibrosis, and cirrhosis if left untreated (Vassilatou, 2018) [70]. In addition, obesity, hypertension, insulin resistance, and systemic inflammation may contribute to chronic kidney disease through progressive renal endothelial injury and glomerular dysfunction.

Women with PCOS also exhibit a higher prevalence of obstructive sleep apnea, particularly in the presence of obesity and hyperandrogenism, which further exacerbates insulin resistance and cardiovascular risk (Tasali *et al*., 2008) [64]. During pregnancy, PCOS is associated with increased rates of gestational diabetes mellitus, gestational hypertension, preeclampsia, preterm birth, miscarriage, and adverse neonatal outcomes (Qin *et al*., 2013) [49]. Furthermore, chronic anovulation results in prolonged unopposed estrogen exposure to the endometrium, substantially increasing the risk of endometrial hyperplasia and endometrial cancer (Barry *et al*., 2014) [7]. Collectively, these cardiometabolic complications highlight that PCOS is a lifelong multisystem disorder requiring early diagnosis, regular metabolic screening, comprehensive lifestyle intervention, and individualized therapeutic management to reduce long-term morbidity and mortality (Cooper *et al*., 2024; Cardinal *et al*., 2010) [13, 17].

Molecular Mechanisms

Several molecular pathways contribute to the development of metabolic syndrome in PCOS.

Oxidative Stress

Excess reactive oxygen species (ROS) damage cellular proteins, lipids, and DNA while impairing insulin receptor function. This structural damage and signaling disruption are heavily documented in Polycystic Ovary Syndrome (PCOS), where excessive ROS levels prompt lipid peroxidation—often measured via increased malondialdehyde (MDA)—and cellular structural mutations (Miao *et al*., 2024; Özer *et al*., 2016) [37, 46]. Concurrently, the accumulation of ROS activates downstream serine kinases that induce inhibitory serine phosphorylation of insulin receptor substrate (IRS) proteins, directly disrupting the critical phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) signaling pathway necessary for metabolic glucose clearance (Guan *et al*., 2022; Miao *et al*., 2024) [22, 37].

Mitochondrial Dysfunction

Reduced adenosine triphosphate (ATP) production contributes to defective glucose metabolism and increased oxidative stress, forming a central component of mitochondrial dysfunction in Polycystic Ovary Syndrome (PCOS) (Iqbal *et al*., 2022) [22]. Structural damage to mitochondria, including reduced cristae and membrane potential, impairs oxidative phosphorylation (OXPHOS) and severely limits ATP synthesis (Iqbal *et al*., 2022) [27].

This localized energy deficit impairs critical metabolic processes, as reduced ATP levels directly hinder downstream insulin signaling pathways and insulin-stimulated glucose uptake in peripheral tissues, accelerating insulin resistance (Kim *et al*., 2008; Malamouli *et al*., 2022) [30, 35]. Concurrently, the uncoupling or inefficiency of the mitochondrial electron transport chain causes electrons to leak, converting molecular oxygen into excessive reactive oxygen species (ROS) (Guan *et al*., 2022; Kim *et al*., 2008) [22, 30].

The resulting elevate in oxidative stress damages mitochondrial DNA (mtDNA) and essential cellular components, while further exacerbating glucose intolerance and follicle arrest in ovarian granulosa cells (Malamouli *et al*., 2022; Iqbal *et al*., 2022) [27, 35].

Gut Microbiota Dysbiosis

Altered intestinal microbiota increases gut permeability and endotoxin translocation, promoting systemic inflammation.

Endothelial Dysfunction

Reduced nitric oxide production impairs vascular relaxation and accelerates atherosclerosis.

Diagnosis

The diagnosis and metabolic evaluation of Polycystic Ovary Syndrome (PCOS) require a comprehensive clinical and laboratory assessment to identify reproductive abnormalities, assess metabolic risk, and exclude other endocrine disorders with similar clinical presentations (Joham *et al*., 2022) [29]. Clinical evaluation begins with a detailed medical and menstrual history, including the age of symptom onset, menstrual irregularities, infertility, and family history of diabetes or cardiovascular disease. Physical examination should include measurement of body mass index (BMI), waist circumference, and blood pressure to assess obesity, central adiposity, and hypertension, all of which are major components of metabolic syndrome. Signs of hyperandrogenism, such as hirsutism, acne, androgenic alopecia, and acanthosis nigricans, should also be carefully evaluated (Thong *et al*., 2020) [66]. Laboratory investigations are essential for assessing glucose metabolism, insulin resistance, lipid abnormalities, hepatic function, and hormonal status. These include fasting plasma glucose, oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), fasting insulin levels, and a complete lipid profile to detect prediabetes, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome. Liver function tests are recommended to screen for non-alcoholic fatty liver disease (NAFLD), while high-sensitivity C-reactive protein (hs-CRP) may be measured as a marker of chronic low-grade inflammation and cardiovascular risk. Hormonal evaluation typically includes serum total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, thyroid-stimulating hormone (TSH), and, when indicated, 17-hydroxyprogesterone to exclude other endocrine disorders. Pelvic ultrasonography is also commonly performed to identify polycystic ovarian morphology. Together, these clinical, biochemical, hormonal, and imaging assessments facilitate accurate diagnosis, comprehensive risk stratification, and the development of individualized management strategies for women with PCOS (Sacks *et al*., 2002) [57].

Management

1. Lifestyle Modification

Lifestyle modification remains the first-line and most effective intervention for the management of Polycystic Ovary Syndrome (PCOS)—recently renamed by global consensus to Polyendocrine Metabolic Ovarian Syndrome (PMOS/PCOS) to better reflect its systemic nature (Teede *et al*., 2023) [65]. This holds particularly true in women who are overweight or obese.

Since obesity, insulin resistance, and chronic inflammation are central to the pathogenesis of the disorder, interventions targeting weight reduction and improved metabolic health can substantially alleviate both reproductive and metabolic abnormalities (Moran *et al*., 2011; Teede *et al*., 2023) [40, 65]. A calorie-controlled diet tailored to individual energy requirements promotes gradual and sustainable weight loss, while dietary patterns such as the Mediterranean diet, which is rich in fruits, vegetables, whole grains, legumes, nuts, olive oil, and fish, have been shown to improve insulin sensitivity and reduce systemic inflammation (Barrea *et al*., 2019 [6]; Hopkins Medicine, 2026). Increased consumption of high-fiber foods slows glucose absorption, enhances satiety, and supports a healthy gut microbiota, whereas limiting refined carbohydrates and sugar-sweetened foods reduces postprandial hyperglycemia and hyperinsulinemia (Moran *et al*., 2011) [40].

Regular physical activity, including moderate-intensity aerobic exercise combined with resistance training, improves glucose uptake by skeletal muscles, enhances insulin sensitivity, preserves lean body mass, and promotes fat loss (Malamouli *et al*., 2022; Teede *et al*., 2023) [35, 65]. Clinical studies consistently demonstrate that a modest weight reduction of 5–10% of initial body weight significantly improves ovulatory function, menstrual regularity, fertility outcomes, hyperandrogenic symptoms, and metabolic parameters such as blood glucose, lipid profile, and blood pressure (Moran *et al*., 2011) [40]. Therefore, comprehensive lifestyle intervention remains the cornerstone of long-term PCOS management and prevention of metabolic syndrome (Teede *et al*., 2023) [65].

2. Pharmacological Therapy

Pharmacological treatment is recommended when lifestyle modification alone is insufficient to control the reproductive, metabolic, or endocrine manifestations of PCOS (Teede *et al*., 2023) [65]. The choice of medication depends on the patient's primary clinical concerns, including insulin resistance, menstrual irregularities, hyperandrogenism, infertility, obesity, or cardiometabolic risk (Cooper *et al*., 2024; Teede *et al*., 2023) [17, 65].

Metformin is the most widely prescribed insulin-sensitizing agent and improves insulin sensitivity by reducing hepatic glucose production, increasing peripheral glucose uptake, and lowering circulating insulin concentrations, thereby restoring ovulation in many women (Moran *et al*., 2010; Teede *et al*., 2023) [41, 65]. Recently, glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide and semaglutide have emerged as promising therapeutic options due to their ability to promote significant weight loss, improve glycemic control, reduce appetite, and decrease cardiovascular risk in women with PCOS (Han *et al*., 2023) [24]. Inositol supplements, particularly myo-inositol and D-chiro-inositol, improve insulin signaling, enhance oocyte quality, and restore ovulatory function with minimal adverse effects (Unfer *et al*., 2017) [69].

Combined oral contraceptives remain the standard therapy for women not seeking pregnancy, as they regulate menstrual cycles, suppress ovarian androgen production, increase hepatic synthesis of sex hormone-binding globulin (SHBG), and improve symptoms such as hirsutism and acne (Cooper *et al*., 2024; Teede *et al*., 2023) [17, 65]. Anti-androgen medications, including spironolactone, finasteride, and flutamide, may be prescribed to reduce androgen-related manifestations, although effective contraception is required because of their teratogenic potential (Cooper *et al*., 2024) [17]. Statins may also be considered in selected patients with dyslipidemia or elevated cardiovascular risk due to their lipid-lowering, anti-inflammatory, and endothelial-protective effects (Cardinal *et al*., 2010) [13]. Overall, pharmacological therapy should be individualized according to the patient's metabolic profile, reproductive goals, and risk factors (Teede *et al*., 2023) [65].

3. Anti-inflammatory Strategies

Chronic low-grade inflammation is increasingly recognized as a therapeutic target in PCOS because it contributes significantly to insulin resistance, endothelial dysfunction, hyperandrogenism, and metabolic syndrome (Guan *et al*., 2022) [22]. Consequently, several nutritional and pharmacological interventions with anti-inflammatory properties have been investigated as adjunctive therapies (Guan *et al*., 2022; Rudnicka *et al*., 2021) [22, 56].

Omega-3 polyunsaturated fatty acids possess potent anti-inflammatory effects by reducing the synthesis of pro-inflammatory cytokines, improving lipid metabolism, enhancing insulin sensitivity, and lowering triglyceride levels (Yang *et al*., 2018) [73]. Vitamin D supplementation has attracted considerable attention because vitamin D deficiency is common among women with PCOS and has been associated with insulin resistance, inflammation, and impaired ovarian function; supplementation may improve metabolic and reproductive outcomes in deficient individuals (Miao *et al*., 2020) [36]. Curcumin, the principal bioactive compound in turmeric, exhibits strong antioxidant and anti-inflammatory activities through inhibition of the nuclear factor-kappa B (NF- B) signaling pathway, thereby reducing oxidative stress and inflammatory cytokine production (Imani *et al*., 2021) [26]. Probiotics may restore gut microbial balance, strengthen intestinal barrier integrity, decrease systemic endotoxemia, and improve insulin sensitivity through modulation of the gut–microbiota axis.

Antioxidants such as vitamins C and E, coenzyme Q10, N-acetylcysteine, and alpha-lipoic acid help neutralize reactive oxygen species, reduce oxidative damage, and improve mitochondrial function (Guan *et al*., 2022; Ramachandran *et al*., 2019) [22, 52]. In addition, dietary polyphenols found in berries, green tea, cocoa, grapes, and other plant-based foods exert anti-inflammatory and antioxidant effects by regulating cellular signaling pathways and reducing oxidative stress (Rudnicka *et al*., 2021) [56]. Although these emerging therapies show considerable promise, further large-scale randomized clinical trials are needed to establish their long-term efficacy and define their role as complementary treatments alongside lifestyle modification and conventional pharmacotherapy in women with PCOS (Guan *et al*., 2022; Teede *et al*., 2023) [22, 65].

Future Perspectives

Recent research suggests that personalized treatment approaches integrating genomics, metabolomics, gut microbiome profiling, and artificial intelligence may improve risk prediction and individualized management of PCOS. Novel agents targeting inflammatory pathways, adipokines, mitochondrial dysfunction, and incretin signaling are being investigated and may offer improved metabolic outcomes beyond conventional therapies.

Table 1: Metabolic Syndrome in Women with Polycystic Ovary Syndrome (PCOS) (Onat *et al*., 2004; Bajaj and DeFronzo, 2003; Javed *et al*., 2026; Murta *et al*., 2026)

Component	Clinical Features in PCOS	Underlying Pathophysiology	Long-term Clinical Consequences
Central Obesity	Increased body mass index (BMI), increased waist circumference, visceral adiposity	Adipocyte hypertrophy, adipokine imbalance, chronic inflammation, increased free fatty acid release	Insulin resistance, metabolic syndrome, cardiovascular disease
Insulin Resistance	Reduced peripheral glucose uptake, compensatory hyperinsulinemia	Defective insulin receptor signaling, impaired IRS-1/PI3K/Akt pathway, GLUT4 dysfunction	Type 2 diabetes mellitus, hyperinsulinemia, hyperandrogenism
Hyperglycemia	Elevated fasting plasma glucose, impaired glucose tolerance, increased HbA1c	Decreased insulin sensitivity and progressive β-cell dysfunction	Prediabetes, type 2 diabetes mellitus
Dyslipidemia	Elevated triglycerides, increased LDL cholesterol, decreased HDL cholesterol	Increased hepatic VLDL production, impaired lipid metabolism, insulin resistance	Atherosclerosis, coronary artery disease, stroke
Hypertension	Elevated systolic and diastolic blood pressure	Endothelial dysfunction, oxidative stress, activation of the renin–angiotensin system	Cardiovascular disease, chronic kidney disease
Hyperandrogenism	Hirsutism, acne, androgenic alopecia, elevated testosterone	Hyperinsulinemia stimulates ovarian theca cells and suppresses SHBG production	Ovulatory dysfunction, infertility, metabolic abnormalities
Chronic Low-grade Inflammation	Elevated hs-CRP, TNF-α, IL-6, IL-1β, MCP-1	Adipose tissue inflammation, macrophage activation, NF-κB signaling	Endothelial dysfunction, insulin resistance, accelerated atherosclerosis
Oxidative Stress	Increased reactive oxygen species (ROS), lipid peroxidation	Mitochondrial dysfunction, chronic inflammation	Cellular damage, endothelial dysfunction, cardiovascular complications
Non-alcoholic Fatty Liver Disease (NAFLD/MASLD)	Elevated liver enzymes, hepatic fat accumulation	Excess free fatty acid deposition, insulin resistance	Fibrosis, cirrhosis, liver dysfunction
Reproductive Dysfunction	Oligomenorrhea, amenorrhea, chronic anovulation, infertility	Hyperandrogenism, follicular arrest, endocrine imbalance	Infertility, pregnancy complications, endometrial hyperplasia
Cardiovascular Risk	Increased carotid intima-media thickness, endothelial dysfunction	Combined effects of obesity, inflammation, dyslipidemia, hypertension, insulin resistance	Coronary artery disease, myocardial infarction, stroke
Overall Metabolic Syndrome	Presence of ≥3 metabolic abnormalities (central obesity, hyperglycemia, hypertension, hypertriglyceridemia, low HDL cholesterol)	Interplay of obesity, insulin resistance, inflammation, oxidative stress, and endocrine dysfunction	Increased risk of type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, and premature mortality

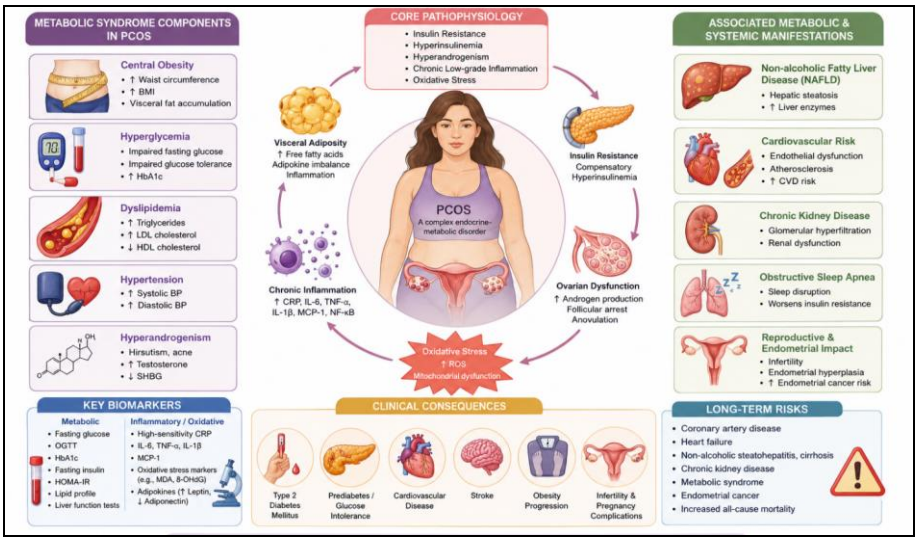

Fig 1: Pathophysiological Mechanisms Underlying Metabolic Syndrome in Women with Polycystic Ovary Syndrome (PCOS)

Conclusion

PCOS extends beyond reproductive dysfunction and should be regarded as a chronic metabolic disorder with lifelong health implications. Obesity, insulin resistance, and chronic low-grade inflammation form the interconnected pathogenic core that links PCOS with metabolic syndrome. Visceral adiposity promotes inflammatory cytokine production and adipokine imbalance, insulin resistance amplifies hyperandrogenism and metabolic dysfunction, and persistent inflammation accelerates cardiovascular and metabolic complications. Early identification of women at high metabolic risk, comprehensive screening for metabolic syndrome, and timely intervention through lifestyle modification, weight management, insulin-sensitizing

agents, and anti-inflammatory therapies are essential to reduce long-term morbidity. Future research aimed at precision medicine and targeted molecular therapies may transform the management of PCOS and improve quality of life for affected women.

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