

## Metabolic Dysregulation in Polycystic Ovary Syndrome: The Central Role of Insulin Resistance and Novel Therapeutic Perspectives

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**Abstract:** Polycystic ovary syndrome (PCOS) is a common endocrine disorder with complex reproductive and metabolic consequences that are often not fully addressed by symptom-oriented management strategies. Increasing evidence shows that metabolic dysfunction, particularly insulin resistance and hyperinsulinemia, plays a central role in the pathophysiology of PCOS and contributes to both reproductive and systemic abnormalities. **Objective:** This study aimed to review and synthesize recent evidence on the metabolic basis of PCOS, with particular emphasis on the role of insulin resistance and hyperinsulinemia as key mechanisms underlying metabolic and reproductive disturbances. **Method:** This study used a narrative review design by analyzing recent peer-reviewed literature related to insulin signaling disturbances, mitochondrial dysfunction, oxidative stress, inflammatory pathways, and emerging therapeutic approaches in PCOS. The selected studies were examined descriptively to identify major pathophysiological patterns and current treatment perspectives. **Findings:** The review found that insulin resistance and hyperinsulinemia are major drivers of PCOS across various phenotypes, including non-obese women. Mitochondrial dysfunction and chronic inflammation were also shown to aggravate metabolic and reproductive impairments. In addition, the findings indicate that improvements in metabolic parameters do not always correspond to normalization of reproductive hormones, highlighting the heterogeneous and multifactorial nature of PCOS. **Implications:** These findings have important implications for clinical practice by supporting the development of personalized and mechanism-based management strategies that integrate metabolic profiling with reproductive goals. Such an approach may improve the effectiveness of long-term treatment and patient outcomes. **Originality:** The originality of this review lies in its integrative metabolic–reproductive framework, which brings together recent mechanistic insights and emerging therapeutic perspectives to reconceptualize PCOS as a systemic metabolic–reproductive disorder rather than a purely reproductive condition.

**Keywords:** Polycystic Ovary Syndrome; Insulin Resistance; Hyperinsulinemia; Metabolic Dysfunction; Mitochondrial Dysfunction; Personalized Therapy

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age and constitutes a major global public health concern. Epidemiological evidence indicates that PCOS affects approximately 6–20% of women worldwide, with prevalence varying according to diagnostic criteria and population characteristics (Deng et al., 2024). Beyond its reproductive manifestations, PCOS imposes

substantial long-term health burdens through its association with metabolic disorders, including insulin resistance, obesity, dyslipidemia, type 2 diabetes mellitus, and cardiovascular disease. These conditions not only compromise reproductive health but also reduce quality of life and increase morbidity across the lifespan, underscoring the importance of PCOS as a systemic health issue rather than a condition confined to gynecological care.

Contemporary literature increasingly conceptualizes PCOS as a complex metabolic–endocrine disorder characterized by marked phenotypic heterogeneity. A substantial body of research identifies insulin resistance and compensatory hyperinsulinemia as central pathophysiological features of PCOS, affecting up to 65–95% of patients regardless of body mass index (Deng et al., 2024; Gkantzios et al., 2025). Mechanistically, hyperinsulinemia exacerbates hyperandrogenism by stimulating ovarian theca cell steroidogenesis and suppressing hepatic sex hormone–binding globulin synthesis, thereby increasing free androgen levels (Zhang et al., 2025). Parallel studies emphasize that obesity, although common in PCOS, primarily acts as a modifier that amplifies metabolic and reproductive disturbances rather than serving as a universal causal factor. The presence of insulin resistance and metabolic dysfunction in lean women with PCOS challenges obesity-centered models and highlights intrinsic metabolic defects independent of excess adiposity (Gkantzios et al., 2025; Li et al., 2025).

Despite extensive investigation, important gaps remain in the existing literature. Prior studies tend to focus on individual components of PCOS pathophysiology, such as insulin resistance, obesity, or hyperandrogenism, often in isolation. Emerging evidence implicates additional metabolic pathways including chronic low-grade inflammation, immune dysregulation, mitochondrial dysfunction, altered amino acid metabolism, and gut microbiota imbalance in the persistence and progression of PCOS (Deng et al., 2024; Li et al., 2025). However, the mechanistic integration of these pathways with insulin resistance, particularly in non-obese PCOS phenotypes, remains incompletely understood. Moreover, current therapeutic strategies remain largely symptom-oriented and phenotype-agnostic, limiting their effectiveness in preventing long-term metabolic complications (Pluta et al., 2025).

This review aims to address these limitations by providing an integrative synthesis of recent evidence on the metabolic dysregulation underlying PCOS, with particular emphasis on insulin resistance and hyperinsulinemia as central drivers of disease pathogenesis. The

review examines how metabolic abnormalities interact with reproductive dysfunction, explores the modifying role of obesity, and evaluates emerging therapeutic perspectives targeting metabolic, inflammatory, and mitochondrial pathways. It is argued that reframing PCOS as a metabolic–reproductive disorder driven by interconnected pathophysiological mechanisms offers a more coherent explanatory framework and supports the development of personalized, multi-target treatment strategies capable of improving both metabolic and reproductive outcomes.

## **METHOD**

### **Unit of Analysis**

The unit of analysis in this study comprises peer-reviewed scientific articles focusing on the metabolic dysregulation of polycystic ovary syndrome (PCOS). The review concentrates on literature addressing insulin resistance, hyperinsulinemia, mitochondrial dysfunction, and emerging metabolic-based therapeutic strategies, which collectively represent the analytical objects of this research.

### **Research Design**

A narrative review design was employed to synthesize and interpret recent developments in the metabolic and endocrine aspects of PCOS. This design was selected to allow integrative analysis of heterogeneous clinical, molecular, and translational studies, particularly in areas where evidence remains conceptually evolving and not yet suitable for systematic review or meta-analysis.

### **Data Sources**

Secondary data were obtained from international scientific databases, namely PubMed, Scopus, and Web of Science. The literature search was limited to peer-reviewed journal articles published between 2024 and 2025 to ensure relevance to current scientific discourse on PCOS-related metabolic mechanisms.

### **Data Collection Technique**

Data collection was conducted through structured literature searching using predefined keywords, including “polycystic ovary syndrome,” “insulin resistance,” “hyperinsulinemia,” “metabolic dysfunction,” “mitochondrial dysfunction,” “flavonoids,”

and “novel therapies.” Articles were screened based on relevance, methodological quality, and contribution to understanding PCOS as a metabolic–reproductive disorder. Five key articles were selected as primary references to provide complementary perspectives while minimizing redundancy.

### **Data Analysis**

Data analysis was performed using narrative synthesis. Qualitative and limited quantitative data, including metabolic indicators, biochemical parameters, and mechanistic insights, were extracted and compared to identify recurring patterns, shared pathways, therapeutic implications, and research gaps. Due to heterogeneity in study design and outcomes, no statistical meta-analysis was conducted. This approach facilitated integrative interpretation of emerging metabolic mechanisms and therapeutic concepts in PCOS.

## **RESULT AND DISCUSSION**

### **Insulin Resistance and Hyperinsulinemia as Central Metabolic Findings in PCOS**

Across the five primary articles analyzed, insulin resistance (IR) and hyperinsulinemia consistently emerge as dominant metabolic abnormalities underlying the pathophysiology of polycystic ovary syndrome (PCOS). Houston and Templeman (2025) report that IR and hyperinsulinemia are present in approximately 60–95% of women with PCOS, irrespective of obesity status, indicating that metabolic dysregulation is intrinsic to the syndrome. These findings are consistent with epidemiological and mechanistic evidence summarized in recent reviews (Deng et al., 2024; Gkantzios et al., 2025).

Mechanistic evidence highlights the presence of selective insulin resistance, characterized by impaired insulin-mediated metabolic signaling through the PI3K–Akt pathway, while mitogenic signaling via the MAPK pathway remains relatively preserved (Houston & Templeman, 2025). This signaling dissociation allows insulin to continue stimulating ovarian steroidogenesis despite reduced glucose uptake in peripheral tissues. Clinically, this mechanism explains the frequent coexistence of hyperinsulinemia and normoglycemia in women with PCOS, while still exacerbating hyperandrogenism and ovulatory dysfunction (Zhang et al., 2025).

Several consistent patterns emerge from the literature, including the persistence of hyperinsulinemia across PCOS phenotypes, selective rather than global insulin resistance, and a strong association between insulin excess and ovarian dysfunction. These observations support the hypothesis that hyperinsulinemia may function as an upstream

metabolic driver in certain PCOS phenotypes, carrying important implications for therapeutic targeting (Houston & Templeman, 2025).

### **Clinical Evidence of Metabolic Modulation: Hydroxychloroquine Versus Metformin**

Clinical intervention studies provide insight into how modulation of metabolic pathways translates into therapeutic outcomes. (Wang et al., 2025) conducted a randomized controlled trial comparing hydroxychloroquine (HCQ) with metformin in obese women with PCOS. After three months of treatment, both interventions significantly improved glucose and lipid metabolism; however, HCQ demonstrated superior enhancement of insulin sensitivity. The insulin sensitivity index increased to  $1.87 \pm 0.21$  in the HCQ group compared with  $1.75 \pm 0.29$  in the metformin group.

In addition to glycemic improvement, HCQ was associated with greater reductions in total cholesterol, triglycerides, and low-density lipoprotein cholesterol (Wang et al., 2025). Despite these metabolic benefits, improvements in reproductive hormone profiles were modest in both treatment arms, with only a downward trend observed in circulating androgen levels.

This dissociation between metabolic improvement and hormonal normalization underscores the complexity of PCOS pathophysiology. Similar patterns have been reported in recent reviews, suggesting that correction of insulin resistance alone does not consistently restore reproductive endocrine balance (Dzienny & Seifer, 2025; Saadati et al., 2025).

### **Heterogeneous Response to Metformin and Reproductive Outcomes**

Evidence from multiple reviews indicates considerable heterogeneity in clinical response to metformin among women with PCOS. Metformin reliably improves insulin resistance, fasting insulin levels, and menstrual regularity, particularly in individuals with obesity or marked metabolic impairment (Saadati et al., 2025). However, its effects on ovulation induction, sustained weight reduction, and clinical hyperandrogenism remain modest and inconsistent (Mahoney & D'Angelo, 2025).

Several studies report that metabolic improvement does not always parallel normalization of androgen levels or ovulatory function, suggesting that reproductive dysfunction may also arise from intrinsic ovarian and neuroendocrine abnormalities

(Dzienny & Seifer, 2025; Mahoney & D'Angelo, 2025). These findings indicate that PCOS encompasses a spectrum of metabolic–reproductive phenotypes rather than a uniform clinical entity.

### **Mitochondrial Dysfunction and Oxidative Stress as Metabolic Amplifiers**

Beyond disturbances in insulin signaling, mitochondrial dysfunction has emerged as a critical amplifier of metabolic impairment in PCOS. (Tharayil & Shukla, 2025) describe how impaired mitochondrial oxidative phosphorylation, excessive reactive oxygen species (ROS) production, and defective fatty acid oxidation contribute to the development and persistence of insulin resistance.

Chronic exposure to elevated glucose and free fatty acids results in incomplete  $\beta$ -oxidation and accumulation of lipid intermediates, including diacylglycerol and ceramides. These metabolites activate stress-sensitive kinases that inhibit insulin receptor substrate signaling, thereby exacerbating insulin resistance (Tharayil & Shukla, 2025). Concurrently, oxidative stress damages mitochondrial DNA and disrupts mitochondrial biogenesis, establishing a self-perpetuating cycle of metabolic dysfunction.

Quantitative evidence indicates that insulin resistance affects up to 75% of lean and 95% of obese women with PCOS, reinforcing the view that mitochondrial dysfunction represents an intrinsic metabolic abnormality rather than a secondary consequence of obesity (Gkantzios et al., 2025; Tharayil & Shukla, 2025).

### **Flavonoids and Phytochemicals as Multi-Target Metabolic Modulators**

Given the multifactorial nature of PCOS, increasing attention has been directed toward therapeutic agents capable of targeting multiple pathogenic pathways simultaneously. Reviews by (Balkrishna et al., 2025; Dutta et al., 2025) highlight the potential of flavonoids and other plant-derived bioactive compounds as multi-target metabolic modulators.

Preclinical studies demonstrate that flavonoids such as apigenin and ellagic acid improve insulin sensitivity through activation of the PI3K–Akt pathway, reduce oxidative stress, and suppress pro-inflammatory cytokines, including TNF- $\alpha$  and IL-6 (Balkrishna et al., 2025). In rodent models of PCOS, these compounds restore ovarian morphology, reduce cystic follicle formation, and normalize estrous cycles.

Preliminary clinical evidence suggests improvements in fasting glucose, insulin levels, lipid profiles, and adipokine balance following flavonoid supplementation (Dutta et al.,

2025). These pleiotropic effects contrast with conventional pharmacotherapies that primarily address isolated clinical features. Complementary dietary interventions, including low-glycemic and Mediterranean dietary patterns, inositol, vitamin D, and omega-3 fatty acids, further support integrated metabolic management strategies (Saeed et al., 2025).

## **Discussion**

The results synthesized in this review support a unified conceptualization of PCOS as a metabolic–endocrine disorder driven by interacting abnormalities in insulin resistance, hyperinsulinemia, mitochondrial dysfunction, inflammation, and ovarian steroidogenesis. Insulin resistance and hyperinsulinemia emerge as central metabolic nodes, while mitochondrial and inflammatory pathways amplify their effects and contribute to disease persistence (Houston & Templeman, 2025; Tharayil & Shukla, 2025).

Comparison with prior studies confirms that while metformin remains effective in improving metabolic parameters, its reproductive benefits are variable and phenotype-dependent (Saadati et al., 2025). Emerging evidence on hydroxychloroquine and flavonoids introduces alternative therapeutic pathways that target immunometabolic and oxidative mechanisms beyond classical insulin sensitization (Balkrishna et al., 2025; Wang et al., 2025).

These findings highlight the limitations of symptom-based treatment approaches and underscore the need for personalized, mechanism-driven management strategies. Integrating metabolic profiling, multi-target pharmacological agents, and dietary interventions may enhance long-term metabolic stability and reproductive outcomes in women with PCOS. Future research should prioritize longitudinal and translational studies to refine phenotype-specific therapeutic frameworks and support evidence-based clinical decision-making.

## **CONCLUSION**

Polycystic ovary syndrome should be understood as a systemic metabolic–endocrine disorder rather than a condition limited to reproductive dysfunction. Evidence synthesized in this review identifies insulin resistance and hyperinsulinemia as central pathophysiological drivers of PCOS, influencing ovarian steroidogenesis, follicular development, and long-term metabolic risk across diverse phenotypes, including lean

women. Mitochondrial dysfunction, oxidative stress, and chronic low-grade inflammation further act as metabolic amplifiers that sustain metabolic–reproductive impairment, explaining why improvements in metabolic parameters do not consistently result in normalization of reproductive hormones.

This review contributes to the scientific literature by integrating recent findings into a unified metabolic–reproductive framework of PCOS. The analysis highlights the interconnected roles of insulin signaling, mitochondrial dysfunction, and immunometabolic pathways, extending current understanding beyond symptom-based models. Emphasis on multi-target therapeutic approaches, including immunomodulatory agents and plant-derived bioactive compounds such as flavonoids, provides conceptual support for more mechanism-driven and phenotype-specific management strategies.

The present study is subject to several limitations. The narrative review design precludes quantitative synthesis and limits causal inference and effect size estimation. Dependence on recent publications may also exclude earlier foundational studies and introduces potential selection bias. Future research should employ longitudinal designs, integrative omics methodologies, and well-controlled clinical trials to validate phenotype-specific mechanisms and assess the long-term effectiveness of multi-target therapeutic interventions across diverse PCOS populations.

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