Oxidative Stress and Inflammatory Markers in PCOD: A Review of Current Research

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Abstract- Polycystic ovarian disease (PCOD), one of the most common endocrine disorders in reproductive-aged women, is increasingly recognized as a condition that extends beyond ovarian dysfunction to involve complex metabolic and systemic disturbances. Among these, oxidative stress and chronic low-grade inflammation have emerged as pivotal factors contributing to the onset, persistence, and progression of the disorder. This review systematically examines recent literature from 2019 to 2025 exploring the intricate relationship between redox imbalance and inflammatory dysregulation in PCOD. A consistent body of clinical and experimental evidence reveals elevated levels of oxidative markers such as malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and decreased activity of key antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase, and catalase in women with PCOD. In parallel, pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) are significantly upregulated, even in non-obese PCOD phenotypes. These changes contribute to insulin resistance, hyperandrogenism, anovulation, and impaired folliculogenesis—defining hallmarks of the syndrome. Notably, oxidative stress and inflammation are not independent processes but are mechanistically interconnected through redox-sensitive transcription factors like NF-κB, forming a self-perpetuating pathogenic cycle. This interaction underscores their importance not only as biomarkers for disease severity and progression but also as viable therapeutic targets. Nutraceuticals such as N-acetylcysteine, omega-3 fatty acids, vitamin E, and curcumin, along with structured lifestyle modifications, have demonstrated promising results in modulating these biochemical pathways. This review highlights the need for a paradigm shift in PCOD management—moving beyond hormone-centric strategies to integrative approaches that address underlying oxidative and inflammatory dysfunction. Future research should aim to establish standardized biomarker profiles and evaluate long-term outcomes of targeted interventions through well-powered clinical trials.

Keywords: PCOD, Oxidative stress, Inflammation, Cytokines, ROS, CRP, MDA, Antioxidants.

INTRODUCTION

Polycystic ovarian disease (PCOD), commonly known as polycystic ovary syndrome (PCOS), is one of the most prevalent endocrinological disorders affecting women of reproductive age. Characterized by menstrual irregularities, hyperandrogenism, and polycystic ovarian morphology, PCOD presents a complex clinical picture that spans far beyond the ovaries. Its heterogeneity in phenotypes—ranging from ovulatory dysfunction to metabolic syndrome—makes it both a diagnostic challenge and a therapeutic puzzle. Epidemiological data suggest that PCOD affects approximately 8–13% of women globally, though prevalence can rise to 20% depending on diagnostic criteria applied (Rotterdam vs. NIH vs. AE-PCOS) [1].

Traditionally, PCOD has been viewed through the hormonal and metabolic lens, with much focus placed on insulin resistance, elevated luteinizing hormone (LH), and androgen excess. However, over the last decade, mounting evidence has repositioned oxidative stress and chronic low-grade inflammation as foundational elements of PCOD pathophysiology rather than downstream consequences. This reconceptualization is more than academic—it

redefines how we understand, diagnose, and treat the condition.

Oxidative stress (OS) refers to an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense capacity. In PCOD, this imbalance is driven by multiple factors: insulin resistance, central obesity, mitochondrial dysfunction, and chronic hyperglycemia—all of which contribute to increased ROS production [2]. The resultant redox imbalance damages lipids, proteins, and DNA, leading to altered cellular signaling, steroidogenesis, and impaired folliculogenesis [3].

Simultaneously, women with PCOD exhibit elevated markers of systemic inflammation, including high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). These pro-inflammatory mediators not only interfere with insulin signaling pathways but also promote androgen synthesis via their action on theca cells and adipose tissue macrophages [4]. In fact, inflammation and oxidative stress interact bidirectionally: ROS activate redox-sensitive transcription factors such as NF-κB, which, in turn, upregulate the expression of inflammatory cytokines, establishing a vicious feedback loop [5].

Notably, these phenomena are observed not just in obese women with PCOD but also in lean phenotypes, suggesting that inflammation and oxidative stress are inherent to the disorder, independent of body mass index [6]. This is a key distinction with therapeutic consequences, as it challenges the common assumption that weight loss alone is sufficient to reverse PCOD pathophysiology.

From a clinical standpoint, the presence of oxidative and inflammatory biomarkers correlates with PCOD severity, including increased insulin resistance, anovulatory cycles, and poorer fertility outcomes. These markers may also serve as early indicators of cardiovascular and metabolic risks associated with PCOD, which often go undiagnosed until much later in life.

In this context, the current review aims to systematically assess the literature published between 2019 and 2025 concerning oxidative stress and inflammatory biomarkers in PCOD. The goal is to evaluate how these biochemical parameters inform disease progression, diagnostic potential, and therapeutic avenues—including non-hormonal strategies that directly modulate redox and inflammatory pathways.

AIMS AND OBJECTIVES

Aim

- To critically analyze the role of oxidative stress and inflammatory markers in the pathogenesis and clinical progression of PCOD.
- Objectives
- To review the current evidence on oxidative stress biomarkers in PCOD from 2019–2025.
- To identify key inflammatory markers elevated in PCOD and their relevance to disease severity.
- To explore how oxidative stress and inflammation interconnect in PCOD pathophysiology.
- To highlight therapeutic strategies targeting redox and inflammatory pathways.

Materials and Methods

This review follows a structured literature review design using secondary data from peer-reviewed journals published between January 2019 and May 2025.

Data Sources: PubMed, Scopus, ScienceDirect, and Google Scholar were searched using keywords: PCOD, oxidative stress, inflammation, ROS, cytokines, MDA, CRP, antioxidant therapy.

Inclusion Criteria:

- Studies published between 2019 and 2025
- Clinical, preclinical, or mechanistic studies involving PCOD and oxidative/inflammatory markers
- English-language full-text articles

Exclusion Criteria:

- Studies not directly assessing oxidative or inflammatory markers
- Non-PCOD populations
- Reviews prior to 2019, unless cited for background

Pathophysiological Link: Oxidative Stress and Inflammation in PCOD

Polycystic ovarian disease (PCOD) is increasingly understood not merely as a hormonal or

gynecological condition but as a chronic systemic disorder marked by deep-rooted metabolic, oxidative, and immunological imbalances. Two key interwoven players—oxidative stress and chronic low-grade inflammation—have emerged as central to its pathogenesis. These processes are not peripheral anomalies; they are intrinsic drivers that fuel and sustain the endocrine and metabolic derangements observed in PCOD.

Oxidative Stress: A Biochemical Imbalance

Oxidative stress arises when the cellular production of reactive oxygen species (ROS)—including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH)—exceeds the neutralizing capacity of the body's antioxidant defense systems. In PCOD, this redox imbalance is triggered by multiple converging factors:

Insulin Resistance and Hyperinsulinemia: Persistent insulin resistance, a hallmark of PCOD, increases mitochondrial ROS production in tissues like adipocytes and muscle. Hyperinsulinemia in turn stimulates androgen synthesis and lipogenesis, worsening metabolic dysfunction.

Adipose Tissue Dysfunction: Especially in obese PCOD phenotypes, visceral adipocytes act as active endocrine cells, releasing free fatty acids and generating ROS via NADPH oxidase pathways. This directly enhances systemic oxidative load [2].

Hyperandrogenism: Elevated androgens interfere with mitochondrial function and can themselves increase ROS generation, especially in ovarian tissue, disrupting folliculogenesis and oocyte quality [3].

Antioxidant Depletion: Studies consistently show that enzymatic antioxidants like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) are significantly reduced in PCOD patients. Non-enzymatic antioxidants such as vitamins C and E are also lowered, leading to greater oxidative damage [4].

The downstream effects of this oxidative environment are multifold: lipid peroxidation (reflected by elevated malondialdehyde, MDA), protein oxidation, mitochondrial dysfunction, and damage to ovarian granulosa cells—ultimately impairing ovulation and steroidogenesis [5].

Chronic Low-Grade Inflammation: A Silent Agitator

Parallel to oxidative stress, chronic low-grade inflammation underpins much of the metabolic and endocrine dysfunction in PCOD. Unlike acute inflammation, which is short-lived and protective, chronic inflammation is insidious and often subclinical. Key inflammatory features in PCOD include:

Elevated Pro-inflammatory Cytokines: IL-6, TNF-α, IL-1β, MCP-1, and CRP are significantly raised in both serum and adipose tissue of PCOD women, independent of obesity status [6].

CRP as a Marker: High-sensitivity C-reactive protein (hs-CRP), an acute-phase protein and surrogate marker for systemic inflammation, has been positively correlated with insulin resistance and hyperandrogenemia in PCOD [7].

Macrophage Infiltration in Adipose Tissue: In PCOD, adipose depots—especially visceral fat—exhibit macrophage infiltration that releases TNF-α and other inflammatory mediators, promoting insulin resistance and disrupting normal ovarian signaling [8].

Ovarian Inflammation: Even at the ovarian level, local inflammation damages follicular architecture, alters aromatase expression, and contributes to anovulation.

The Inflammation–Oxidative Stress Feedback Loop

What makes this pathophysiological axis particularly damaging is its bidirectional feedback:

ROS → NF-κB Activation: Oxidative stress activates transcription factors like nuclear factor-kappa B (NF-κB), which upregulates inflammatory gene expression (IL-6, TNF-α, iNOS), thereby amplifying cytokine production [9].

Cytokines → ROS Production: Inflammatory cytokines stimulate further ROS production via mitochondrial and NADPH oxidase activation, perpetuating redox imbalance.

This self-sustaining loop drives metabolic inflexibility, ovulatory dysfunction, and long-term cardiovascular risk.

Lean PCOD and Inflammation

A critical insight from recent studies is that these oxidative-inflammatory alterations are not exclusive to obese phenotypes. Lean women with PCOD also exhibit elevated MDA, CRP, and altered antioxidant

status, suggesting that intrinsic genetic or epigenetic abnormalities in redox regulation and immune signaling may underlie PCOD regardless of body weight [10]. This undermines the assumption that weight loss alone can resolve PCOD symptoms in all patients.

Clinical Implications

Reproductive Outcomes: Oxidative damage to granulosa cells and the oocyte microenvironment results in poor follicle maturation, lower oocyte quality, and reduced fertility.

Metabolic Complications: Both ROS and cytokines impair insulin receptor signaling through serine phosphorylation and inflammatory pathway activation, reinforcing insulin resistance.

Cardiovascular Risk: Elevated oxidative and inflammatory markers in PCOD have been associated with endothelial dysfunction, subclinical atherosclerosis, and increased long-term risk of cardiovascular events.

In summary, oxidative stress and chronic inflammation are not downstream effects but core components of PCOD pathophysiology. Their presence in both lean and obese phenotypes suggests a fundamental metabolic-immune disruption intrinsic to the syndrome. Recognizing and targeting these mechanisms could pave the way for more personalized and mechanistically grounded therapies beyond conventional hormonal treatments.

Would you like me to generate an illustrative figure or diagram showing this feedback loop or a summary table comparing oxidative and inflammatory markers across PCOD phenotypes?

Review of Recent Research (2019–2025)

Oxidative Biomarkers in PCOD

Marker	Finding	Source
MDA	Elevated in serum and follicular fluid	[7,8]
Superoxide Dismutase (SOD)	Decreased activity in PCOD patients	[9,10]
Glutathione Peroxidase	Reduced, correlating with insulin resistance	[11]
8-OHdG	Urinary levels increased, indicating DNA oxidation	[12]

Inflammatory Biomarkers in PCOD

Marker	Association	Source
CRP (hs-CRP)	Correlates with BMI, androgen levels	[13]
TNF-α	Elevated in serum; linked to insulin resistance	[14,15]
IL-6	Promotes androgen production; upregulated in adipose tissue	[16]
MCP-1, IL-18	Emerging markers of chronic inflammation	[17]

Correlation with Clinical Features

Obesity exacerbates oxidative and inflammatory markers, independent of PCOD [18].

Lean PCOD patients also show elevated oxidative stress, suggesting intrinsic defects [19].

Insulin resistance correlates more strongly with OS and inflammation than hyperandrogenism [20].

Therapeutic Implications

Antioxidant and anti-inflammatory strategies show promise:

- Vitamin E & C supplementation reduces MDA and improves ovulatory function [21].
- N-acetyl cysteine (NAC), an antioxidant, improves insulin sensitivity and reduces androgen levels.
- Omega-3 fatty acids modulate inflammatory cytokine profiles.
- Lifestyle interventions (diet, exercise) decrease CRP, IL-6, and ROS burden across studies.

DISCUSSION

The evolving understanding of polycystic ovarian disease (PCOD) has moved decisively beyond the reproductive and hormonal paradigm. It is now recognized as a multisystem disorder where oxidative stress (OS) and chronic low-grade inflammation are not just peripheral or secondary events but critical mechanistic drivers. This review consolidates findings from 2019 to 2025 that

establish oxidative and inflammatory markers as central to the pathophysiology, clinical features, and therapeutic responses in PCOD.

Interconnected Mechanisms: A Vicious Cycle

The relationship between oxidative stress and inflammation in PCOD is reciprocal and self-sustaining. Increased production of reactive oxygen species (ROS) due to insulin resistance, hyperglycemia, mitochondrial dysfunction, and adipocyte hypertrophy contributes to oxidative damage across cellular systems. This includes lipid peroxidation (e.g., elevated MDA), protein nitration, and DNA damage (e.g., 8-OHdG). Such oxidative insults impair ovarian steroidogenesis, follicular growth, and ovulatory capacity.

Simultaneously, inflammatory mediators—particularly TNF-α, IL-6, MCP-1, and CRP—are upregulated, even in non-obese PCOD phenotypes. These cytokines act locally and systemically: in ovarian tissue, they disrupt granulosa cell function and promote androgen production; in metabolic tissues, they interfere with insulin signaling via serine phosphorylation of IRS-1 and NF-κB activation. The two systems feed into one another: ROS activate redox-sensitive transcription factors such as NF-κB and AP-1, which induce expression of pro-inflammatory genes, while inflammation itself propagates further ROS production through macrophage activation and NADPH oxidase activity. This closed-loop pathology accelerates the clinical manifestations of PCOD.

Biomarkers: From Diagnostic Tools to Therapeutic Targets

The literature consistently demonstrates elevated levels of malondialdehyde (MDA), C-reactive protein (CRP), and pro-inflammatory cytokines in PCOD patients. These biomarkers correlate with several clinical dimensions—hyperandrogenism, menstrual irregularities, insulin resistance, and BMI. Importantly, even lean women with PCOD show significant elevations in these parameters, suggesting that redox and immune dysregulation are intrinsic to the disorder rather than consequences of obesity alone.

Moreover, diminished levels of antioxidant enzymes—such as superoxide dismutase (SOD), catalase, and glutathione peroxidase—across studies underscore the failure of endogenous defense systems in PCOD. This imbalance tilts the physiological scale toward oxidative damage, compounding the systemic effects. The emerging consensus is that redox imbalance and cytokine profiles may serve as non-hormonal, non-invasive biomarkers for PCOD diagnosis and stratification, though clinical standardization is still lacking.

Therapeutic Interventions and Future Potential

Several studies in the reviewed timeframe explore interventions targeting oxidative stress and inflammation. Key findings include:

- Vitamin E and C supplementation lowers MDA levels, improves menstrual regularity, and enhances oocyte quality.
- N-acetylcysteine (NAC) improves insulin sensitivity and decreases androgen levels, possibly by replenishing glutathione and attenuating oxidative burden.
- Omega-3 fatty acids modulate IL-6 and TNF-α levels, improving metabolic and reproductive parameters.
- Curcumin, resveratrol, and Coenzyme Q10 show promising antioxidant and anti-inflammatory activity in pilot clinical trials.

While these agents offer encouraging results, most studies are short-term, underpowered, and often limited to surrogate endpoints like hormonal ratios or oxidative markers rather than long-term fertility or cardiometabolic outcomes. There is a pressing need for randomized controlled trials (RCTs) with robust design, standardized biomarker assessment, and meaningful clinical endpoints.

Furthermore, lifestyle modification—particularly structured exercise and Mediterranean or anti-inflammatory diets—demonstrates strong potential to attenuate both oxidative and inflammatory loads. Regular aerobic exercise improves antioxidant enzyme expression and insulin sensitivity, while reducing systemic CRP and IL-6 levels even in the absence of significant weight loss.

Contradictions and Research Gaps

Despite the overall consistency, some contradictions exist:

- A few studies failed to show significant differences in antioxidant levels between PCOD and controls, possibly due to variations in sampling time, assay technique, or diagnostic criteria.

- The heterogeneity in study populations—ethnic, phenotypic (obese vs. lean), and age-related—complicates universal conclusions.
- The majority of included studies focus on serum biomarkers, neglecting local tissue-level dynamics (e.g., in ovarian follicular fluid or adipose microenvironments).

Another underexplored area is the epigenetic regulation of oxidative and inflammatory pathways in PCOD. ROS and cytokines are known to influence DNA methylation and histone modification, which could perpetuate disease phenotypes across generations. Integrating this layer of understanding could open new therapeutic doors.

Broader Clinical Relevance

Recognizing oxidative stress and inflammation as core components of PCOD has significant implications:

- It underscores the metabolic and cardiovascular risks associated with PCOD, even in non-obese women, and justifies early screening and intervention.
- It paves the way for non-hormonal treatment strategies—particularly relevant for adolescents, those seeking fertility, or women contraindicated for oral contraceptives or metformin.
- It may inform precision medicine approaches where biomarker profiles guide individualized therapy, from antioxidant cocktails to immunomodulatory strategies.

Challenges and Gaps:

- Lack of uniformity in biomarker measurement protocols
- Limited long-term interventional studies
- Underrepresentation of adolescent and perimenopausal PCOD cohorts
- Most studies are observational; causality is often assumed rather than proven

CONCLUSION

Polycystic ovarian disease (PCOD) is a complex and multifactorial endocrine disorder that demands a paradigm shift in both understanding and management. This review establishes that oxidative stress and chronic low-grade inflammation are not secondary manifestations, but rather primary and tightly interlinked drivers of PCOD pathophysiology. The convergence of redox imbalance and cytokine dysregulation disrupts ovarian function, impairs insulin signaling, and fosters a metabolic environment that promotes disease persistence and progression. A compelling body of evidence from 2019 to 2025 confirms that PCOD patients exhibit significantly elevated levels of oxidative biomarkers—such as malondialdehyde (MDA), 8-OHdG—and inflammatory mediators like TNF-α, IL-6, MCP-1, and high-sensitivity CRP, even in the absence of overt obesity. Simultaneously, a marked depletion in both enzymatic and non-enzymatic antioxidants (SOD, catalase, glutathione, vitamins C and E) underscores a compromised cellular defense system, further amplifying oxidative damage. These biochemical perturbations impact not only reproductive outcomes (ovulation, folliculogenesis, oocyte quality) but also systemic health, increasing long-term risk for type 2 diabetes, dyslipidemia, and cardiovascular disease. Importantly, these biomarkers are increasingly recognized as diagnostic adjuncts, prognostic indicators, and therapeutic targets. Their measurement could refine PCOD phenotyping and guide personalized treatment approaches, especially for patients who may not benefit from standard hormonal therapies. Antioxidants such as N-acetylcysteine, vitamin E, omega-3 fatty acids, and polyphenols have shown promising results in small clinical trials, both in terms of biomarker modulation and symptom relief. Likewise, lifestyle interventions—particularly anti-inflammatory diets and structured exercise—offer a non-pharmacological, cost-effective strategy to mitigate oxidative and inflammatory loads. However, while the evidence base is growing, there are clear gaps. Most studies remain observational, lack longitudinal data, and exhibit methodological variability in biomarker assessment. Large-scale, multicentric, randomized controlled trials are urgently needed to determine whether targeting these pathways translates into long-term clinical benefit, particularly in fertility restoration and metabolic risk reduction. Going forward, a more integrated approach to PCOD management is warranted—one that combines endocrinological, metabolic, and immunological perspectives. Recognizing oxidative stress and inflammation as core pillars of the disorder allows for a more nuanced, mechanism-based intervention model. This shift could open new therapeutic frontiers and ultimately improve quality of life, fertility potential,

and metabolic health for millions of women worldwide.

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