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Systemic Low-Grade Chronic Inflammation and Cardiometabolic Risk Factors in Polycystic Ovary Syndrome

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Abstrak: Polycystic ovary syndrome is one of the most common endocrine and metabolic disorders affecting women of reproductive age, with reported prevalence estimates ranging from five to twenty percent depending on the diagnostic criteria applied. Although the condition has historically been classified as a reproductive disorder defined by irregular ovulation, excess androgen production, and polycystic ovarian morphology, a growing body of evidence now positions polycystic ovary syndrome as a multisystem metabolic disease. This review examines the role of systemic low-grade chronic inflammation in the development of polycystic ovary syndrome and its close relationship with cardiometabolic risk factors such as insulin resistance, visceral obesity, abnormal lipid profiles, and early atherosclerotic changes. The review draws on systematic reviews, meta-analyses, and original research published between 2011 and 2026 and discusses molecular mechanisms, including immune cell infiltration of adipose tissue, dysregulated adipokine secretion, activation of the NLRP3 inflammasome, alterations of the intestinal microbial community, and micronutrient deficiencies. The evidence indicates that excess insulin secretion, excess androgen production, and chronic low-grade inflammation form a mutually reinforcing cycle that drives both the reproductive and metabolic features of the syndrome, ultimately increasing long-term cardiovascular disease risk. Clinical implications for screening and long-term management are discussed alongside limitations of the current evidence base.

Keywords: polycystic ovary syndrome; systemic low-grade inflammation; insulin resistance; NLRP3 inflammasome; cardiometabolic risk; adipokines; intestinal microbiota

Introduction

In Polycystic ovary syndrome affects between six and twenty percent of women of childbearing age worldwide, making it the most frequently diagnosed hormonal disorder in this population.[1] Other epidemiological studies report a somewhat narrower prevalence range of five to fifteen percent, reflecting differences in diagnostic criteria and the populations examined.[2] Clinically, the condition is defined according to the Rotterdam consensus criteria established in 2003, which require the presence of at least two of the following three features, after other causes of irregular ovulation or excess androgen production have been excluded: chronic absence or irregularity of ovulation; clinical or biochemical evidence of excess androgen production; and polycystic morphology of the ovaries as seen on ultrasound examination.[3] For many years, polycystic ovary syndrome was viewed primarily through a gynecological lens. However, over the past two decades, an expanding body of research has repositioned the condition as a systemic metabolic disorder with consequences that extend well beyond fertility and menstrual regularity. Women with this condition show a substantially higher prevalence of resistance to the normal action of insulin, accumulation of fat around internal organs, abnormal blood lipid profiles, impaired tolerance to glucose, and the cluster of abnormalities known as metabolic syndrome, compared with women of similar age who do not have the condition. Importantly, these abnormalities frequently appear at a younger age than they do in the general female population.[4]

A concept that has gained particular prominence in explaining this convergence of reproductive and metabolic abnormality is systemic low-grade chronic inflammation. According to this model, the long-term metabolic consequences observed in affected women are linked to a persistent, low-intensity

inflammatory state, in which excess insulin secretion, excess androgen production, and chronic inflammation interact within a self-reinforcing cycle; some researchers additionally propose that dysfunction of the sympathetic branch of the autonomic nervous system contributes a fourth interacting component to this cycle.[5] The purpose of the present review is to examine, in a structured manner, the mechanisms through which systemic low-grade chronic inflammation contributes to the development of polycystic ovary syndrome, and to characterize its relationship with the cardiometabolic abnormalities that define the long-term health consequences of the condition.[6]

METHODS

This narrative review is based on a structured search of peer-reviewed biomedical literature indexed in PubMed, PubMed Central, Frontiers, and MDPI journal platforms, covering publications from 2011 through 2026. Search terms included combinations of the following concepts: polycystic ovary syndrome, chronic low-grade inflammation, cardiometabolic risk, the NLRP3 inflammasome, adipokines, and resistance to insulin action. Priority was given to systematic reviews, meta-analyses, and recent original research articles that reported measurements of inflammatory markers, examined adipose tissue physiology, or evaluated cardiovascular outcomes in populations of women with the condition.[7]

Given the heterogeneity of study designs, patient populations, geographic settings, and outcome measures identified across the literature, findings were synthesized narratively rather than pooled through formal statistical meta-analysis. Ten primary sources were selected for detailed discussion based on their relevance, recency, and methodological rigor, including two systematic reviews with meta-analysis, one guideline-informing systematic review, and several original laboratory investigations.[8]

RESULTS

A substantially higher infiltration of immune cells, including macrophages and lymphocytes, together with elevated concentrations of the pro-inflammatory mediators interleukin-6 and tumor necrosis factor alpha, has been documented across multiple organ systems in women with polycystic ovary syndrome — not only within reproductive tissue but also within the cardiovascular system, the intestine, the liver, the thyroid gland, and the brain.[9] This finding indicates that the inflammatory process associated with the condition is not confined to the ovary itself but represents a genuinely body-wide phenomenon. A systematic review and meta-analysis conducted by Bansal and colleagues, which screened studies published between 2014 and 2024 across four major databases and ultimately included forty-four studies identifying ninety-four distinct biomarkers, confirmed that circulating interleukin-6 concentrations are significantly elevated in affected women compared with unaffected controls, with this effect remaining statistically robust after correction for potential publication bias.[10] Table 1. Beyond interleukin-6, additional markers commonly implicated in the inflammatory profile of the condition include high-sensitivity C-reactive protein, tumor necrosis factor alpha, standard C-reactive protein, adiponectin, interleukin-18, vascular endothelial growth factor, interleukin-8, interleukin-1 beta, sex hormone-binding globulin, leptin, and vascular cell adhesion molecule 1.[11]

Table 1. Principal Inflammatory and Vascular Biomarkers Reported to Be Altered in Women with Polycystic Ovary Syndrome

Biomarker	Biological Category	Reported Direction of Change	Source
High-sensitivity C-reactive protein	Acute-phase protein	Increased	Dutta and Maddukuri, 2024
Interleukin-6	Pro-inflammatory cytokine	Increased	Bansal et al., 2025

Tumor necrosis factor alpha	Pro-inflammatory cytokine	Increased	Deng et al., 2024
Interleukin-1 beta and interleukin-18	Inflammasome-derived cytokines	Increased	Alenezi et al., 2023
Plasminogen activator inhibitor type 1	Coagulation-related factor	Increased	Rudnicka et al., 2021; Dutta and Maddukuri, 2024
Homocysteine	Metabolic amino-acid derivative	Increased	Deng et al., 2024
Adiponectin	Adipose-derived hormone	Decreased	Bansal et al., 2025
Leptin	Adipose-derived hormone	Increased	Bansal et al., 2025
Vascular endothelial growth factor and vascular cell adhesion molecule 1	Endothelial markers	Increased	Bansal et al., 2025; Rudnicka et al., 2021
Fibrinogen and endothelin-1	Vascular and coagulation markers	Increased	Dutta and Maddukuri, 2024
Trimethylamine-N-oxide	Gut-microbial metabolite	Increased	Dutta and Maddukuri, 2024

Excess accumulation of adipose tissue, particularly fat deposited around abdominal organs, is associated with the release of hormone-like signaling molecules called adipokines, which regulate insulin sensitivity and overall energy balance, together with increased infiltration of immune cells that produce additional pro-inflammatory cytokines and C-reactive protein. Adipose tissue inflammation of this kind is now understood to be mechanistically driven, at least in part, by activation of a multiprotein cytosolic complex known as the NLRP3 inflammasome, which, once triggered, causes the maturation and release of the cytokines interleukin-1 beta and interleukin-18.[12] A consequence of this activation process is systemic low-grade chronic inflammation, considered a defining feature of both obesity and resistance to insulin action.[13] The systematic review and meta-analysis conducted by Alenezi and colleagues, examining the NLRP3 inflammasome and its associated components caspase-1, the adaptor protein ASC, and interleukin-1 beta across studies of obesity and polycystic ovary syndrome, found consistent evidence that inflammasome components are positively correlated with adipose tissue mass and with markers of insulin resistance. Building on this work, a more recent original investigation by Alenezi, Alshammari, Khan, and Amer directly compared gene and protein expression of NLRP3, interleukin-1 beta, caspase-1, and the adaptor protein PYCARD in subcutaneous and visceral adipose tissue samples obtained from women with and without the condition. Somewhat unexpectedly, this study found that caspase-1 gene expression and NLRP3 protein levels were significantly higher in the non-affected comparison group rather than in the affected group, a finding the authors attributed to possible compensatory regulatory mechanisms and to the potential presence of subclinical inflammatory conditions, such as undiagnosed pelvic inflammatory disease or endometriosis, among some control participants.[14] This result illustrates the genuine complexity of interpreting inflammatory marker data in cross-sectional study designs and cautions against overly simplistic linear models of inflammasome involvement in this condition.

Intestinal Microbial Community and Pharmacological Modulation of Inflammation

An additional and increasingly recognized dimension of the inflammatory profile associated with polycystic ovary syndrome involves the community of microorganisms residing in the intestine. Alterations in the composition of this microbial community have been linked to increased production of the metabolite trimethylamine-N-oxide, which, owing to its pro-atherogenic biological activity, is associated with elevated cardiovascular risk in affected populations.[14] Notably, part of the therapeutic benefit of metformin, a widely used insulin-sensitizing medication in the management of this condition, appears to be mediated through anti-inflammatory and microbiome-modulating mechanisms rather than through glucose-lowering action alone. Metformin treatment has been shown to alleviate features of the condition by modulating the composition of the gut microbial community, reducing circulating levels of bacterial lipopolysaccharide, and decreasing both plasma and ovarian tissue concentrations of tumor necrosis factor alpha, interleukin-6, and interleukin-17A.[15] This observation supports the broader conclusion that inflammation functions as an active and potentially modifiable component of disease pathophysiology, rather than merely as a passive marker of disease severity. Table 2. Cardiovascular risk factors associated with polycystic ovary syndrome are well documented and include resistance to insulin action, elevated blood pressure, hypertensive disorders occurring during pregnancy, abnormal blood lipid profiles, gestational and early-onset type 2 diabetes, and the cluster of abnormalities known as metabolic syndrome — all of which tend to appear at a younger age than in women without the condition, a pattern compounded by the elevated prevalence of excess body weight in this population

Table 2. Cardiometabolic Risk Factors Associated with Polycystic Ovary Syndrome and Their Relationship to Chronic Inflammation

Cardiometabolic Factor	Relationship to Chronic Inflammation
Accumulation of fat around abdominal organs	Alters secretion of adipokines and promotes immune cell infiltration of adipose tissue
Resistance to insulin action	Functions as both a driver and a consequence of chronic low-grade inflammation; excess weight and insulin resistance together provoke chronic inflammation, which further amplifies circulating inflammatory marker concentrations
Abnormal blood lipid profile	Elevated triglyceride and total cholesterol concentrations accompanied by reduced concentrations of protective high-density lipoprotein cholesterol, contributing to adverse cardiovascular outcomes
Elevated blood pressure	Associated with impaired function of the blood vessel lining, which is promoted by chronic inflammatory mediators
Metabolic syndrome	Well documented among affected women, manifesting at a younger age than in the general female population
Early, subclinical narrowing and hardening of the arteries	Promoted by trimethylamine-N-oxide and other pro-atherogenic metabolites derived from intestinal bacteria
Overall long-term cardiovascular disease risk	International guideline bodies recommend proactive, ongoing cardiovascular risk assessment given the elevated risk profile, notwithstanding the comparatively low absolute risk observed before menopause

DISCUSSION

The findings synthesized in this review support a pathophysiological model in which polycystic ovary syndrome arises from, and is subsequently perpetuated by, a self-reinforcing interaction among excess insulin secretion, excess androgen production, and chronic low-grade inflammation, with dysfunction of the sympathetic nervous system proposed by some researchers as a fourth contributing element. Within this model, resistance to the normal action of insulin promotes inflammation within adipose tissue; this inflammation, in turn, impairs the normal cellular response to insulin and worsens excess androgen production, which further exacerbates both metabolic and reproductive dysfunction. The overall result is a cycle in which reproductive and metabolic pathology cannot meaningfully be separated from one another. The NLRP3 inflammasome occupies a particularly central position within this proposed model, functioning as a molecular sensor that converts signals of metabolic stress — such as excess accumulation of lipids and elevated blood glucose concentrations — into an active inflammatory response through the release of interleukin-1 beta and interleukin-18. The documented, though evidently complex, pattern of dysregulation in adipose tissue associated with polycystic ovary syndrome provides a plausible mechanistic bridge between the hormonal abnormality of excess androgen production and the metabolic abnormality of insulin resistance and positions this inflammasome as a candidate target for future therapeutic intervention. At the same time, the unexpected finding of elevated inflammasome components in comparison subjects in the most recent adipose tissue study demonstrates that this relationship is unlikely to be simple or unidirectional, and that individual variation, disease duration, and unmeasured confounding inflammatory conditions may substantially influence observed results. The role of intestinal microbial community disruption and its downstream metabolite trimethylamine-N-oxide represents a comparatively newer but increasingly important line of evidence linking polycystic ovary syndrome to accelerated blood vessel damage. The observation that metformin's clinical benefit is partly attributable to modulation of the gut microbial community and reduction of circulating bacterial lipopolysaccharide and inflammatory cytokines lends further support to the conclusion that the relationship between the gut, systemic inflammation, and metabolism is not merely correlative but plausibly causal and potentially modifiable through both pharmacological treatment and lifestyle-based intervention. From a clinical standpoint, these mechanistic insights reinforce the recommendation from international guideline-writing bodies that women with polycystic ovary syndrome undergo proactive and ongoing cardiovascular risk assessment, even though absolute rates of cardiovascular events remain comparatively low during the reproductive years before menopause. Given that cardiovascular disease represents a major and largely preventable cause of death among women, and that polycystic ovary syndrome is a highly prevalent condition, the elevated cardiometabolic risk associated with this syndrome constitutes a meaningful public health concern extending well beyond the management of fertility during reproductive age.

Limitations of the Current Evidence Base

Several limitations of the existing literature deserve acknowledgment. The great majority of studies examining inflammatory biomarkers in this condition employ a cross-sectional design, which restricts the ability to draw firm conclusions regarding the direction of causality between inflammation and metabolic dysfunction. Substantial heterogeneity exists across studies with respect to how the condition itself is defined, the distribution of body weight within study populations, and the laboratory methods used to measure cytokine concentrations, all of which complicate direct comparison of findings across the literature. Furthermore, as illustrated by the unexpected inflammasome findings among the comparison subjects noted above, subclinical confounding inflammatory conditions are not always adequately excluded during participant recruitment, potentially attenuating or even reversing observed differences between affected and unaffected groups.

CONCLUSION

The evidence reviewed here supports the conceptualization of polycystic ovary syndrome as a multisystem disorder in which systemic low-grade chronic inflammation functions as a central pathophysiological mechanism linking reproductive dysfunction to cardiometabolic disease. Elevated concentrations of pro-inflammatory cytokines, dysregulated secretion of adipose-derived hormones,

activation of the NLRP3 inflammasome, and disruption of the intestinal microbial community converge to sustain a self-perpetuating cycle involving excess insulin secretion, excess androgen production, and chronic inflammation. This cycle appears to underlie the accelerated development of insulin resistance, abnormal lipid profiles, elevated blood pressure, and early blood vessel damage observed in affected women, frequently at a younger age than in the general population. Clinical management of this condition should therefore extend beyond reproductive outcomes to include systematic cardiometabolic risk assessment, lifestyle-based interventions to reduce inflammation, and consideration of pharmacological agents such as metformin, whose clinical benefits appear to be mediated in part by modulation of the inflammatory axis. Future research employing longitudinal study designs and standardized panels of inflammatory biomarkers is needed to clarify the direction of causal pathways and to identify novel therapeutic targets within this interconnected network linking inflammation, metabolism, and reproductive function.

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