

INFLAMMATION IN POLYCYSTIC OVARIAN SYNDROME: ROLE IN ETIOPATHOGENESIS AND ITS CLINICAL IMPLICATIONS

INFLAMACIÓN EN EL SÍNDROME DE OVARIO POLIQUÍSTICO: ROL EN LA ETIOPATOGENIA Y SUS IMPLICANCIAS CLÍNICAS

Edelbert Anthonio Almeida ¹, Prasanna Bharathi ², Nikhil Pal ², Sana Ahmed ³

Filiation:

¹ Father Muller Medical College Hospital, Department of Biochemistry, Research area, Karnataka, India

² University of Delhi, Medicine school, Department of Biochemistry, Delhi, India

³ Haseena Begum Multispecialty Hospital, Medicine area, Department of Obstetrics and Gynecology, Uttar Pradesh, India

How to cite the article: Almeida EA, Bharathi P, Pal N, Ahmed S. Inflammation in polycystic ovarian syndrome: Role in etiopathogenesis and its clinical implications. International Journal of Maternal and Fetal Health. 2026; 11 (1): r19-r26. DOI: 10.47784/rismf.2026.11.1.448

Funding: No external funding was received

Conflicts of interest: No conflicts of interest related to this manuscript

Correspondence:

Edelbert Anthonio Almeida
email: dreducms@gmail.com

Received: 22-08-2025

Review: 19-10-2025

Approved: 10-02-2026

Early access: 11-03-2026

Published: 11-03-2026

ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive-aged women, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Beyond reproductive features, PCOS is strongly associated with metabolic disturbances like insulin resistance, dyslipidemia, obesity, and increased cardiovascular risk. Recent evidence implicates chronic low-grade inflammation as a central mechanism linking metabolic and reproductive abnormalities in PCOS. Women with PCOS consistently demonstrate elevated inflammatory mediators that are believed to impair insulin signaling, exacerbate hyperandrogenism, and disrupt ovarian function, contributing to anovulation and poor oocyte quality. Clinically, inflammatory biomarkers correlate with obesity, insulin resistance, and androgen levels, suggesting prognostic value for cardiometabolic risk stratification. Anti-inflammatory interventions, including lifestyle modification, insulin sensitizers, statins, nutraceuticals, and emerging cytokine inhibitors such as anakinra, demonstrate potential in improving both reproductive and metabolic outcomes. Understanding the inflammatory underpinnings of PCOS not only advances our etiopathogenic insight but also opens avenues for targeted diagnostic and therapeutic strategies aimed at mitigating long-term complications.

Key words: Polycystic ovary syndrome, Inflammation, Disease management (Source: MeSH, NLM)



INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder, affecting 5–20% of women in reproductive age group (1). It is characterized by a triad of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Beyond reproductive dysfunction, PCOS is associated with significant metabolic complications, including insulin resistance, dyslipidemia, obesity, and an elevated risk of type 2 diabetes and cardiovascular disease (2).

The pathogenesis of PCOS is multifactorial, involving a complex interplay of genetic, hormonal, metabolic, and environmental factors. Dysregulation of the hypothalamic–pituitary–ovarian (HPO) axis, increased luteinizing hormone secretion, and ovarian theca cell hyperactivity drive androgen excess, while insulin resistance and compensatory hyperinsulinemia exacerbate both metabolic and reproductive abnormalities (3).

Recent evidence highlights the role of chronic low-grade inflammation as a key contributor to PCOS pathophysiology. Women with PCOS often exhibit elevated levels of pro-inflammatory markers (e.g. high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), IL-18, monocyte chemoattractant protein-1 (MCP-1)) and altered immune cell profiles (increased leukocytes, Th1/Th17 bias, reduced Tregs), independent of obesity (4,5,6). These inflammatory mediators impair insulin signaling, promote oxidative stress, and contribute to endothelial dysfunction, thereby linking PCOS to long-term cardiometabolic risks (7). Moreover, inflammation has been implicated in ovarian dysfunction, with cytokines disrupting folliculogenesis and oocyte maturation (8). The interaction between hyperandrogenism, insulin resistance, and inflammatory pathways creates a vicious cycle that perpetuates disease progression.

Given its heterogeneous presentation and multifaceted pathophysiology, PCOS requires individualized diagnostic and therapeutic strategies. Understanding the contribution of inflammation not only provides insights into disease mechanisms but also opens new avenues for targeted interventions aimed at improving reproductive, metabolic, and cardiovascular outcomes.

INFLAMMATORY PATHWAYS IN PCOS

PCOS involves activation of innate immune pathways. Adipose tissue in PCOS becomes infiltrated by pro-inflammatory macrophages (shift from M2 to M1) that secrete cytokines like IL-6, TNF- α , IL-1 β and MCP-1.(4) These adipokines and free fatty acids chronically stimulate intracellular pathways (e.g. NF- κ B) in metabolic and ovarian cells, amplifying inflammation (4,9). Notably, ovarian granulosa cells in PCOS show activation of NF- κ B and assembly of the NLRP3 inflammasome, triggered by elevated IL-1 β and IL-18 in the follicular fluid (4,5,9). This inflammasome activation causes oxidative stress and disrupts granulosa cell function (10). Other innate mediators (e.g. Toll-like receptors, advanced glycation end-products) may also be engaged by excess glucose/lipids, feeding the cycle of “metaflammation.” In PCOS, even local immune cells contribute chemokines like MCP-1 and macrophage migration inhibitory factor (MIF) are elevated, altering monocyte/macrophage trafficking in the ovary (10).

KEY INFLAMMATORY BIOMARKERS

PCOS is associated with elevated levels of multiple inflammatory and adipokine biomarkers. Important examples include:

- **C-Reactive Protein (CRP):** A liver-derived acute-phase protein, CRP levels have been documented to be higher in PCOS than in healthy controls (11). This elevated hs-CRP reflects chronic inflammation and correlates with insulin resistance, obesity and dyslipidemia in PCOS (12). CRP is a downstream marker induced by IL-6/TNF- α and is associated with increased cardiovascular risk in PCOS.
- **Interleukin-6 (IL-6):** A pleiotropic cytokine from macrophages, adipocytes and ovarian cells, IL-6 levels have also been shown to be higher in PCOS (13). IL-6 directly promotes insulin resistance and hyperinsulinemia, and it is linked to obesity and metabolic syndrome in PCOS (12,14). IL-6 has been proposed as a marker bridging metabolic and reproductive dysfunction; higher IL-6 also correlates with greater cardiovascular risk (15).
- **Tumor Necrosis Factor- α (TNF- α):** This pro-inflammatory cytokine from adipose macrophages is upregulated in most PCOS

studies (16). TNF- α interferes with insulin signaling (impairing the insulin receptor) and disrupts ovarian steroidogenesis (17).

- Interleukin-1 β (IL-1 β): A key inflammasome cytokine, IL-1 β levels are significantly elevated in PCOS. IL-1 β strongly amplifies inflammation, promotes ovarian androgen production and interferes with insulin signaling (18). In PCOS, IL-1 β dysregulates follicle maturation and oocyte quality (19).
- Interleukin-18 (IL-18): Related to IL-1, IL-18 is secreted by macrophages and is elevated in PCOS (17). IL-18 promotes insulin resistance, oxidative stress and endothelial dysfunction. It is implicated in metabolic (hyperinsulinemia, obesity) and ovarian (anovulation, hyperandrogenism) abnormalities correlating well with BMI, IR and androgen levels in PCOS patients (20,21).
- Interleukin-8 (IL-8/CXCL8): A chemokine secreted by monocytes, endothelial and granulosa cells, IL-8 is also documented to be elevated in PCOS, especially in obese/insulin-resistant cases. IL-8 recruits neutrophils and drives angiogenesis and oxidative stress. High IL-8 in follicular fluid correlates with poor oocyte quality, anovulation and hyperandrogenism (22,23).
- Monocyte Chemoattractant Protein-1 (MCP-1) and MIF: MCP-1 and MIF are chemokines that regulate monocyte trafficking. In PCOS, serum and follicular MCP-1 are increased, promoting macrophage infiltration of the ovary. MIF, a macrophage-derived factor, is also elevated in PCOS (and in insulin resistance/obesity) (24). These chemokines may alter the ovarian immune environment and disturb normal ovulation (22,25)
- Adipokines (Leptin, Adiponectin): Dysregulated adipokines contribute to PCOS inflammation. Leptin (pro-inflammatory) is high in PCOS, especially with obesity. Leptin correlates inversely with sex hormone binding globulin and directly with CRP/TNF, linking adiposity to hyperinsulinemia and androgen excess. In contrast, adiponectin (anti-inflammatory, insulin-sensitizing) is markedly reduced in PCOS. Low adiponectin correlates with higher BMI, IR and androgens, further aggravating inflammation (26,27,28).

- Sex Hormone-Binding Globulin (SHBG): SHBG serve as carrier molecules of sex hormones in plasma. Studies have documented decreased levels of SHBG levels in PCOS, reflecting inflammation and insulin resistance. Low levels of SHBG increase free androgens, exacerbating hyperandrogenic and metabolic symptoms (29,30).

INFLAMMATION IN PCOS PATHOPHYSIOLOGY

Insulin Resistance

Chronic inflammation is intimately linked to the insulin resistance (IR) seen in PCOS. Pro-inflammatory cytokines interfere with insulin signaling for instance, TNF- α induces serine phosphorylation of the insulin receptor substrate, blunting downstream signaling (31) and resulting in compensatory hyperinsulinemia. This hyperinsulinemia feeds back to worsen PCOS: insulin acts like a trophic factor on ovarian theca cells to boost androgen production. Adipose inflammation further fuels this cycle: visceral fat macrophages in PCOS secrete IL-6 and TNF- α , promoting IR. Thus, inflammation and IR amplify each other in PCOS (32).

Hyperandrogenism

Inflammation also contributes to androgen excess. Insulin resistance and its compensatory hyperinsulinemia—stimulates ovarian theca cells to make more androgens (insulin mimics LH) (32). In addition, inflammatory cytokines have direct steroidogenic effects: IL-1 β and IL-18 in the follicle disrupt normal steroidogenesis and drive androgen synthesis. Elevated IL-1 β correlates with higher serum testosterone and androstenedione in PCOS (33,34,35). Inflammatory cytokines also reduce SHBG production in the liver, increasing free testosterone (29). Overall, inflammation and hyperinsulinemia synergize to produce and maintain the hyperandrogenic state of PCOS. Conversely, inflammatory inhibition (e.g. blocking IL-1 signaling) can blunt ovarian androgen output (36).

Ovulatory Dysfunction

Inflammation perturbs the normal immune-regulated process of ovulation. In healthy ovaries, a transient local inflammatory surge (cytokines,

prostaglandins, macrophage activity) triggers follicular rupture. In PCOS, however, a chronic inflammatory milieu disrupts this balance. Elevated IL-1 β , IL-18 and IL-8 have been found in PCOS follicular fluid, correlating with granulosa cell stress and follicle arrest (37,38). For example, NF- κ B and NLRP3 activation in granulosa cells leads to mitochondrial damage, oxidative stress and apoptosis, impairing oocyte maturation (39). IL-8 overproduction promotes aberrant angiogenesis and follicular atresia. Immune cell dysregulation also plays a role: PCOS ovaries often show excess pro-inflammatory T-helper cells (Th1/Th17) and macrophages with a destructive phenotype, while regulatory T-cells (Tregs) are reduced (40). These changes likely hinder normal follicle development, leading to anovulation and poor oocyte quality in PCOS.

Recent studies highlighting the role of inflammation in PCOS:

- **IL-1 Pathway Blockade:** A 2024 proof-of-concept trial (the “Fertil” study) treated PCOS women with the IL-1 receptor antagonist anakinra (100 mg/day for 4 weeks). Anakinra significantly reduced CRP and blunted the rise in androgens, suggesting that blocking IL-1-driven inflammation can attenuate hyperandrogenemia (36). This is among the first interventional trials directly linking cytokine blockade to hormonal improvements in PCOS.
- **Granulosa Cell Mechanisms:** Mechanistic work has identified new molecular triggers of ovarian inflammation. For example, thioredoxin-interacting protein which is upregulated by testosterone was shown to bind NLRP3 and drive inflammasome activation in granulosa cells. In PCOS models, knocking down TXNIP reduced oxidative stress, inflammation and follicular damage (37,38). This uncovers a specific link between androgens, oxidative stress and NLRP3-mediated inflammation in PCOS.
- **Novel Cytokines:** Unexpectedly, levels of recently discovered anti-inflammatory cytokines (IL-27 and IL-38) were found to be elevated in PCOS patients in a 2024 study (41). Along with rises in TNF- α and IL-6, the increase in IL-27/IL-38 suggests complex immune-endocrine dysregulation. These findings imply that

compensatory anti-inflammatory signals are upregulated in PCOS, possibly as feedback to chronic inflammation. The precise roles of IL-27 and IL-38 in PCOS remain to be defined.

- **Other Insights:** Emerging data continue to link gut dysbiosis, adipokine signaling and inflammasome activation in PCOS. For instance, chronic endotoxemia from altered gut flora may engage TLR4/NF- κ B pathways in PCOS (42). Reports also describe imbalances in Th17-related cytokines (e.g. IL-17) in PCOS.

CLINICAL RELEVANCE OF INFLAMMATION IN PCOS

Although PCOS is defined by reproductive criteria, its inflammatory component has important clinical implications.

Diagnostic and Prognostic Implications

Inflammation markers are not part of formal PCOS diagnostic criteria, but elevated hs-CRP, and inflammatory cytokines are a common finding, often correlating with metabolic parameters. Some experts have proposed using hs-CRP and even IL-6 to screen PCOS patients for cardiometabolic risk, since these markers predict insulin resistance and atherosclerosis, but it is still under debate. Similarly, persistently high inflammatory biomarkers identify PCOS patients at greater risk of metabolic syndrome, type 2 diabetes and cardiovascular disease. For instance, IL-6 levels correlate with markers of CVD risk (endothelial dysfunction, dyslipidemia) (43), and low adiponectin/high CRP portend worse metabolic outcomes. Thus, inflammation profiling (CRP, cytokines) may help stratify PCOS severity and guide prevention of long-term complications. However, there are no clear-cut guidelines of the same.

Therapeutic

Inflammation offers new treatment targets. Insulin-sensitizing drugs (metformin, thiazolidinediones) and weight loss are known to reduce CRP/IL-6 in PCOS (44). Statins also lower inflammation and androgen levels. More directly, targeting inflammatory pathways has shown promise: for example, anakinra therapy in PCOS improved hormonal and metabolic parameters. Even antioxidants or nutraceuticals (e.g. omega-3 fatty

acids, vitamin D, curcumin) are being investigated for their capacity to dampen PCOS inflammation.

ANTI-INFLAMMATORY TREATMENT STRATEGIES

Several anti-inflammatory interventions have been explored in PCOS:

- Cytokine Inhibitors: IL-1 blockade with anakinra (as noted) reduced CRP and showed trends toward lower androgens. Similarly, NF-κB inhibitors have been tested: in one small study, salsalate (an NF-κB pathway inhibitor) improved ovarian steroid metabolism and hinted at better ovulatory function (45).
- Metabolic Modulators: Traditional PCOS treatments also have anti-inflammatory effects. Metformin lowers CRP/IL-6 over time, partly by reducing visceral fat. Pioglitazone (a PPARγ agonist) has known anti-inflammatory properties and has been shown to decrease CRP and improve endothelial function in PCOS (though weight gain is a drawback) (46). Statins have been used off label in PCOS and can reduce CRP as well as testosterone. Recent reviews suggest statins “may be useful” to reduce PCOS inflammation and metabolic risk (albeit evidence is moderate) (47).
- Lifestyle and Supplements: Weight loss and exercise remain cornerstone interventions: even modest weight reduction markedly lowers CRP and inflammatory cytokines in PCOS. Several nutraceuticals with anti-inflammatory activity have shown benefit. For example, supplementation with curcumin (500 mg twice daily) improved insulin sensitivity in obese PCOS women and tended to lower hs-CRP levels in trials (48). Omega-3 fatty acids, vitamin D, N-acetylcysteine, and probiotics are also under study for their capacity to reduce PCOS inflammation and improve ovulation.

CONCLUSION

To conclude, PCOS represents a complex endocrine-metabolic disorder in which chronic low-grade inflammation plays a pivotal role in the etiopathogenesis and clinical progression. Inflammatory cytokines and chemokines drive insulin resistance, hyperandrogenism, and ovulatory dysfunction, thereby linking reproductive

manifestations with metabolic and cardiovascular risk. Conventional therapies such as metformin, thiazolidinediones, and lifestyle modification exert beneficial anti-inflammatory effects, while novel strategies targeting cytokine pathways show promise in improving endocrine and metabolic profiles. Targeting inflammation represents a critical step toward personalized management of PCOS, with the potential to improve reproductive outcomes, reduce metabolic risk, and enhance long-term health in this heterogeneous population.

BIBLIOGRAPHIC REFERENCES

1. Ganie MA, Vasudevan V, Wani IA, Baba MS, Arif T, Rashid A. Epidemiology, pathogenesis, genetics & management of polycystic ovary syndrome in India. *Indian J Med Res.* 2019;150(4):333-344. doi: 10.4103/ijmr.IJMR_1937_17
2. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. *Endocr Rev.* 2015;36(5):487-525. doi: 10.1210/er.2015-1018
3. Escobar-Morreale H. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol.* 2018;14:270-284. doi: <https://doi.org/10.1038/nrendo.2018.24>
4. Banerjee S, Cooney LG, Stanic AK. Immune Dysfunction in Polycystic Ovary Syndrome. *Immunohorizons.* 2023;7(5):323-332. doi: 10.4049/immunohorizons.2200033.
5. Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. *Frontiers in Endocrinology (Lausanne).* 2020;11:604. doi:10.3389/fendo.2020.00604
6. Patel S. Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy. *Clinical Endocrinology (Oxford).* 2018;89(5):545-552. doi:10.1111/cen.13802
7. González F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids.* 2012;77(4):300-305. doi:10.1016/j.steroids.2011.12.003
8. Liu R, Zhang C, Shi Y, Zhang F, Li L, Wang X, et al. The role of chronic inflammation in polycystic ovary syndrome: a systematic review and meta-analysis. *Journal of Ovarian Research.* 2021;14:38. doi:10.1186/s13048-021-00781-1
9. Liu Y, Liu H, Li Z, Fan H, Yan X, Liu X, et al. The Release of Peripheral Immune Inflammatory Cytokines Promote an Inflammatory Cascade in

- PCOS Patients via Altering the Follicular Microenvironment. *Front Immunol.* 2021;12:685724. doi: 10.3389/fimmu.2021.685724
10. Li Q, Zhou JM, Yang J, Zhang H, Wang H, Guo X, et al. Increased granulosa cell oxidative stress and NLRP3 inflammasome activation in women with PCOS. *J Clin Endocrinol Metab.* 2020;105(10):dgz315
 11. Bansal B, Thazhuthadath Kishore A, Kathiresan S, Farook Ghachi A, Pradhan S, Paul S, et al. A Systematic Review of Inflammatory Markers in Polycystic Ovary Syndrome (PCOS) and Meta-Analysis of Interleukin-6 (IL-6) in Case-Control Studies. *Cureus.* 2025;17(4):e82350. doi: 10.7759/cureus.82350
 12. Chen Y, Wu Y, Xu Y, Zhong J, Chen J, Zhao Y. Elevated serum IL-18 levels in polycystic ovary syndrome: correlation with insulin resistance and hyperandrogenism. *J Reprod Immunol.* 2019;132:29-35
 13. Bahri Khomami M, Joham AE, Boyle JA, Piltonen TT, Arora C, Silagy M, et al. Increased interleukin-6 levels in women with PCOS: a systematic review, meta-analysis and meta-regression. *Hum Reprod Update.* 2019;25(5):706-720.
 14. Zeb S, Gul R, Ashraf, Rumman. Comparative Analysis of Interleukin-6 Levels in Polycystic Ovary Syndrome (PCOS) Patients With and Without Insulin Resistance. *Cureus.* 2025;17(4):e81878. doi: 10.7759/cureus.81878.
 15. Geraci G, Riccio C, Oliva F, Gabrielli D, Colivicchi F, Grimaldi M, et al. Women with PCOS have a heightened risk of cardiometabolic and cardiovascular diseases: statement from the Experts Group on Inositol in Basic and Clinical Research and PCOS (EGOI-PCOS) and Italian Association of Hospital Cardiologists (ANMCO). *Front. Cardiovasc. Med.* 2025; 12:1520490. doi: 10.3389/fcvm.2025.1520490
 16. Deng H, Chen Y, Xing J, Zhang N, Xu L. Systematic low-grade chronic inflammation and intrinsic mechanisms in polycystic ovary syndrome. *Front Immunol.* 2024;15:1470283. doi: 10.3389/fimmu.2024.1470283.
 17. Ha LX, Li WX, Du YD, Yuan YY, Qu XX. Tumor Necrosis Factor Alpha Level in the Uterine Fluid of Patients with Polycystic Ovary Syndrome and Its Correlation with Clinical Parameters. *J Inflamm Res.* 2022;15:6015-6020. doi: 10.2147/JIR.S382808.
 18. Padder KA, Jahan N, Yousuf MA, Shah IA, Bhat GA, Khurshid R, et al. Deciphering the interplay between oxidative stress and inflammation in polycystic ovary syndrome: outcome of a case-control study. *J Ovarian Res.* 2025;18(1):196. doi: 10.1186/s13048-025-01734-y
 19. Shang J, Wang S, Wang A, Li F, Zhang J, Wang J, et al. Intra-ovarian inflammatory states and their associations with embryo quality in normal-BMI PCOS patients undergoing IVF treatment. *Reprod Biol Endocrinol.* 2024;22(1):11. doi: 10.1186/s12958-023-01183-6.
 20. Kabakchieva P, Gateva A, Velikova T, Georgiev T, Yamanishi K, Okamura H, et al. Elevated levels of interleukin-18 are associated with several indices of general and visceral adiposity and insulin resistance in women with polycystic ovary syndrome. *Arch Endocrinol Metab.* 2022;66(1):3-11. doi: 10.20945/2359-3997000000442.
 21. Yang Y, Qiao J, Li R, Li MZ. Is interleukin-18 associated with polycystic ovary syndrome? *Reprod Biol Endocrinol.* 2011;9:7. doi: 10.1186/1477-7827-9-7.
 22. Banerjee S, Jaimes FL, Mohamed MA, Zettel A, Graupe NG, Cooney LG, et al. High-dimensional immune profiling of follicular fluid and systemic circulation reveals distinct immune signatures in women with polycystic ovary syndrome. *Front Immunol.* 2025; 16:1628031. doi: 10.3389/fimmu.2025.1628031
 23. Wang C, Feng Y, Chen Y, Lin X, Li X. Proximity extension assay revealed novel inflammatory biomarkers for follicular development and ovarian function: a prospective controlled study combining serum and follicular fluid. *Front. Endocrinol.* 2025;16:1525392. doi: 10.3389/fendo.2025.1525392
 24. Mejia-Montilla J, Álvarez-Mon M, Reyna-Villasmil E, Torres-Cepeda D, Santos-Bolívar J, Reyna-Villasmil N, et al. Factor inhibitor de la migración de macrófagos en mujeres obesas y no obesas con síndrome de ovarios poliquísticos. *Endocrinol Nutr.* 2015;62:31-37
 25. Glinborg D, Andersen M, Richelsen B, Bruun JM. Plasma monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha are increased in patients with polycystic ovary syndrome (PCOS) and associated with adiposity, but unaffected by pioglitazone treatment. *Clin Endocrinol (Oxf).* 2009;71(5):652-8. doi: 10.1111/j.1365-2265.2009.03523.x
 26. Orszulak D, Niziński K, Matonóg A, Zięba-Domalik M, Stojko R, Drosdzol-Cop A. Adipokines as biochemical marker of polycystic ovary syndrome in adolescents - review. *Front Endocrinol (Lausanne).* 2025; 16:1475465. doi: 10.3389/fendo.2025.1475465
 27. Hamad SS, Ahmed SN. Determination of insulin resistance, adiponectin and leptin in overweight

- women with polycystic ovarian syndrome. *Middle East Fertil Soc J*.2025; 30:29. <https://doi.org/10.1186/s43043-025-00243-8>
28. Prasad GS, Saikia UK, Bhuyan AK, Baro A. A Study of Serum Adiponectin Levels in Patients with Polycystic Ovarian Syndrome and its Correlation with Various Cardiometabolic Risk Markers. *J Hum Reprod Sci*. 2023;16(4):299-306. doi: 10.4103/jhrs.jhrs_95_23.
 29. Guo X, Chen L, He J, Zhang X, Shui X. Genetically predicted high sex hormone binding globulin was associated with decreased risk of polycystic ovary syndrome. *BMC Women's Health*.2024; 24: 357. <https://doi.org/10.1186/s12905-024-03144-6>
 30. Ciura D, Owczarek AJ, Franik G, Kocelak P, Markuszewski L, Madej P, et al. A cross-sectional study of the association between circulating sex hormone-binding globulin levels and selected adipokines in women with polycystic ovary syndrome. *Front. Med*. 2023; 10:1183961. doi: 10.3389/fmed.2023.1183961
 31. Yousuf SD, Rashid F, Zargar MA, Mudassar S, Islam K, Nazir S et al. Genotypic and metabolic implications of tumor necrosis factor- α (TNF- α) –1031 (T/C) polymorphism in Kashmiri women with polycystic ovary syndrome (PCOS): a case–control study. *Egypt J Med Hum Genet*.2025;26(1):150. <https://doi.org/10.1186/s43042-025-00778-5>
 32. Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *J Clin Endocrinol Metab*. 1998;83(6):2001-5. doi: 10.1210/jcem.83.6.4886
 33. Xu T, Xiang Y, Huang Z, Zhu Q, Wu H, Cai J, et al. Hyperandrogenism-mediated YAP activation drives ovarian inflammation and pyroptosis in PCOS: implications for follicular dysfunction. *J Ovarian Res*. 2025;18(1):170. doi: 10.1186/s13048-025-01757-5
 34. Fox CW, Zhang L, Sohni A, Doblado M, Wilkinson MF, Chang RJ, et al. Inflammatory Stimuli Trigger Increased Androgen Production and Shifts in Gene Expression in Theca-Interstitial Cells. *Endocrinology*. 2019;160(12):2946-2958. doi: 10.1210/en.2019-00588
 35. Raja-Khan N, Urbanek M, Rodgers RJ, Legro RS. The role of TGF- β in polycystic ovary syndrome. *Reprod Sci*. 2014;21(1):20-31. doi: 10.1177/1933719113485294
 36. Wälchli-Popovic M, Monnerat S, Taylor AE, Gilligan LC, Schiffer L, Arlt W, et al. Effects of interleukin-1 receptor antagonism in women with polycystic ovary syndrome—the FertIL trial. *Front. Endocrinol*.2024;15:1435698. doi: 10.3389/fendo.2024.1435698
 37. Wang Y, Yang J, Wang Y, Chen Y, Wang Y, Kuang H, et al. Upregulation of TXNIP contributes to granulosa cell dysfunction in polycystic ovary syndrome via activation of the NLRP3 inflammasome. *Mol Cell Endocrinol*. 2023;561:111824. doi: 10.1016/j.mce.2022.111824.
 38. Yang W, Ma Y, Wu Y, Lei X, Zhang J, Li M. Study on the effects of Mogroside V in inhibiting NLRP3-mediated granulosa cell pyroptosis and insulin resistance to improve PCOS. *J Ovarian Res*. 2025;18(1):10. doi: 10.1186/s13048-024-01563-5.
 39. İlhan G, Bacanakgil BH, Vuruşkan AK, Eken MK, Karasu AFG, Bilgiç BE, et al. The effect of individual oocyte matched follicular fluid oxidant, antioxidant status, and pro- and anti-inflammatory cytokines on IVF outcomes of patients with diminished ovarian reserve. *Medicine (Baltimore)*. 2023;102(4):e32757. doi: 10.1097/MD.00000000000032757
 40. Ma M, Wang M, Xu F, Hao S. The Imbalance in Th17 and Treg Cells in Polycystic Ovarian Syndrome Patients with Autoimmune Thyroiditis. *Immunol Invest*. 2022 ;51(5):1170-1181. doi: 10.1080/08820139.2021.1915329
 41. Shruthi S, Nirmaladevi V, Aravindhan V. Increased circulating levels of novel anti-inflammatory cytokines IL-27 and IL-38 are associated with immunoendocrine dysregulation and altered redox stress in polycystic ovarian syndrome. *J Reprod Immunol*. 2024;166:104388. doi: 10.1016/j.jri.2024.104388.
 42. Liu J, Liu Y, Li X. Effects of intestinal flora on polycystic ovary syndrome. *Front Endocrinol (Lausanne)*. 2023;14:1151723. doi: 10.3389/fendo.2023.1151723
 43. Sharma C, Suliman A, Al Hamad SM, Yasin J, Abuzakouk M, AlKaabi J, et al. Association of Biomarkers for Dyslipidemia, Inflammation, and Oxidative Stress with Endothelial Dysfunction in Obese Youths: A Case-Control Study. *Diabetes Metab Syndr Obes*. 2024;17:2533-2545. doi: 10.2147/DMSO.S458233
 44. Kumari R, Singh A, Banerjee BD, Grover C, Guleria K. Impact of Metformin Therapy on Chronic Inflammatory Markers Serum Fractalkine and CRP Levels in Polycystic Ovary Syndrome: A Pilot Study on Chronic Inflammatory Markers and Clinical Outcomes. *J Obstet Gynaecol India*. 2025;75(2):115-121. <https://doi.org/10.1007/s13224-025-02100-0>
 45. González F, Mather KJ, Considine RV, Abdelhadi OA, Acton AJ. Salicylate administration suppresses the inflammatory response to nutrients and improves ovarian function in polycystic ovary

- syndrome. *Am J Physiol Endocrinol Metab.* 2020;319(4):E744-E752. doi: 10.1152/ajpendo.00228.2020
46. Naka KK, Kalantaridou SN, Kravariti M, Bechlioulis A, Kazakos N, Calis KA, et al. Effect of the insulin sensitizers metformin and pioglitazone on endothelial function in young women with polycystic ovary syndrome: a prospective randomized study. *Fertil Steril.* 2011;95(1):203-9. doi: 10.1016/j.fertnstert.2010.06.058
47. Kolnikaj TS, Herman R, Janež A, Jensterle M. The Current and Emerging Role of Statins in the Treatment of PCOS: The Evidence to Date. *Medicina (Kaunas).* 2024;60(2):244. doi: 10.3390/medicina60020244
48. Sohaei S, Amani R, Tarrahi MJ, Ghasemi-Tehrani H. The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled clinical trial. *Complement Ther Med.* 2019;47:102201. doi: 10.1016/j.ctim.2019.102201

Contributions:

The authors equally contributed to this paper in the conception, literature review and analysis, drafting and editing, and final approval of the submission.