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Immunological abnormalities in PCOS

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Abstract

PCOS (Polycystic Ovary Syndrome) is a condition associated with irregular ovulation, hyperandrogenism and metabolic disturbances. It affects 10-15% of reproductive ages and it is a common reason for infertility. The basis of PCOS is chronic low-grade inflammation, which is expressed by an increase in inflammatory biomarkers such as CRP, IL6, IFN gamma, TNF alpha, IL10, 17,18 MCP-1 and an increase in the percentage of lymphocytes especially Th1 and macrophages, eosinophils compared to the healthy population. The hormonal imbalances in PCOS may contribute to dysregulation of the immune system, leading to the production of a diverse range of autoantibodies for a spectrum of systemic connective tissue diseases, lupus erythematosus, scleroderma, dermatomyositis, polymyositis, and Sjögren's syndrome. This article reviews the results of previous research on this topic. It was prepared to summarize the latest knowledge about immunological abnormalities in PCOS and to define new therapeutic drug action points.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine and metabolic disorder affecting 10-15% of reproductive-aged women (Wang et al. 2023), It represents the leading cause of infertility in this population. To date, three diagnostic frameworks for PCOS have been developed: the National Institutes of Health (NIH) criteria established in 1990, the Rotterdam Criteria formulated in 2003, and the guidelines issued by the International PCOS Network in 2018. The NIH Criteria approach the presence of all three factors for diagnosis: infrequent ovulation or anovulation, clinical or biochemical evidence of androgen excess and exclusion of alternative etiologies that could explain the observed symptoms (Christ and Cedars 2023). The Rotterdam Criteria is a more inclusive approach that requires fulfillment of at least two out of the following three criteria: infrequent ovulation or anovulation, clinical or biochemical evidence of androgen excess, polycystic ovaries on ultrasound examination (defined by ≥12 follicles per ovary or increased ovarian volume exceeding 10 cm^3) (Smet and McLennan 2018).

However, according to the International PCOS Network guidelines from 2018, the ovary volume is approximately 10 cm³ and/or there are at least 20 follicles with a 2–9 mm diameter in each organ (Kostroun et al. 2023). The Rotterdam criteria have gained wider acceptance due to their increased sensitivity for diagnosing PCOS, particularly in cases where not all three NIH criteria are met. Implementing a stricter antral follicle count threshold (≥20 follicles per ovary) in the 2018 PCOS diagnostic criteria significantly reduces the number of women receiving a PCOS diagnosis. Interestingly, this revised criteria identifies a population with a higher risk of developing metabolic syndrome. Women diagnosed using the 2018 criteria exhibit a more severe metabolic profile, characterized by elevated BMI, cholesterol, triglycerides, total testosterone, and free testosterone levels, compared to those diagnosed solely by the Rotterdam criteria (Teede et al. 2023).

In most women with PCOS, other hormonal abnormalities such as insulin resistance and increased LH (luteinizing hormone) to FSH (follicle stimulating hormone) ratio are observed (Sarray and Almawi 2016). This hormonal dysregulation manifests in a constellation of clinical features, including oligomenorrhea or amenorrhea, infertility, hirsutism, signs of androgen excess, obesity, androgenic alopecia, and acne, hypertriglyceridemia, low levels of sex hormone binding protein (SHBG), higher risk of endometrial cancer, type II diabetes and hypertension (Niccoli et al. 2011, Zhao et al. 2023).

An analysis of biochemical parameters revealed significantly elevated levels of total and free testosterone in women diagnosed using the 2018 criteria compared to those diagnosed solely by the Rotterdam criteria. Importantly, no significant differences were identified in testosterone bioavailability or dehydroepiandrosterone sulfate (DHEA-S) levels between the two study groups. Additionally, anti-Müllerian hormone (AMH) concentrations were significantly higher in the group diagnosed using the 2018 criteria (Kostroun et al. 2023).

Kostroun et al. observed a distinct metabolic profile in women solely fulfilling the Rotterdam criteria (2003) but not the 2018 Polycystic Ovary Syndrome diagnostic criteria. This group exhibited significantly lower body mass index (BMI), total cholesterol, triglycerides, total and free testosterone, and anti-Müllerian hormone (AMH) levels (Kostroun et al. 2023). Additionally, they displayed a higher multiparity prevalence than women diagnosed under the 2018 criteria (Smet and McLennan 2018). An analysis of biochemical parameters revealed significantly elevated levels of total and free testosterone in women diagnosed using the 2018 criteria compared to those diagnosed solely by the Rotterdam criteria. Importantly, no significant differences were identified in testosterone bioavailability or dehydroepiandrosterone sulfate (DHEA-S) levels between the two study groups. Additionally, anti-Müllerian hormone (AMH) concentrations were significantly higher in the group diagnosed using the 2018 criteria (Kostroun et al. 2023).

Table 1. Changes in PCOS diagnostic criteria over the years.

National Institutes of Health 1990	Rotterdam Criteria 2003	Androgen Excess PCOS Society 2006	International Evidence-Based Guideline for the Assessment and Management of PCOS 2018
infrequent ovulation or anovulation; signs of androgen excess (clinical or biochemical); exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism	excess androgen activity; oligoovulation and/or anovulation; ≥12 follicles per ovary or increased ovarian volume exceeding 10 cm³	excess androgen activity; oligoovulation and/or anovulation; exclusion of other entities that would cause excess androgen activity	ovary volume is approximately 10 cm³ and/or there are at least 20 follicles with a diameter of 2–9 mm in each organ

The management of PCOS is grounded in evidence-based practices, prioritizing lifestyle modifications to achieve weight reduction as a cornerstone intervention (Panidis et al. 2013). Pharmacological approaches include the use of hypoglycemic agents such as metformin and thiazolidinediones, particularly rosiglitazone, alongside myo-inositol. Ovulation induction is commonly achieved with selective estrogen receptor modulators, notably clomiphene. (Hoeger et al. 2021) Additionally, for the treatment of hyperandrogenemia, oral contraceptives with anti-androgenic properties, such as cyproterone acetate-containing formulations, are frequently employed (Pkhaladze et al. 2021).

2. The role of immune cells in PCOS

2.1. T Lymphocyte cells and their potential role in Polycystic Ovary Syndrome pathophysiology

The results of previous research have shown that imbalanced T-cell types contribute to immune dysfunction in PCOS (Banerjee et al. 2023, Zhang et al. 2021). Clinical data indicates a significant elevation in

white blood cell counts, including lymphocytes, macrophages, and eosinophils in patients with PCOS compared to healthy controls. (Hu et al. 2020). This elevation may be further amplified by obesity, a common comorbidity in PCOS (Gagliani et al. 2015). Chronic inflammation can interfere with essential physiological processes, including ovulation and embryo implantation (Hu et al. 2020).

T helper 17 cells, a subpopulation of CD4+ (Cluster of differentiation 4) T lymphocytes, are known for their pro-inflammatory role (Zhang et al. 2017). They primarily produce interleukin-17, a cytokine that activates various immune responses (Gagliani et al. 2015). Th17 cells play a crucial role in mucosal immunity and pathogen clearance however, they have also been implicated in the pathogenesis of autoimmune and inflammatory diseases. (Gagliani et al. 2015). Recent data indicate that Th17 cells are involved in pregnancy-related pathologies, including recurrent spontaneous abortion and preeclampsia (Nasri et al. 2018, Stokkeland et al. 2022). They exhibit a complex differentiation program, influenced by factors like signal transducer and activator of transcription 3 (STAT3) and transcription factors RORγt (Retineic-acid-receptor-related orphan nuclear receptor gamma) and RORα (Retineic-acid-receptor-related orphan nuclear receptor alpha) (Nasri et al. 2018). Depending on the cytokine milieu they encounter, Th17 cells can differentiate into either protective or pathogenic effector cells (Maddur et al. 2012).

The balance between Th17 cells and regulatory T cells (Tregs) is critical for maintaining immune homeostasis. An imbalance could manifest as either a decrease in Treg numbers or an increase in Th17 cells, leading to a higher Th17/Treg ratio (Nasri et al. 2018). Research by Nasri et al. observed a trend toward Th17 dominance in PCOS, potentially contributing to pregnancy-related complications like recurrent miscarriages and preeclampsia (Nasri et al. 2018).

Zhang et al. hypothesize that obesity, a common comorbidity in PCOS, might further exacerbate Th17 cell expansion due to elevated androgen and estrogen levels (Zhang et al. 2017). The elevated Th17/Treg ratio observed in PCOS patients aligns with the increased levels of inflammatory markers often reported in the disease. The pro-inflammatory cytokines produced by Th17 cells, such as IL-17A, IL-17F, IL-21, and IL-22 (Interleukin-17A, -17F, -21, -22) might contribute to tissue damage and inflammation seen in PCOS (Maddur et al. 2012). While the exact mechanisms remain under investigation, the potential involvement of Th17 cells in PCOS pathogenesis opens new avenues for research. Understanding the mechanisms by which Th17 cells interact with other immune cells and contribute to the inflammatory environment in PCOS may lead to the development of novel therapeutic strategies targeting this pathway (Zhang et al. 2017).

PCOS is characterized by an elevation in type 1 T helper lymphocytes (Th1) and a concomitant reduction in type 2 T helper lymphocytes (Th2) cells within follicular fluid (Nasri et al. 2018). Supporting the hypothesis of chronic inflammation in PCOS pathogenesis, Qin Lang et al. demonstrated a significant increase in Th1 lymphocytes and a decrease in the number of Th2 cells within follicular fluid from PCOS patients using both flow cytometry and ELISA techniques (Qin et al. 2016).

However, it is unclear whether Th1 cells also shift to the environment and contribute to the systemic immunity of PCOS patients. Th1/Th2 imbalance has also been observed in infertile women with recurrent pregnancy loss and those experiencing implantation failure following in vitro fertilization (IVF) (Nasri et al. 2018). Fatemeh Nasri et al. documented a notable decline in Th1 levels in PCOS patients compared to healthy controls. Nevertheless, the prevailing body of research suggests an upregulation of Th1 and Th17 cells alongside a downregulation of regulatory T cells (Tregs) and Th2 cells in PCOS, indicative of a dysregulated immune response (Zhang et al. 2017, Nasri et al. 2018).

Women with PCOS, especially those who are obese and have higher estrogen and androgen levels, might have an overactive immune system (Barber et al. 2019). An excess fat tissue and hormone imbalance can tip the balance in their immune system- instead of having more anti-inflammatory cells that fight infection calmly, they end up with more inflammatory cells that can cause harm (Gong et al. 2018). Th1 cell percentage and Th1/Th2 ratio were significantly higher in PCOS patients compared to the control group, accompanied by elevated testosterone level, LH, LH/FSH, FINS, HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index, and reduced E2/T (Estradiol/ Testosterone) (Gong et al. 2018). Interestingly, the Th1/Th2 ratio increased with increasing BMI and WC (Waist Circumference) and a significant difference in Th1/Th2 ratio was observed between WC subgroups of PCOS (Gong et al. 2018).

2.2 The role of Natural killer cells (NK) in PCOS

Women with PCOS exhibit a decrease in NK cell population (Sala Elpidio et al. 2018). NK cells are critical components of innate immunity, mediating early non-specific responses and immune surveillance. These lymphocytes exert cytotoxic activity, eliminating aberrant cells including damaged, virally infected, harboring intracellular pathogens and cancerous cells (Whiteside 1990). The reduced NK cell levels in PCOS patients may contribute to a homeostatic imbalance within the female reproductive tract, potentially leading to characteristic PCOS symptoms such as menstrual irregularities and infertility. Zhang et al. emphasize that NK cells are in higher amounts in the fluid surrounding oocytes in women with PCOS. This suggests that the immune system may be involved in folliculogenesis and corpus luteum development (Sala Elpidio et al. 2018).

T lymphocytes are an aggressive type of immune cell involved in the pathogenesis of various chronic inflammatory conditions, including autoimmune diseases, atherosclerosis, coronary artery disease and type 2 diabetes mellitus (Niccoli et al. 2011). Unlike their conventional helper T cell counterparts, CD4(+)CD28(-) T cells are primed to release inflammatory molecules and cytotoxic substances directly. This destructive duo can damage tissues and worsen inflammatory pathways. Patients with higher numbers of these cells tend to experience more severe disease courses and poorer outcomes. Niccoli et al. showed that an increase in CD4–CD28 (-)T cells was observed in women with PCOS (Niccoli et al. 2011).

2.3 The role of Dendritic cells in PCOS

The dendritic cells (DCs) are specialized antigen-presenting cells that are involved in adaptive immune responses. They secrete inflammatory mediators that promote the proliferation of T lymphocytes, particularly Th17 and Th1 cell subsets (Zhang et al. 2017). Zhang et al. reported a reduction in the number of DCs with CD 11c expression (CD11c+ HLA-DR+ DCs) in the follicular fluid of PCOS patients, potentially contributing to ovarian dysfunction. Conversely, they observed an increase in CD45+ leukocytes in the follicular fluid, suggesting a state of chronic low-grade inflammation linked to disruption of ovulation in PCOS (Zhang et al. 2017). They noticed a positive correlation between HLA-DR expression on DCs in follicular fluid and serum estradiol (E2) levels on the day of human chorionic gonadotropin (hCG) administration. An abnormal cytokine profile was also observed in follicular fluid isolated from PCOS patients. These findings collectively suggest a potential link between impaired DC function, follicular inflammation, and abnormal ovarian function in PCOS (Zhang et al. 2017).

Table 2. Summary of immune cells involved in the pathophysiology of PCOS with clinical meaning.

Immune cells	Description	Serum concentrations	References
CD4+CD28 (null) T	base of chronic inflammatory conditions, autoimmune diseases, atherosclerosis, coronary instability and dm2 and persistent viral infections	↑	(Niccoli et al. 2011)
CTLA4-	suppresses the activation of T cells	↓	(Su et al. 2018)
DCs	secrete inflammatory mediators that promote the proliferation of T lymphocytes, particularly Th17 and Th1 cell subsets, a positive correlation between HLA-DR expression on DCs in follicular fluid and serum E2 levels on the day of hCG administration	↓	(Niccoli et al. 2011)
macrophage M1	cells activate various control proteins like IRF5, NF-κB, AP-1, and STAT1; this boosts their ability to kill microbes and triggers the release of powerful inflammatory messengers, including IFN-γ, IL-1, IL-6, IL-12, IL-23, and TNFα	↑	(Mosser and Edwards 2008)
macrophage M2	plays an anti-inflammatory role by producing cytokines (IL-10 and TGF-beta) that prevent the activation of the inflammatory pathway triggered by IL-1	↓	(Wang et al. 2023)
NK	kills infected (viral or bacterial) and cancerous cells, interacts with other immune cells to modulate immune responses, recognizes and eliminates tumor cells	↓	(Wang et al. 2023)
Th1	secrete cytokines (IFN-γ, TNF-β) that enhance macrophage activity, enabling them to efficiently kill ingested microbes, and contribute to inflammatory responses, essential for containing infections. Help activate CD8+ T cells, which eliminate influence antibody production, favoring those that promote phagocytosis (opsonizing antibodies), interact with other immune cells to maintain a balanced immune response, preventing excessive inflammation or immune suppression	↑	(Wang et al. 2023)
Th17	the pro-inflammatory role, involved in pregnancy-related pathologies, including recurrent spontaneous abortion and preeclampsia	↑	(Yang et al. 2021)
Th2	play a crucial role in immune responses to extracellular parasites and allergens, produce cytokines like IL-4, IL-5, and IL-13, which stimulate the production of antibodies and activate immune cells such as eosinophils and basophils, involved in allergic reactions and inflammatory diseases	↓	(Wang et al. 2023)

Treg	prevent autoimmune diseases by establishing and maintaining immunologic self-tolerance, suppressing of allergy and asthma, inducting tolerance against dietary antigens, i.e. oral tolerance, inducting maternal tolerance to the fetus, suppressing of pathogen-induced immunopathology, regulating the effector class of the immune response suppression of T-cell activation triggered by weak stimuli, control of the magnitude of the immune response by effector Th cells, protect of commensal bacteria from elimination by the immune system, prevent of T cells that have been stimulated by their true high-affinity agonist ligand from killing cells that only express low-affinity T-cell receptor (TCR) ligands such as the self peptide-major histocompatibility complex (MHC) molecule that positively selected the T cell	↓	(Wang et al. 2023, Corthay 2009)

3. Changes in immune molecule levels in women with PCOS

Some studies have shown that the levels of inflammatory elements such as C-reactive protein (CRP), interleukin-1β, interleukin-17, interleukin-18, IL 23, Il-10, Interferon-gamma (IFN γ), TNF-α are significantly different compared to healthy controls (Niccoli et al. 2011, Akcalı et al. 2014). However, the level of inflammatory markers in obese women with and without PCOS did not differ. Existing research suggests no significant differences in serum concentrations of leptin, resistin, and adiponectin between obese patients with PCOS and obese controls (Niccoli et al. 2011) .

Moreover, some researchers have revealed elevated cytokine release from mononuclear cells upon exposure to lipopolysaccharides during a fasting state in women with PCOS (González et al. 2014). This observation suggests a pre-activated state of these immune cells, independent of a patient's body mass index. This preactivation may play a significant role in the pathogenesis of PCOS, potentially contributing to the development of insulin resistance and hyperandrogenism, both cardinal features of the disorder (Fulghesu et al. 2011). Furthermore, women with PCOS exhibit significantly elevated levels of pro-inflammatory cytokines including IL-1β, a central mediator in the inflammatory response (Mobeen et al. 2016). Compared to healthy controls, IL-1β plays a crucial role in driving inflammation through various mechanisms (Mobeen et al. 2016).

Diverse cell types secrete it in response to a wide range of stimuli, including viral, bacterial, and fungal antigens. IL-1β exerts its potent pro-inflammatory effects by stimulating the production of other cytokines such as IFN-γ, IL-6, and TNF-α. Additionally, it promotes IL-6 secretion by T lymphocytes, amplifying the inflammatory cascade, and modulates B lymphocyte development, impacting their functionality and antibody production.

Furthermore, pregnant women with PCOS exhibit notable alterations in serum cytokine profiles throughout gestation, suggesting that the inflammatory dysregulation characteristic of PCOS extends into pregnancy and may influence maternal and fetal outcomes. These findings underscore the importance of monitoring and managing inflammation in this patient population (Mobeen et al. 2016).

3.1 Interleukin-6

IL-6, a pleiotropic cytokine with pyrogenic properties and the ability to induce acute phase protein synthesis, has been investigated for potential associations with polycystic ovary syndrome. IL-6 contributes to the development of insulin resistance and promotes androgen overproduction (González et al. 2014). Despite numerous studies, the link between serum IL-6 levels and the PCOS phenotype remains unclear. Recent meta-analyses suggest that IL-6 levels may not be a differentiating factor between PCOS patients and controls (Deligeoroglou et al. 2012). In a comparison between women with PCOS and controls, non-obese women with PCOS exhibited elevated serum interleukin-6 levels independent of body mass index. IL-6 levels were higher in women with hirsutism (Akcalı et al. 2014). No significant differences in IL-6 levels were observed between obese women with PCOS and obese control subjects (Sathyapalan and Atkin 2010). Interestingly, IL-6 concentrations were significantly increased in obese but not lean women with PCOS compared to the matched control group. It is supposed that observed inflammatory changes are likely a consequence of obesity rather than PCOS-related features such as depression or hormonal imbalances (Sarray and Almawi 2016, Glintborg and Andersen 2010).

Fulghesu et al. observed a positive correlation between interleukin-6 concentration and monocyte response intensity upon lipopolysaccharide stimulation in women with PCOS exhibiting insulin resistance (Fulghesu et al. 2011). This correlation was not seen with other cytokines, suggesting a specific modulation of the immune response in this population (Fulghesu et al. 2011). In turn, González et al. demonstrated a positive correlation between serum IL-6 levels and the severity of both insulin resistance and hyperandrogenism in PCOS patients, with higher IL-6 concentrations associated with greater severity. Additionally, they observed a

proportional increase in IL-6 levels with increasing adipose tissue percentage. Interestingly, the study induced hyperandrogenemia in healthy lean women and found it triggered nutrient-induced proinflammatory cytokine production by mononuclear cells in response to glucose (González et al. 2014). This suggests that hyperandrogenism might precede and initiate nutrient-induced inflammation in PCOS, but may not be essential for its chronic persistence. Furthermore, suppressing hyperandrogenemia in lean PCOS women did not diminish the inflammatory state, implying a more complex interplay (González et al. 2014).

3.2 Tumor necrosis factor α (TNFα)

No connection was found between plasma TNF-α and PCOS in existing studies (Deligeoroglou et al. 2012). However, some studies show increased TNF levels in women with PCOS (Akcalı et al. 2014). Additionally, it contributes to peripheral insulin resistance, enhances phagocytosis by immune cells, promotes neutrophil recruitment, induces androgen overproduction and disrupts the hypothalamic-pituitary-ovarian axis (Deligeoroglou et al. 2012).

González et al. study showed that TNFα concentration secreted by mononuclear cells exhibited a negative correlation with peripheral tissue insulin sensitivity, as measured by OGTT. This association was further supported by positive correlations between TNFα and serum levels of testosterone, androstenedione, and LH in both PCOS and healthy patients. While the LH correlation suggests a potential role for inflammation in driving pituitary LH oversecretion and subsequent androgen overproduction in PCOS, the direct effects of inflammation within the ovary are already well understood (González et al. 2014).

In vitro studies suggest a potential role for TNF-α in the pathogenesis of PCOS. These studies demonstrate that TNF-α can influence the reproductive axis in rats by stimulating theca cell proliferation and steroidogenesis, potentially impacting ovarian hormone production. Additionally, TNF-α may exert an apoptotic effect on rat ovarian theca cells, which could contribute to abnormal ovarian function, potentially contributing to anovulation. TNF-α may also be linked to impaired insulin activity, although the exact mechanisms remain under investigation (Deligeoroglou et al. 2012).

However, the role of TNF-α in human PCOS remains unclear. While in vitro findings suggest its involvement, case-control studies yield conflicting data regarding a potential association between TNF-α concentration and PCOS occurrence. Furthermore, two meta-analyses of existing human data fail to conclusively establish an unambiguous link between plasma TNF-α concentrations and PCOS diagnosis (Deligeoroglou et al. 2012). TNFα, a well-established pro-inflammatory cytokine, contributes to obesity-mediated systemic insulin resistance by inhibiting insulin receptor tyrosine kinase activity in both skeletal muscle and adipose tissues. However, its role extends beyond inflammation. TNFα is demonstrably essential for processes critical for female fertility, including follicle formation, oocyte maturation, and androgen synthesis. Paradoxically, it also exerts insulin-desensitizing effects. Furthermore, TNFα plays a pivotal role in the apoptosis of endothelial cells within the ovarian granulosa and luteal compartments, ultimately leading to follicular atresia and luteolysis. Consequently, its concentration directly impacts oocyte quality. Intriguingly, TNFα may also promote a state of hyperandrogenism and obesity independent of PCOS. TNFα is implicated in the pathogenesis of polycystic ovary syndrome (PCOS) through its potential roles in inducing insulin resistance, stimulating androgen production, and disrupting the hypothalamic-pituitary-ovarian axis. This potential exists for a vicious cycle, where coexisting PCOS may exacerbate these effects (Deligeoroglou et al. 2012, Serin et al. 2021).

As proposed by Cong Hu et al., chronically elevated androgen levels in PCOS patients could promote the conversion of macrophages to the M1 phenotype, leading to further pro-inflammatory cytokine such as TNF alpha secretion and worsening of clinical symptoms (Hu et al. 2020).

3.3. Cluster of differentiation 154 (CD154)

CD154 plays a crucial role in B cell maturation and functions (Lederman et al. 1994). Sarray et al.identified soluble CD40 Ligand (sCD40L) as a highly sensitive and specific predictor of PCOS, independent of body mass index. These researchers proved that a reduction in sCD40L levels was observed in women with PCOS compared to women from the control group, regardless of body weight (Sarray and Almawi 2016). Notably, altered sCD40L levels were associated with PCOS, demonstrating a negative correlation with age, insulin levels, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index, Luteinizing Hormone (LH), free testosterone, Ferriman-Androgen Index (FAI), and hirsutism.

Conversely, a positive correlation between sCD40L and Sex Hormone Binding Globulin (SHBG) was observed. However, Sarray et al., CD40L emerged as a more robust biomarker for PCOS compared to IL-6 and TNF-α. Additionally, elevated CD40L levels were associated with both type 2 diabetes and hypercholesterolemia, suggesting a potential link (Sarray and Almawi 2016). Further studies proposed that insulin resistance and hyperglycemia may act as upstream regulators of CD40L expression and release (Dahan and Reaven 2019).

3.4 Interleukin 17

IL-17 is another cytokine with significantly elevated levels in women with PCOS (Nasri et al. 2018). It is primarily produced by activated T lymphocytes and plays a crucial role in orchestrating the immune response against extracellular bacteria. It exerts its effects through a cascade of events: stimulation of various cell types by acting on epithelial and endothelial cells, fibroblasts, and macrophages, inducing the production of other pro-inflammatory cytokines like IL-6, IL-8, TNF-α, and granulocyte colony-stimulating factor (G-CSF), synergistic interactions- it interacts with other cytokines, particularly granulocyte colony-stimulating factor (GM-CSF), to further amplify its pro-inflammatory effects and modulation of antigen presentation: IL-17 influences the maturation of dendritic cells, potentially impacting their ability to present antigens to other immune cells (Gagliani et al. 2015).

3.5 Interleukin-18

IL-18 emerges as another potential contributor to PCOS pathology. Elevated IL-18 levels observed in PCOS patients are known to induce robust inflammatory responses, implicating its role in the pathogenesis of various inflammatory and autoimmune disorders including type 1 diabetes, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, and psoriasis (Boraschi and Dinarello 2006).Serum concentration of IL-18 has a positive correlation with body mass index and insulin resistance.

Notably, elevated IL-18 levels are observed even in lean individuals, with a further increase in obese and insulin-resistant patients. In contrast, another study observed that elevated levels of interleukin-18 are irrespective of a patient's insulin resistance or obesity status. Notably, the presence of both increased BMI and insulin resistance leads to a further rise in IL-18 concentrations (Kabakchieva et al. 2022). This association between IL-18 and PCOS extends beyond reproductive health, as increased IL-18 levels have been linked to heightened cardiovascular risk and increased carotid intima-media thickness. These findings suggest a potential role for IL-18 in the development of carotid atherosclerosis in women with PCOS (Deligeoroglou et al. 2012).

3.6 Interleukin-23 and 10

The study revealed a significant decrease in IL-23 concentration in the PCOS patient (Zhang et al. 2017). In contrast, there is observed a statistically significant elevation of IL-10 levels in PCOS patients compared to the control group (Zhang et al. 2017). Qin et al. using the flow cytometry method have noted a slight decrease in IL-10 concentration with a simultaneous increase in IL-2 in the population of patients with PCOS, while the IL-4 concentration in the group of women with and without PCOS did not differ (Qin et al. 2016).

3.7 C-reactive protein (CRP)

CRP levels exhibit a positive correlation with insulin resistance, body weight, fat mass, HOMA-IR, free testosterone levels and hirsutism (Hu et al. 2011).The study showed that hs-CRP (high-sensitivity C-reactive protein) levels are very effective in determining whether a patient has PCOS (Lin et al. 2011).Treatment with metformin or 17 β -estradiol in combination with cyproterone acetate has been shown to significantly reduce CRP concentrations (Deligeoroglou et al. 2012).

The role of CRP in the pathogenesis and diagnostics of PCOS remains unclear. Some studies report a 96% increase in serum CRP levels in female PCOS patients compared to healthy controls, while others observe similar levels in both groups (Deligeoroglou et al. 2012).In turn, different studies suggest statistically significant differences in CRP levels between lean PCOS patients and healthy controls, as well as between normal-weight and obese PCOS patients (Deligeoroglou et al. 2012). However, another study showed no difference in CRP levels between lean PCOS patients and healthy control group but did identify a difference between PCOS patients with normal and impaired glucose tolerance. A study by Makled et al in 2011 demonstrated elevated CRP levels in PCOS patients, independent of their body weight (Hefler-Frischmuth et al. 2010). This suggests CRP may be a marker of inflammation in PCOS beyond the effects of obesity.

However, some studies say that hsCRP increases only in obese PCOS patients, but not in lean ones (Benson et al. 2008). Some research suggests a link between PCOS and chronic inflammation. Studies by Yue-Shan Lin et al. and Diamanti-Kandarakis et al. demonstrate elevated levels of hs-CRP, a marker of inflammation, in women with PCOS. These elevated levels persist even after accounting for factors like obesity and insulin resistance (Lin et al. 2011).

Furthermore, Sarray and Almawi's study suggests no significant difference in hs-CRP) levels between women with PCOS and healthy controls (Sarray and Almawi 2016). This aligns with prior research indicating hs-CRP's association with obesity, potentially independent of PCOS diagnosis. Further investigation is warranted to elucidate the specific influence of obesity on hs-CRP levels in this context (Zhao et al. 2021).

Pregnant women diagnosed with polycystic ovary syndrome exhibited elevated CRP levels at week 10 of gestation. Additionally, a distinct pattern of cytokine production was observed throughout pregnancy in this group (Stokkeland et al. 2022). Interestingly, the dynamics of these changes were significantly modulated by the mother's

BMI, smoking status, and fetal sex. The analysis elevated an inverse relationship between CRP and HDL-C levels in PCOS patients. This suggests a potential link between PCOS and increased risk of atherosclerosis and cardiovascular disease (CVD) (Stokkeland et al. 2022).

3.8 Intercellular adhesion molecule-1 and sE-selectin

Diamanti-Kandarakis et al. observed increased plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin, additional inflammatory markers, in PCOS patients. Their study also found that metformin treatment significantly reduced these markers after six months, suggesting a potential therapeutic role in managing inflammation associated with PCOS (Lin et al. 2011).

3.9 Interferons (IFN)

IFN expression, a cytokine known to activate immune system cells and regulate antigen presentation to T lymphocytes, was significantly elevated in PCOS patients compared to the control group (Gong et al. 2018). Fatemeh Nasri et al. study shows statistically significant higher production of IFN-γ compared with healthy control ones (Nasri et al. 2018).

3.10 Leptin, Resistin, and Adiponectin

Thozhukat Sathyapalan's research suggests no significant differences in serum concentrations of leptin, resistin, and adiponectin between obese patients with PCOS and obese controls (Sathyapalan and Atkin 2010). Fulghesu et al. proved the relationship between two adipose tissue-derived hormones, leptin and adiponectin, in both healthy individuals and women diagnosed with PCOS (Fulghesu et al. 2011). A positive correlation was observed between leptin levels and body mass index in both healthy controls and PCOS patients (Fulghesu et al. 2011). This suggests that leptin, primarily produced by fat cells, increases proportionally with body fat content, regardless of PCOS status. Adiponectin is a lipokine with anti-inflammatory effects, its levels were significantly lower in all PCOS groups compared to healthy controls. This finding suggests a potential role for adiponectin dysregulation in PCOS pathogenesis, independent of body mass index (Fulghesu et al. 2011, Sathyapalan and Atkin 2010).

3.11 Chemoattractant protein 1

MCP1 (monocyte chemoattractant protein-1) also known as CCL2 (chemokine C-C motif ligand 2) acts as a critical recruiters of immune cells to the inflammatory site. Hu et al suggest elevated MCP-1 levels in PCO patients. MCP-1, a chemokine secreted by adipocytes among others, has been linked to insulin resistance potentially through mechanisms like reduced glucose uptake in muscle cells by CCL2. Furthermore, MCP-1 correlates positively with blood triglycerides, a risk factor for atherosclerosis and cardiovascular disease, including acute coronary syndrome, in PCOS patients. Notably, CCL2 has also been implicated in the development of psoriasis, rheumatoid arthritis, and atherosclerosis in other contexts (Hu et al. 2011).

3.12 Lipoxygenase 5 (LOX-5)

LOX-5, an enzyme known to exacerbate conditions like obesity, atherosclerosis, and insulin resistance by increasing inflammatory molecules, presents a surprising paradox in PCOS. While LOX-5 activity is typically expected to be elevated, research reveals lower levels of inflammatory mediators in women with PCOS compared to healthy controls (Szczuko et al. 2017). This counterintuitive finding suggests a potential dysregulation of inflammatory pathways specific to PCOS.

Table 3. Serum concentration of immune markers in PCOS.

Immune molecules	Description	Serum concentrations	References
CD154	plays a crucial role in B cell maturation and functions with a negative correlation with age, insulin levels, HOMA-IR index, Luteinizing Hormone (LH), free testosterone, Ferriman-Androgen Index (FAI), and hirsutism	↓	(Dahan and Reaven 2019)
CRP	a positive correlation with insulin resistance, body weight, fat mass, HOMA-IR, free testosterone levels and hirsutism, markers of inflammation	↑	(Wang et al. 2023)

IFNy	activate immune system cells and regulate antigen presentation to T lymphocytes	↑	(Jorgovanovic et al. 2020)
IL-10	cytokine synthesis inhibitory factor	↑	(Iyer and Cheng 2012)
IL-17	exerts its effects through a cascade of events: stimulation of various cell types by acting on epithelial and endothelial cells, fibroblasts, and macrophages, inducing the production of other pro-inflammatory cytokines like IL-6, IL-8, TNF-α, and G-CSF, synergistic interactions	↑	(Wang et al. 2023)
IL-18	induces robust inflammatory responses, implicating its role in the pathogenesis of various inflammatory and autoimmune disorders including type 1 diabetes, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, and psoriasis. Serum concentrations of IL-18 exhibit a positive association with body mass index and insulin resistance	↑	(Wang et al. 2023, Boraschi and Dinarello 2006`)
IL-2	influences the direction immature immune cells (Th lymphocytes) take, pushing them to become Th1 cells. It also works alongside other molecules (IL-4 and IL-5) to boost the activity of B cells, another type of immune cell	↑	(Wang et al. 2023, Purkerson et al. 1988)
IL-23	boosts the immune system by increasing immune cell activity and production, as well as triggering the creation of proteins that fight infection	↓	(Wang et al. 2023)
IL-6	induces the synthesis of acute-phase proteins, contributes to the development of insulin resistance and promotes the overproduction of androgens	↑	(Sarray and Almawi 2016)
MCP-1 (CCL-2)	acts as critical recruiters of immune cells to the inflammatory site, it is linked to insulin resistance, correlates positively with blood triglycerides, a risk factor for atherosclerosis and cardiovascular disease, including acute coronary syndrome	↑	(Hu et al. 2011)
sICAM-1, E Selectin	inflammatory markers	↑	(Lin et al. 2011)
TNF-α	an apoptotic effect on rat ovarian theca cells, contributing to anovulation it stimulates hepatocytes to synthesize acute-phase reactants, including C-reactive protein, contributes to peripheral insulin TNFα concentration, enhances phagocytosis by immune cells, promotes neutrophil recruitment, and induces androgen overproduction and disrupts the hypothalamic-pituitary-ovarian axis, a negative correlation with peripheral tissue insulin sensitivity, and serum levels of testosterone, androstenedione, and LH in both PCOS and healthy patients	↑	(González et al. 2014, Deligeoroglou et al. 2012)

4. Conclusions

Emerging evidence suggests a critical role for the immune system in the pathogenesis of Polycystic Ovary Syndrome. Patients with PCOS often exhibit obesity and elevated levels of estrogens and androgens. This hormonal status may lead to persistent stimulation of the immune system, characterized by an increase in pro-inflammatory cell populations like M1 macrophages, Th1 cells, and Th17 cells. Conversely, there appears to be a concomitant decrease in the number of anti-inflammatory cells, such as M2 macrophages and Tregs. Additionally, antigen-presenting cells may exhibit altered function. This dysregulation of the immune microenvironment can

have two potential consequences. Firstly, it can lead to the production of autoantibodies, potentially contributing to the development of autoimmune diseases frequently observed in PCOS patients. Secondly, a breakdown in immune tolerance may create a chronic inflammatory state that disrupts ovarian follicle development and ovulation.

Current treatment strategies for PCOS primarily focus on managing symptoms through exercise, oral insulin-sensitizing drugs and oral contraceptives. While these approaches can improve short-term ovulation outcomes, a deeper understanding of the underlying etiology of PCOS is necessary. Due to the heterogeneous nature of PCOS, a definitive cure is currently unavailable. Treatment strategies are formulated based on a patient's age, primary concerns (e.g., menstrual irregularities, infertility, metabolic risk), and medical history. This individualized approach ensures optimal management of the various symptoms and potential complications associated with PCOS. The findings summarized here highlight the potential of targeting the immune system for improved treatment efficacy. Further research efforts aimed at elucidating the precise mechanisms linking hormonal and immune factors in PCOS are crucial. This knowledge will pave the way for the development of novel, targeted therapies that address the underlying immune dysfunction in PCOS patients.

Additionally, exploring immunomodulatory interventions holds promise for the future of PCOS management. Addressing the challenges associated with translating these findings into effective clinical therapies will be a key area of focus in the coming years.

5. Disclosures

Author's Contributions

Conceptualization, Joanna Barcińska; methodology, Aleksandra Ostrowska-Czyżewska; formal analysis, Dominika Szwed; investigation, Aleksandra Ostrowska-Czyżewska; resources, Dominika Szwed; data curation, Joanna Barcińska; writing - original draft, Joanna Barcińska; writing - review and editing, Aleksandra Ostrowska-Czyżewska and Dominika Szwed; visualization, Aleksandra Ostrowska-Czyżewska; supervision, Joanna Barcińska; project administration, Joanna Barcińska.
All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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