From inflammation to ovulation: Rethinking PCOS pathophysiology


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Abstract

Polycystic-Ovary Syndrome (PCOS) is a common endocrinological disorder in women belonging to active reproductive age, marked by hyperandrogenism, recurrent anovulation, and polycystic ovarian morphology. Recent findings indicate a substantial correlation between PCOS and persistent low-grade systemic inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and several adipokines having prominent role as inflammatory biomarkers. As of 2025 WHO statistics and factsheets, approximately 6-13% of women are experiencing this disorder worldwide with a prevalence of 3.7-22.5% in India. Approximately 70% of the suffering population goes undiagnosed. The bidirectional association between inflammation and PCOS suggests that inflammation may serve as both a result and a contributor to the syndrome's clinical manifestations. Comprehending the inflammatory mechanisms of PCOS may facilitate the development of innovative therapeutic strategies aimed at inflammatory pathways to regulate and alleviate the symptoms.

Keywords: Polycystic-ovary syndrome, inflammatory mechanism, inflammatory biomarkers

1. Introduction

1.1. The PCOS-insulin-inflammation triangle

Chronic inflammation and insulin resistance are closely related with progression of PCOS. Insulin resistance feeds hyperinsulinemia and availability of free androgen in circulation while the inflammatory mechanisms exacerbate the insulin signalling. They collectively work together to cause reproductive and metabolic dysfunctions in the ovarian cycle.(1) Inflammation impairs insulin signalling. Pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β interfere with insulin signalling by activating stress related kinases such as JNK, IKKβ and p38 MAPK which phosphorylate the Insulin Receptor Substrate (IRS) protein on serine residues instead of tyrosine. (2) Additionally, Suppressor of Cytokine Signalling (SOCS) proteins are also induced by this inflammatory response further inhibiting insulin receptor activity. (3) Inhibition of downstream insulin signalling ultimately results into insulin resistance. These metabolic changes due to elevated free fatty acids and glucose in circulation trigger a series of complexities like oxidative stress and mitochondrial dysfunction, activated inflammatory responses in hepatic and adipose tissues and macrophage infiltration into them. The disrupted insulin signalling also hinders hepatic production of Sex Hormone Binding Globulin (SHBG) which in turn escalates free androgen availability in the blood circulation leading to vicious PCOS symptoms like hirsutism, alopecia, acne and unwanted belly fact.(4) Figure no. 1 describes the interwinding relation between inflammatory triggers, insulin resistance and progression of PCOS.

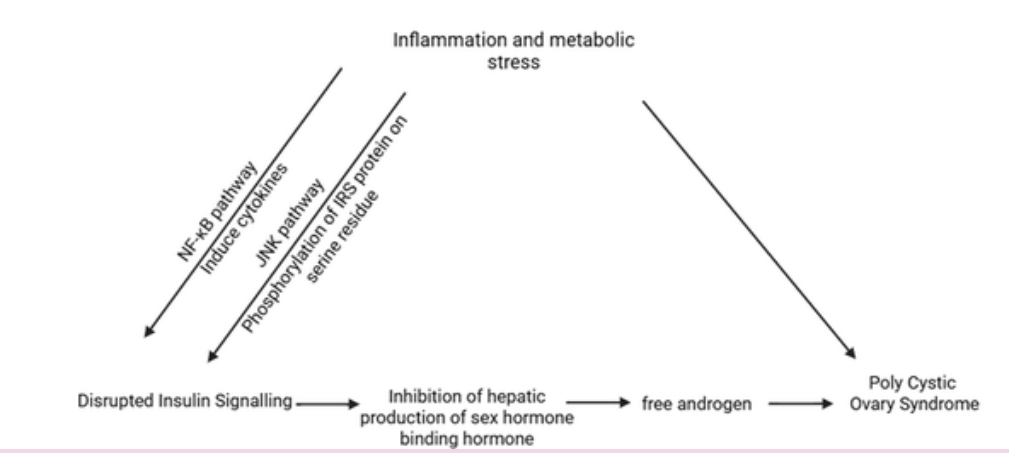

Figure 1. Inflammation and metabolic stress trigger activation of the NF-κB and JNK signalling pathways, resulting in cytokine production and the phosphorylation of insulin receptor substrate (IRS) proteins on serine residues respectively. The metabolic changes further interfere with standard insulin signalling process subsequently hindering the hepatic synthesis of SHBG. The decrease in SHBG elevates free androgen levels in circulation, a significant factor in the pathogenesis of PCOS.

2. Role of inflammatory mediators in the genesis of PCOS and associated metabolic disorders

The pathophysiological pathway of development of PCOS is complex and multifactorial, with chronic low-grade inflammation playing a key role in its progression. Women with PCOS frequently exhibit elevated levels of systemic inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and various pro-inflammatory adipokines such as leptin and resistin. This inflammatory milieu not only contributes to reproductive dysfunction but also increases the risk of prolonged metabolic complications, including type 2 diabetes mellitus and cardiovascular diseases. (5) Furthermore, local inflammation within ovarian tissue can impair follicular development and ovulatory functions, perpetuating the anovulatory state typical of PCOS. A typical role of inflammatory mediators towards ignition of poly-cysts is discussed in the Table no. 1 and Figure no. 2 below.

Table 1. Summarises the inflammatory mediators and their role in development of a poly cystic ovary via various mechanistic pathways (5–9)

S. N.	Inflammatory mediators involved	Role of inflammatory mediators in development of PCOS
1.	**C-Reactive Protein (CRP)**	CRP is linked with insulin resistance and endothelial dysfunction, contributing to both metabolic and cardiovascular complications of PCOS.
2.	**Tumor Necrosis Factor-alpha (TNF-α)**	TNF-α interferes insulin signalling pathway by promoting insulin resistance. It stimulates androgen production by ovarian theca cells, contributing to hyperandrogenism. Also involved in the recruitment of immune cells that exacerbate local ovarian inflammation.
3.	**Interleukin-6 (IL-6)**	IL-6 is elevated in PCOS and promotes hepatic production of CRP. It impairs insulin action in adipose and muscle tissues, worsening insulin resistance. IL-6 may disrupt folliculogenesis and ovulation through inflammatory damage to ovarian tissue.

4.	**Interleukin-1β (IL-1β)**	Plays a role in follicular arrest and anovulation by interfering with granulosa cell function.Contributes to ovarian inflammation and disruption of steroidogenesis.
5.	**Monocyte Chemoattractant Protein-1 (MCP-1)**	MCP-1 levels are increased in PCOS, promoting macrophage infiltration into adipose and ovarian tissues. Macrophages secrete additional cytokines, thereby exacerbatin inflammation and insulin resistance.
6.	**Leptin**	Leptin levels are often elevated in PCOS, especially in obese individuals. It acts as a pro-inflammatory adipokine, stimulating TNF-α and IL-6 production. Alters hypothalamic-pituitary-ovarian axis function, potentially affecting ovulation.
7.	**Resistin**	Promotes insulin resistance by disrupting insulin receptor signalling pathways. It has pro-inflammatory properties that contribute to systemic inflammation in PCOS.
8.	**Nuclear Factor-kappa B (NF-κB)**	A key transcription factor activated by inflammatory signals. Drives expression of cytokines and chemokines, contributing to chronic inflammation and insulin resistance in PCOS.

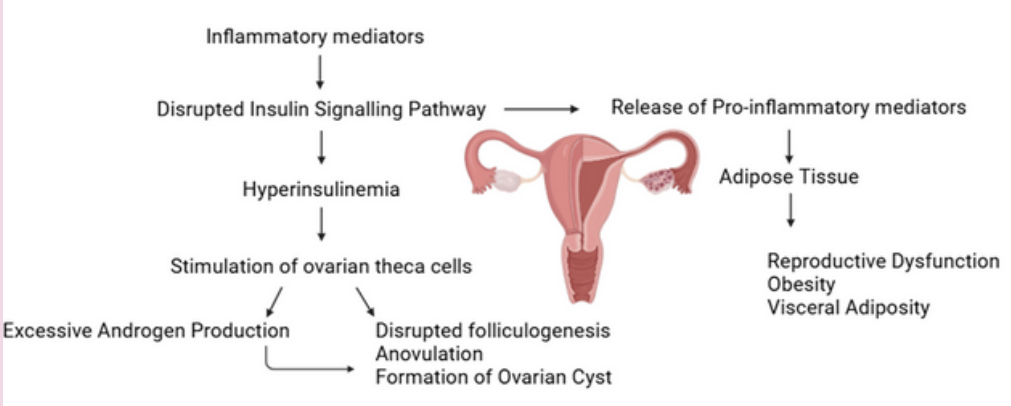

Figure 2. Depicts the pathophysiological pathway of PCOS development due to altered insulin signalling pathway caused by inflammatory mediators. Apart from disturbed folliculogenesis and reproductive functions, these inflammatory mediators are also responsible for inhibition of hepatic production of sex hormone binding globulin. As a result, free androgen becomes available in blood stream which is responsible for vicious symptoms of PCOS like acne outbreaks, alopecia and hirsutism (5,10,11)

3. Anti-inflammatory agents: New potential for fighting PCOS

Although the treatment or management of PCOS is mainly dependent upon the patient's need; anti-inflammatory agents offer novel options. Metformin, an insulin-sensitizing medication used to treat PCOS, also reduces inflammation. Metformin lowers inflammatory indicators like CRP and TNF-α, reducing systemic inflammation. Metformin lowers insulin and indirectly reduces androgen by enhancing insulin sensitivity, restoring regular ovulatory cycles. (12) Some recent trials are also focussing on salicylate derivatives and ibuprofen.(13) Meanwhile, Poly Unsaturated Fatty Acids (PUFAs) have emerged as potent servers. Omega-3-fatty acids, in particular Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) have proven to show significant anti-inflammatory properties and are increasingly recognised for their potential in management of PCOS by modulating the production of pro-inflammatory cytokines. Omega-3 supplementation improves insulin sensitivity, lowers blood triglycerides, and lowers androgen in PCOS women. Menstrual regularity and ovulatory frequency may also benefit from omega-3s (14).

4. Conclusion

Infertility, menstrual irregularities, hyperandrogenism, weight loss and metabolic disease management are the goals of current treatment regimen of PCOS. Underlying molecular mechanism of pathophysiology of PCOS is the recent research goal and moreover role of chronic inflammation in progression of disease is expanding. Future therapeutic strategy for PCOS may include anti-inflammatory medications.

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