Indian Journal of Modern Research and Reviews

This Journal is a member of the *'Committee on Publication Ethics'*

Online ISSN: 2584-184X

Research Article

Analyzing Genetic, Epidemiological, and Inflammatory Markers in Polycystic Ovary Syndrome (PCOS) And Their Correlation with Clinical Manifestations

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Abstract

Polycystic Ovary Syndrome (PCOS) is a common multifaceted endocrine disorder that affects women of childbearing age globally. Its aetio-pathogenesis is still not fully elucidated as it is on the cross-talk of genetic, epidemiological and inflammatory factors. The current paper is a review of the genetic, population determinants, and inflammatory biomarkers hypothesised to have a joint effect in determining the clinical features of PCOS. Several candidate genes important in steroidogenesis (CYP11A1, CYP17A1), gonadotropin signalling (FSHR, LHCGR) and metabolism regulation (INSR, PPARG) are tested for their association with hyperandrogenism, follicular dysfunction and insulin sensitivity. Epidemiological determinants (age, ethnicity, obesity, lifestyle behaviours and early-life exposures) are explored in terms of disease risk and severity. Inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha) and modulated adipokines are similarly reviewed in the spectrum of chronic low-grade inflammation. In conclusion, the results highlight the relevance of multivariate evaluation to enhance PCOS diagnosis, risk stratification and individualised treatment.

Keywords: Polycystic Ovary Syndrome; steroidogenesis; adipokines; hirsutism; metabolism regulation

Introduction

Polycystic ovary syndrome (PCOS) is an unexplained, heterogeneous, endocrine condition in women of reproductive age all over the globe. It is estimated that its prevalence is between 6% and 20% basing on the different diagnosis criteria (NIH, 1990), Rotterdam (2003), and the AE-PCOS (2006) criteria (Lizneva et al., 2016). PCOS clinically is associated with recurrent anovulation, hyperandrogenism, metabolic and ultrasound-determined polycystic ovarian morphology. Even though PCOS aetiology is still incompletely comprehended, being a result of the interplay between genetic factors, epidemiological issues, and incessant low-grade inflammation (Azziz et al., 2016). Over 15 of the susceptibility loci associated with steroidogenesis (CYP11A1, CYP17A1), insulin signalling (INSR, IRS1), gonadotropin regulation (FSHR, LHCGR), and metabolism (PPARG) were found in genome-wide association studies (GWAS) (Day et al., 2018). These genetic variations influence follicular maturation, androgen biosynthesis and insulin resistance, which are significant causes of the clinical phenotype.

Article History

- **ISSN**: 2584-184X
- **Received:** 05 Jan 2024
- **Accepted**: 26 Feb 2024
- **Published:** 28 Feb 2024
- **MRR:**2(2) Feb. 2024:62-69

- **Peer Review Process:** Yes
- **Plagiarism Checked**: Yes

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Age, ethnicity, obesity, diet and lifestyle, and early-life exposures are all epidemiological determinants that have a significant effect on PCOS expression and severity. There is evidence of a high prevalence rate of PCOS among South Asian women and a greater number of symptoms among those with high BMI or central adiposity (Teede et al., 2018). Moreover, early life exposure to androgens, low birth weight and maternal hyperglycemia in pregnancy have also been linked with PCOS in later life, making it developmental. A large number of studies have now placed PCOS as a chronic low-grade inflammation characterised by the presence of products of inflammatory cytokine C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and distorted adipokine signalling (González, 2012). These inflammatory factors enhance insulin resistance and hyperandrogenism to form a cycle that propagates itself and results in the clinical phenotypes of PCOS, such as menstrual anomalies, hirsutism, acne, infertility, and chronic cardiometabolic risk. Considering this multifactorial aetiology, the interaction between the genetic, epidemiological, and inflammatory markers is important in clarifying the heterogeneity of the disease and forecasting and enhancing the clinical performance, as well as the diagnostic and therapeutic management. This paper seeks to combine these biological and environmental variables in a bid to assess their relationship with clinical manifestations and give a holistic view of the pathophysiology of PCOS.

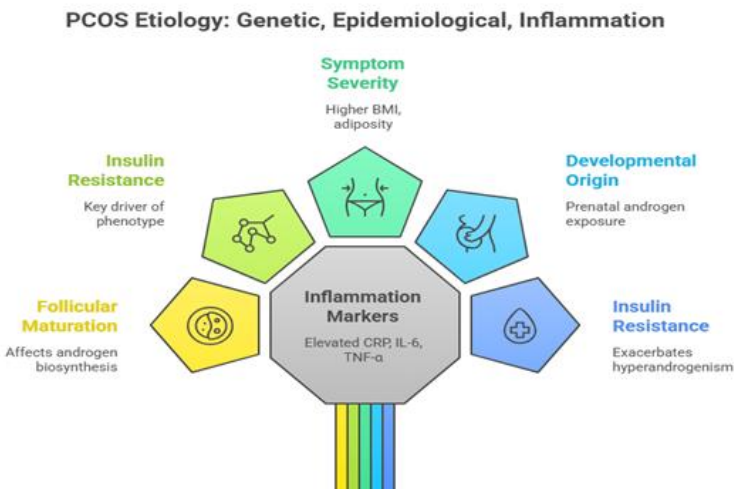


Figure 1. Aetiology: Genetic, Epidemiology, Inflammation Markers

2. Genetic Markers Associated With PCOS

Polycystic ovary syndrome (PCOS) has a strong genetic basis, familial cluster, and twin studies show that the susceptibility of PCOS is genetically determined in 40 to 70 percent (Vink et al., 2006). Genome-wide association studies (GWAS) and candidate gene studies have provided several available genetic sources of endocrine dysfunction, metabolic disruptions and ovarian dysregulation typical of PCOS.

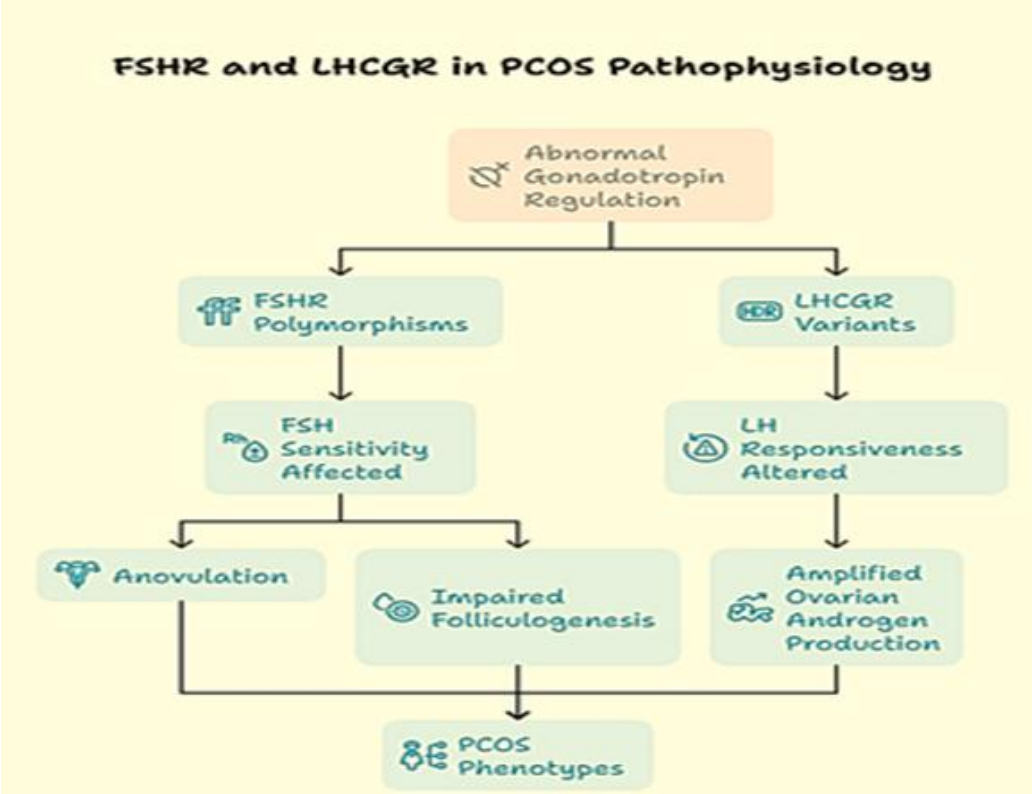


Figure 2: Fshr and Lhcgr in Pcos Pathophysiology

2.1. Genes Involved in Steroidogenesis

Steroidogenesis genes are central in the pathophysiology of PCOS since they encode crucial enzymes for ovarian steroid hormone biosynthesis. Of these, CYP11A1, CYP17A1 and CYP19A1 have been significantly involved in PCOS. Promoter polymorphisms of the CYP11A1gene, which codes for the side-chain cleavage enzyme for cholesterol, have been linked to an increase in androgen production. Also, CYP17A1 determines activities of 17-hydroxylase and 20-lyase , with results of genetic variation in this gene associated with hyperandrogenism and increased serum testosterone concentration (Diamanti-Kandarakis et al., 1999). Furthermore, CYP19A1, which encodes the enzyme (aromatase) responsible for the production of estrogen by the preovulatory follicle, exhibits variants detrimental to regular folliculogenesis. Taken together, these genetic defects lead to the overproduction of ovarian androgens, which is a key clinical characteristic of PCOS.

2.2. Gonadotropin Signalling Pathway Genes

Genes of the gonadotropin signalling pathway, in particular FSHR and LHCGR, have an essential role related to the altered relative gonadotropin regulation observed in PCOS. Polymorphisms of the FSHR gene may also modulate ovarian responsiveness to FSH, leading to abnormal folliculogenesis and chronic anovulation as observed in PCOS (Laven et al., 2003). Conversely, polymorphisms in LHCGR (luteinizing hormone/chorionic gonadotropin receptor) modulate ovarian response to luteinizing hormone with the potential of increased androgenic function by thecal cells. Genome-wide association studies (GWAS) have also substantiated and extended strong associations of these loci with a range of PCOS phenotypes, confirming their relevance to both disease predisposition and clinical presentation (Day et al., 2018).

2.3. Insulin Signalling and Metabolic Regulation Genes

Polycystic ovary syndrome (PCOS) is a metabolic disorder characterised by insulin resistance, and many genes in the insulin signalling pathway are known to be involved in its pathogenesis. Mutations of the INSR (insulin receptor) gene lead to decreased insulin binding and signal transduction, with the development of hyperinsulinemia, enhanced ovarian androgen production, and associated metabolic abnormalities (Mukherjee et al., 2013). Mutation in IRS-1 (insulin receptor substrate-1), specifically Gly972Arg polymorphism, has a strong relationship with insulin resistance, compensatory hyperinsulinemia and ovulatory disturbances in PCOS women (Dunaif et al., 1995). PPARG, a central gene involved in adipocyte differentiation and glucose metabolism, has also been investigated extensively in PCOS. The Pro12Ala variant of PPARG is related to increased insulin sensitivity and commonly presents with less severe clinical and metabolic characteristics of PCOS (DeUgarte et al., 2005).

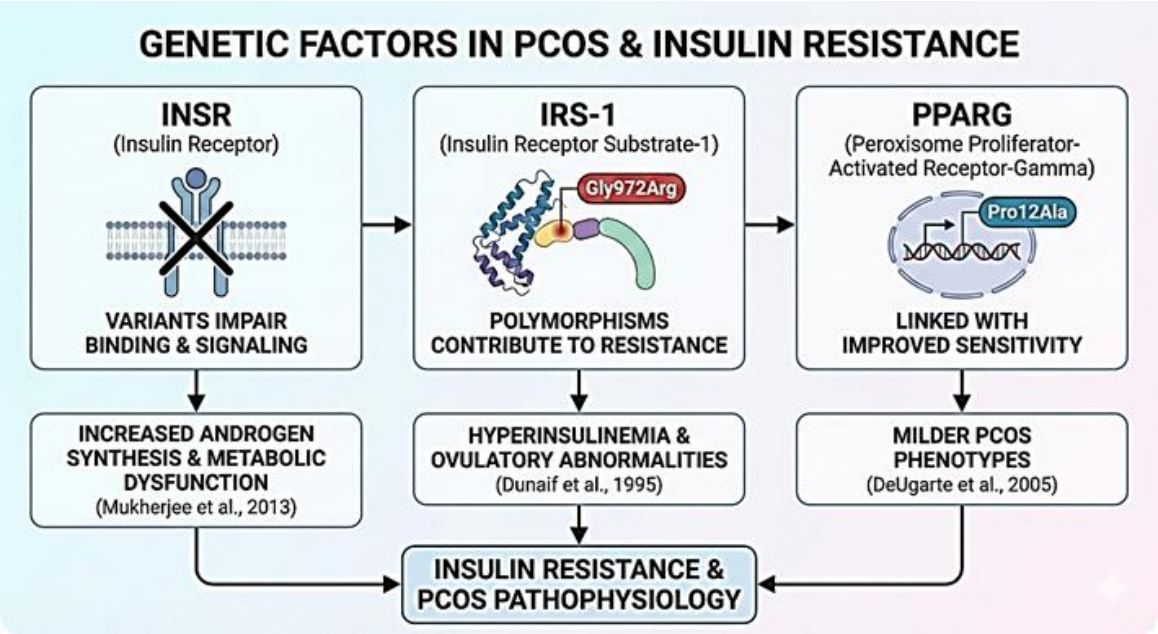


Figure :3. Genetic factors in PCOS and insulin resistance

2.4. Genes of Inflammatory and Immune-Related.

Chronic low-grade inflammation is a recognised feature of Polycystic Ovary Syndrome (PCOS), and genetic variations in Inflammatory cytokines such as TNF-α and IL-6 contribute to this process. Polymorphisms in the promoter region of the TNF-α gene enhance cytokine expression and have been associated

with increased insulin resistance and hyperandrogenism in women with PCOS (San Millan et al., 2004). Similarly, variants in the IL-6 gene are linked to elevated circulating IL-6 levels, which can exacerbate metabolic disturbances and negatively influence reproductive function. Together, these genetic factors highlight the close connection between inflammation and endocrine dysfunction in the pathogenesis of PCOS.

2.5. Newly Identified GWAS Loci

The recent high-scale GWAS have found over 15 loci to be linked to PCOS as follows:

- DENND1A- plays a role in the biosynthesis of androgens and the malfunction of granulosa cells.
- THADA- associated with energy metabolism and apoptosis pathways.
- TOX3-follicle ovarian association.
- YAP1- controls the growth and development of the ovarian cells and the follicles.

All these loci describe marked differences in the PCOS risk and phenotype expression (Day et al., 2018).

3. Epidemiological Determinants

Polycystic Ovary Syndrome (PCOS) exhibits high epidemiological variability due to the impact of demographic, lifestyle, environmental and childhood determinants. These determinants determine the occurrence and phenotypic manifestations of PCOS in populations. Following these trends is critical to discover vulnerable populations and shaping prevention and control measures.

3.1. Age and Reproductive Stage

PCOS is primarily known to be diagnosed in women of reproductive age, where the onset of symptoms can be as early as adolescence. Studies indicate that menstrual irregularity, acne, and hyperandrogenism become more noticeable in their teenage years; at the same time, the metabolic issues (such as insulin resistance and dyslipidemia) become more evident with age (Teede et al., 2018). The difference in the manifestation of symptoms throughout the lifespan makes it difficult to diagnose it uniformly.

3.2. Ethnicity and Geographic Variation

The prevalence of PCOS has great ethnic variations:

- South Asian women are more prevalent and with more severe metabolic characteristics such as insulin resistance, central obesity (Wijeyaratne et al., 2011).
- East Asian women have less severe hyperandrogenic symptoms and increased ovulatory dysfunction (Chen et al., 2019).
- Hispanic and Middle Eastern environments depict higher metabolic syndrome rates, which indicate a stronger metabolic phenotype.

These ethnic variations point to the impact of genetic-environment interactions and cultural determinants, including diet and lifestyle.

3.3. Obesity and Lifestyle Factors

One of the epidemiological determinants of PCOS severity is obesity. PCOS women are overweight and obese (approximately 50-70% of the population is overweight), and hyperinsulinemia, hyperandrogenism, and anovulatory cycles are strongly correlated with increased BMI (Lim et al., 2019). Another aggravating factor is a sedentary lifestyle, high-glycemic diets and low physical activity, which increase metabolic and reproductive abnormalities. Gain of weight, especially visceral adiposity, not only worsens the already present symptoms of PCOS but can also precipitate the development of PCOS in the patient who is genetically inclined.

3.4. Family History and Hereditary Risk

There is a high familial aggregation shown by PCOS. Women who have a first-degree family member who has PCOS are at a higher risk of getting the disorder at 2-5 times (Azziz et al., 2016). The presence of a family history of type 2 diabetes, obesity, or metabolic syndrome is also a predisposing factor as a result of common genetic and environmental factors.

3.5. Early-Life Exposures

Increasing attention has been focused on developmental causes of PCOS. There are several prenatal and perinatal variables that were linked to elevated risks of PCOS:

- Fetuses that are exposed to prenatal androgens develop their reproductive axis.
- Gestational diabetes mellitus (GDM) raises the risk of androgens and metabolism in the offspring..
- Low birth weight, preterm birth. Clinical characteristics of disturbed metabolic programming, in addition to postpartum symptoms of PCOS in adolescence (Ibanez et al., 2017).

These results confirm the theory that environmental exposures at sensitive stages may predispose people to PCOS in adulthood.

3.6. Environmental and Endocrine-Disrupting Chemicals (EDCs)

Metabolic dysfunction and disturbed steroidogenesis have been associated with exposure to endocrine disruptors like bisphenol A (BPA), phthalates and pesticides. The women with PCOS have increased serum BPA that is associated with insulin resistance and androgen excess (Kandaraki et al., 2011). Even though the issue of causality is being studied, the EDCs are becoming essential environmental modifiers.

3.7. Socioeconomic Factors

The socioeconomic status (SES) determines lifestyle habits, eating patterns, access to medical care, and stressful conditions-all of which manipulate the risk of PCOS and the severity of the symptoms. The women with low SES backgrounds tend to have elevated obesity rates, slower diagnosis, and consequently more problems with metabolism (Dokras et al., 2017).

4. Inflammatory Markers in PCOS

Polycystic Ovary Syndrome (PCOS) is being discussed as a symptomatic low-grade inflammatory syndrome prone to chronic production of the proinflammatory systems, oxidative stress, as well as immune dysfunction. Female victims of PCOS have high concentrations of inflammatory biomarkers regardless of obesity, an indication of inherent inflammation in the pathophysiology of the syndrome (González et al., 2020).

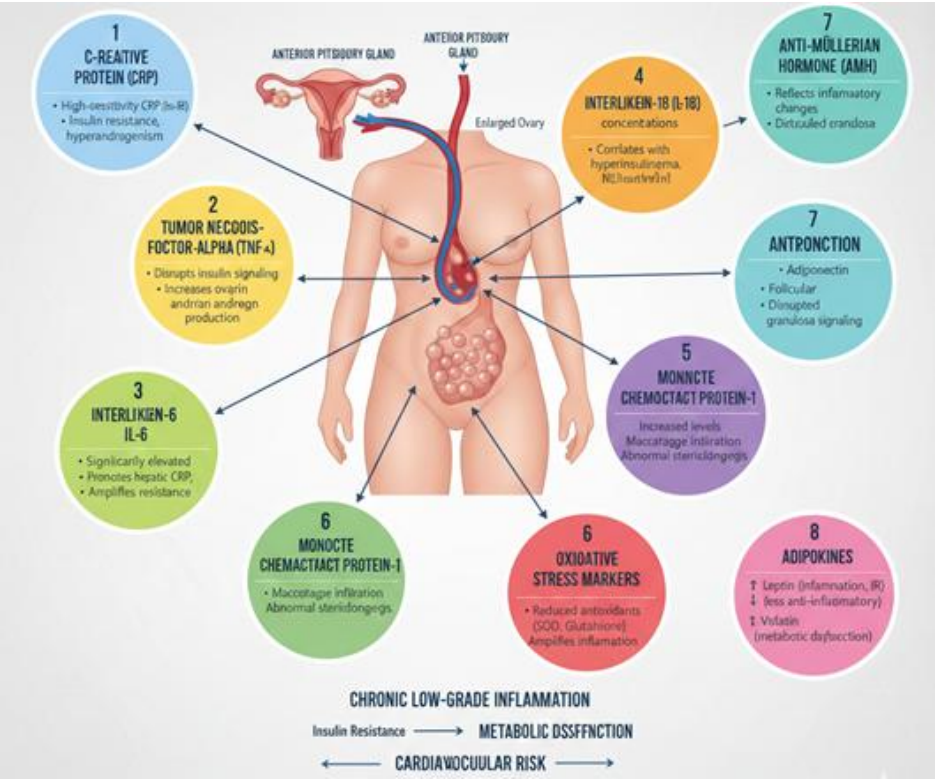


Figure 4: Inflammatory markers in PCOS

4.1. C-Reactive Protein (CRP)

Another indicator of low-grade inflammation is that hs-CRP is consistently raised in PCOS. Hs-CRP is highly associated with insulin resistance, hyperandrogenism, dysfunctional endothelium, and cardiometabolic risk (Kelly et al., 2019). The hs-CRP levels are higher even in normal-weight patients with PCOS, which supports an inflammatory condition and not adiposity.

4.2. Tumour Necrosis Factor-Alpha (TNF-α)

TNF- α is an adipocyte- and immune-cell-produced factor involved in the disturbance of insulin signalling. Women experiencing PCOS have shown that their TNF-alpha levels are elevated and are associated with insulin resistance, as well as the upsurge of ovarian androgen production as a result of CYP17A1 activity stimulation (Repaci et al., 2011). TNF- α also augments the anovulatory condition by reducing the granulosa cell performance.

4.3. Interleukin-6 (IL-6)

One key cytokine associated with metabolic inflammation is IL-6. The researches indicate quite high levels of IL-6 in patients with PCOS, especially in cases of obesity or metabolic patients. IL-6 stimulates liver production of CRP and the increase of insulin resistance through a decrease in insulin receptor signalling (Escobar-Morreale, 2018).

4.4. Interleukin-18 (IL-18)

IL-18 is linked to long-term inflammation, endothelial dysfunction and cardiovascular risk. High levels of IL-18 in PCOS patients are related to hyperinsulinemia and visceral adiposity (Samy et al., 2019). The activation of NLRP3

Inflammasomes in transcription with IL-18 may play a role in the ovarian malfunction.

4.5. Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1 mediates the action of monocyte recruitment to inflammatory regions. Higher levels of MCP-1 in PCOS mean that it increases the infiltration of macrophages in adipose tissue, a process that fosters inflammation at the local and systemic levels (Duleba & Dokras, 2019). There is also an abnormal steroidogenesis and follicular arrest associated with MCP-1.

4.6. Oxidative Stress Markers

Oxidative stress is elevated in women diagnosed with PCOS, as levels of malondialdehyde (MDA) increased and the levels of antioxidants, such as superoxide dismutase and glutathione, were low (Victor et al., 2019). The oxidative stress enhances the inflammation and leads to the endothelial malfunction, infertility, as well as metabolic issues.

4.7. Anti-Müllerian Hormone (AMH) as an Inflammatory Indicator

Even though AMH has traditionally been used as an indicator of ovarian reserve, recent findings indicate AMH to be a reflection of inflammatory changes within the ovarian microenvironment based on follicular excess and disturbed granulosa cell signalling (Pigny et al., 2016).

4.8. Role of Adipokines

Adipokines, such as leptin, adiponectin, resistin, and visfatin, are involved in the processes of chronic inflammation in PCOS.

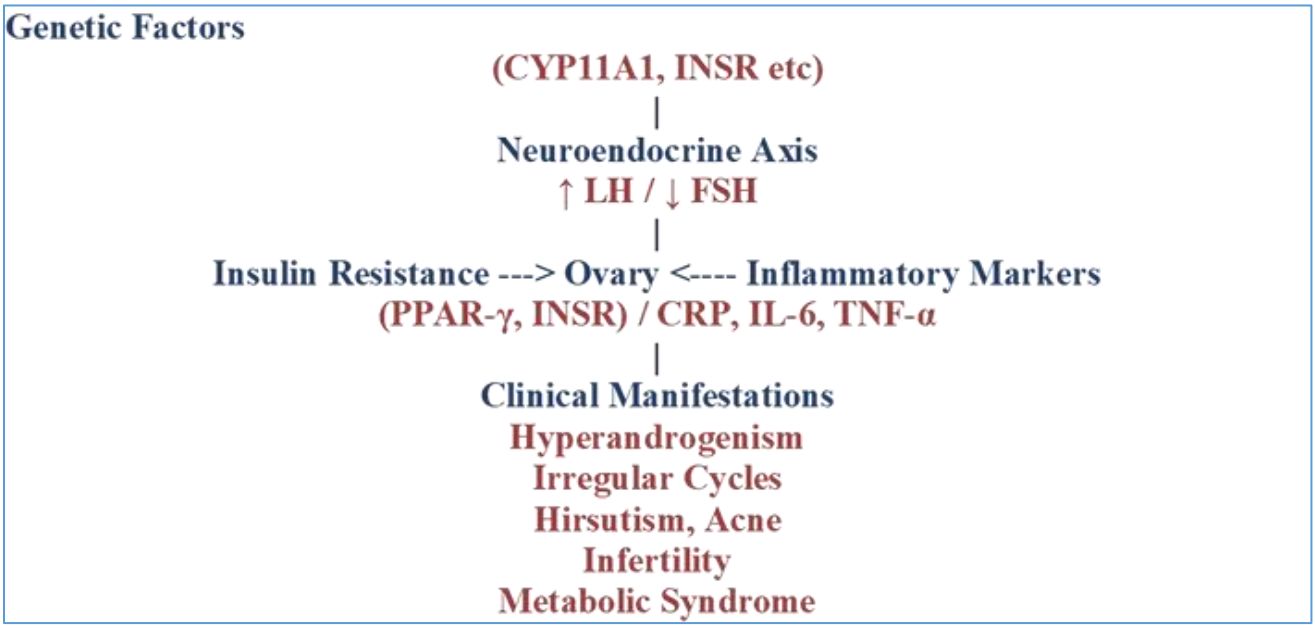
- The leptin level increases, and it encourages inflammation and insulin resistance.
- The levels of adiponectin are low, and the anti-inflammatory effect is minimised.
- Visfatin and resistin are elevated, which adds to the malfunction of the metabolism (Li et al., 2020).

5. Clinical Implications

The pathophysiological factors that lead to PCOS include:

- Insulin resistance
- Hyperandrogenism
- Anovulation
- Cardiometabolic complications
- Endothelial dysfunction
- Infertility

The anti-inflammatory interventions, including lifestyle change, vitamin D, omega-3, metformin, and inositols, demonstrate some potential to reduce the inflammatory medications and enhance metabolic and reproductive functions.



6. DISCUSSION

The genetic, epidemiological and inflammatory dimensions of PCOS findings bring into light the multifactorial characteristic of the disorder that calls for the consonant integration of the biological framework in explaining clinical heterogeneity. This argument is a synthesis of evidence that demonstrates the mechanism of genetic predisposition, environmental exposures, and chronic low-grade inflammation as they interrelate to generate the entire spectrum of metabolic and reproductive manifestations seen in PCOS.

6.1. Playing Genetic Susceptibility and Hormonal Dysregulation.

DENND1A, FSHR, LHCGR, THADA, and INSR are genetic markers that have repeatedly been associated with major PCOS phenotypes, hyperandrogenism, anovulation, and resistance to insulin (McAllister et al., 2014; Day et al., 2018). Alterations in these genes disrupt gonadotropin and ovarian steroidogenesis, which are some of the factors leading to follicular arrest and the upsurge in androgens. Nevertheless, genetic predisposition does not justify the differences in populations entirely, and it is also implied that the interaction of genes and the environment is at the heart of PCOS pathogenesis. To use the case of INSR variants as an example, being exposed to these variants may pre-program people to be insulin resistant, but the magnitude of such metabolic derangements is enhanced through obesity, a sedentary lifestyle, and high-glycemic diets (Goodarzi et al., 2011). In this way, the genetic risk produces a background vulnerability which is influenced by epidemiological factors.

6.2. Epidemiological Factors Modulating Clinical Severity

Obesity, sedentary lifestyle, urbanisation, dieting patterns, and premature initiation of menstruation are epidemiological determinants that play an important role in the expression of PCOS symptoms (Azziz et al., 2016). Indeed, obesity, e.g., worsens insulin resistance and hyperandrogenism, raising the risk of ovulatory dysfunction, menstrual cycle problems, and cardiometabolic issues. Geographical variability is also contributing to this. In South Asian populations, it was noted to have a higher prevalence rate, probably because the area is genetically clustered as well as has a high level of visceral obesity and insulin resistance (Kumari et al., 2018). Moreover, hormonal imbalance is caused by psychological stress and endocrine-disturbing chemicals, which further aggravate the severity of the symptoms.

6.3. Central Pathophysiological Mechanism Inflammation.

PCOS is highly likely to be viewed as a chronic inflammatory pathology that is independent of body mass index. The presence of elevated levels of inflammatory markers, including hs-CRP, IL-6, TNF-alpha, MCP-1, and IL-18, proves the persistent low-grade systemic inflammation (Gonzaalez et al., 2020; Escobar-Morreale, 2018). This inflammatory condition has direct pathways with insulin resistance via the lack of insulin receptor signalling and interests in inducing oxidative stress. Hyperinsulinemia, in its turn, triggers ovarian theca cells to excessively produce androgens and leads to a vicious circle in which the two disrupted processes, metabolic and reproductive, are perpetuated. There is also the impact of inflammation on the integrity of the microenvironment in the ovaries. The cellular malfunction of granulosa cells, excessive reactive oxygen species (ROS), and NLRP3 inflammasome activation damage the follicular development, resulting in anovulation and polycystic ovarian morphology (Samy et al., 2019). Therefore, inflammation is not an incidental consequence but a fundamental cause that can connect abnormalities of the endocrine and metabolism.

6.4 Combined Model of PCOS Pathophysiology.

After considering genetic predisposition, epidemiology and inflammation in a joint perspective, a definite interaction is perceived: Genetic variants establish a platform of the modified metabolic susceptibility and hormonal communications.

- Genetic variants establish a platform for the modified metabolic susceptibility and hormonal communications.
- Metabolic load is further modified by environmental and lifestyle components to cancer, obesity, oxidative stress and insulin sensitivity regulation.
- Chronic inflammation is a mediator that increases hormonal imbalance, excess androgen and metabolic imbalance.

The triad is used to describe the high level of clinical heterogeneity in Humboldt terms of clinical manifestations of mild ovulatory dysfunction in slim women and more dramatic profiles of obese people with metabolic syndrome-like data. It also explains how multifocus interventions (e.g., weight reduction + anti-inflammatory agents + insulin sensitisers) are beneficial in comparison to monotherapies.

6.5. Clinical Implications

Knowledge about the multi-level pathophysiology of PCOS has several significant clinical implications:

- Genetic screening of high-risk people can be used to prevent long-term complications.
- The tracking of inflammatory biomarkers can allow a more insightful understanding of risk into metabolism and a response of the treatment.
- Unique medicine strategies, which include the use of genetics, inflammatory screening, and behavior patterns, could enhance treatment outcomes.
- Also other lifestyle interventions are necessary because they regulate the level of inflammation and insulin resistance.

Besides, innovative treatments, including anti-inflammatory nutraceuticals, microbiome-specific therapy, and accurate hormone manipulation, are promising, effective, underlying cause, as opposed to symptom-only, therapy.

7. CONCLUSION

PCOS is considered a polygenic disease, which develops via multigenic predisposing, epidemiologic or inflammatory factors. Genetic advances have discovered numerous loci genes of the gonadotropin signalling, steroidogenesis, and insulin pathways (LHCGR, FSHR, DENND1A, THADA and INSR among others) that lead to a substantially increased predisposition for PCOS. These inherited predispositions

together with epidemiologic factors such as obesity, physical inactivity, urban diets early puberty and environmental endocrine disruptor exposure integrate to create a spectrum of metabolic and reproductive phenotypes. A pivotal biological target that might connect the genetic predisposition, environmental insult and clinical expression is chronic low-grade inflammation. Increased inflammatory factors, such as hs-CRP, IL-6 and TNF-α, MCP-1 and IL-18 as well as oxidative stress markers lead to insulin resistance (IR), hyperandrogenism (HA) and endothelial dysfunction affecting folliculogenesis. This situation of inflammation not only aggravates metabolic derangements but also is central in the pathogenesis of ovulation disorder and infertility.

Together, these mechanisms underscore PCOS as a systemic metabolic disorder rather than solely a reproductive condition. Understanding these interconnected pathways enables earlier diagnosis, improved risk stratification, and targeted therapeutic strategies. Interdisciplinary management addressing inflammation, insulin resistance, lifestyle modification, and genetic risk offers the greatest potential for improving long-term reproductive and metabolic outcomes. Future research should focus on longitudinal cohorts, gene environment interactions, inflammation-targeted therapies, and personalized treatment approaches to reduce long-term cardiometabolic risks associated with PCOS.

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