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DETERMINANTS OF POLYCYSTIC OVARIAN SYNDROME (PCOS): GENETIC RISK, ENVIRONMENTAL MODIFIERS AND CLINICAL IMPLICATIONS – A NARRATIVE REVIEW

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age worldwide. It is a heterogeneous condition characterised by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Although the exact aetiology remains unclear, emerging evidence suggests that PCOS results from a complex interaction between genetic susceptibility and environmental modifiers. Familial clustering and twin studies indicate a significant heritable component, while genome-wide association studies have identified several candidate genes associated with ovarian function, insulin signalling, and androgen biosynthesis. Environmental factors—including obesity, sedentary lifestyle, dietary patterns, endocrine-disrupting chemicals, and psychosocial stress—further contribute to the phenotypic expression and severity of the syndrome. These determinants not only influence reproductive health but also increase the risk of metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, infertility, and psychological distress. Understanding the multifactorial determinants of PCOS is essential for early identification, prevention strategies, and holistic management. This narrative review synthesises current evidence on genetic risk factors, environmental modifiers, and their clinical implications, with emphasis on relevance to clinical and nursing practice.

Key Words: *Polycystic ovary syndrome; Genetic risk; Environmental modifiers; Insulin resistance; Hyperandrogenism; Clinical implications; Women's health*

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age worldwide. It is estimated to affect approximately 8–13% of women globally, although prevalence varies depending on diagnostic criteria and population characteristics (World Health Organization, 2023). PCOS is characterised by a constellation of clinical features including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, as defined by the widely accepted Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group criteria (2004). Beyond reproductive dysfunction, PCOS is increasingly recognised as a complex multisystem disorder with significant metabolic, psychological, and long-term cardiovascular consequences (Azziz et al., 2016).

The pathophysiology of PCOS is multifactorial and remains incompletely understood. Emerging evidence suggests that PCOS results from a complex interaction between genetic susceptibility and environmental influences, which together contribute to hormonal imbalance, insulin resistance, and ovarian dysfunction (Dapas et al., 2020; Goodarzi et al., 2011). Familial clustering and twin studies strongly support a heritable component, with first-degree relatives demonstrating increased risk of metabolic and reproductive abnormalities (Goodarzi et al., 2011). Genome-wide association studies have identified multiple susceptibility loci associated with ovarian steroidogenesis, gonadotropin signalling, and insulin pathways, highlighting the polygenic nature of the disorder (Dapas et al., 2020).

However, genetic predisposition alone does not fully explain the heterogeneity observed in clinical presentation. Environmental modifiers—including obesity, dietary patterns, sedentary lifestyle, endocrine-disrupting chemicals, and psychosocial stress—play a crucial role in triggering or exacerbating phenotypic expression (Barrea et al., 2021; Escobar-Morreale, 2018). Obesity, in particular, acts synergistically with hyperinsulinemia to amplify hyperandrogenism and worsen reproductive dysfunction, thereby intensifying

clinical manifestations (Escobar-Morreale, 2018). Additionally, early-life exposures and epigenetic mechanisms are increasingly being explored as contributors to disease onset and intergenerational transmission risk (Dumesic et al., 2015).

The clinical implications of these determinants are substantial. Women with PCOS are at increased risk for infertility, type 2 diabetes mellitus, dyslipidaemia, hypertension, endometrial hyperplasia, and adverse pregnancy outcomes (Azziz et al., 2016; Teede et al., 2018). Furthermore, psychological comorbidities such as anxiety, depression, and reduced quality of life are highly prevalent, underscoring the need for holistic and multidisciplinary management approaches (Teede et al., 2018). Recognising the interplay between genetic risk and environmental modifiers is therefore essential for early identification, risk stratification, prevention strategies, and individualised clinical management.

Given the growing global burden of PCOS and its long-term health consequences, a comprehensive understanding of its determinants is critical. This narrative review aims to synthesise current evidence regarding genetic susceptibility, environmental contributors, and their clinical implications, with a particular emphasis on informing evidence-based practice and preventive strategies in women's health care.

GENETIC RISK FACTORS IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

Polycystic Ovarian Syndrome (PCOS) often runs in families, which suggests that genetics plays an important role in its development. Women who have a mother or sister with PCOS are more likely to develop the condition themselves (Azziz et al., 2016). Studies involving twins have also shown that genes contribute significantly to PCOS, with heritability estimates ranging from 60% to 70% (Vink et al., 2006). This means that more than half of the risk of developing PCOS may be influenced by inherited factors.

Family History and Hereditary Risk

Family studies have found that first-degree relatives of women with PCOS frequently show similar symptoms such as irregular menstruation, excess hair growth, insulin resistance, and metabolic problems (Goodarzi et al., 2011). Even male relatives may show metabolic issues such as insulin resistance or early baldness, which may reflect shared genetic traits. This pattern supports the idea that PCOS has a strong hereditary component.

Family aggregation studies consistently demonstrate that polycystic ovary syndrome (PCOS) clusters within families, supporting a strong hereditary component. First-degree female relatives of women with PCOS exhibit a significantly higher prevalence of menstrual irregularities, hyperandrogenism, insulin resistance, and polycystic ovarian morphology compared to the general population (Legro et al., 1998; Kahsar-Miller et al., 2001). Sisters of affected women have been shown to have a 20–40% increased risk of developing PCOS or related metabolic abnormalities, suggesting shared genetic susceptibility.

Twin studies further reinforce the heritable nature of PCOS. In a Dutch twin-family study, Vink et al. (2006) estimated heritability to be approximately 70%, indicating that genetic factors account for a substantial proportion of phenotypic variation. Similarly, studies conducted in different ethnic populations have replicated familial clustering patterns, suggesting that genetic risk is consistent across diverse populations (Goodarzi et al., 2011).

Importantly, hereditary risk is not limited to female relatives. Male relatives of women with PCOS have been reported to exhibit metabolic disturbances, including insulin resistance and early-onset androgenic alopecia, implying that susceptibility genes may influence broader endocrine and metabolic pathways (Legro et al., 2002). This observation supports the hypothesis that PCOS represents a systemic metabolic-genetic condition rather than a disorder confined solely to ovarian dysfunction.

Moreover, emerging research suggests that genetic predisposition may interact with intrauterine and epigenetic factors. Daughters of women with PCOS may be exposed to higher androgen levels in uterus, potentially predisposing them to future reproductive and metabolic dysfunction (Dumesic et al., 2015). Such intergenerational transmission highlights the complex interplay between inherited genetic variants and developmental programming.

While no single gene mutation has been identified as causative, the cumulative effect of multiple susceptibility loci appears to increase familial risk (Dapas et al., 2020; Day et al., 2018). Thus, family history remains one of the most important clinical indicators for early screening and preventive intervention.

Genes Related to Hormone Imbalance

PCOS is mainly characterised by increased levels of male hormones (androgens). Some genes are involved in controlling hormone production in the ovaries. Variations in these genes may lead to increased androgen production, which contributes to symptoms such as acne, hirsutism, and irregular periods (Escobar-Morreale, 2018).

Research has identified certain genes that affect how the ovaries respond to hormones such as luteinising hormone (LH) and follicle-stimulating hormone (FSH). Changes in these genes may interfere with normal ovulation and follicle development (Day et al., 2018). However, no single gene causes PCOS. Instead, many small genetic changes together increase the risk.

Genes Related to Insulin Resistance

Insulin resistance is common in women with PCOS, even in those who are not overweight. Some genes influence how the body responds to insulin. When these genes do not function normally, the body produces more insulin to compensate. High insulin levels can stimulate the ovaries to produce more androgens, worsening PCOS symptoms (Azziz et al., 2016; Dapas et al., 2020).

This shows that genetic factors affecting metabolism are closely linked to hormonal imbalance in PCOS.

Polygenic Nature of PCOS

PCOS is considered a **polygenic disorder**, meaning that many genes contribute to its development rather than one single gene mutation. Large genetic studies have identified several gene regions associated with ovarian function, hormone regulation, and metabolism (Dapas et al., 2020). However, these genetic variations only increase susceptibility—they do not guarantee that a woman will develop PCOS.

Interaction Between Genes and Environment

It is important to understand that genes alone do not cause PCOS. Environmental factors such as obesity, diet, physical inactivity, and stress can interact with genetic susceptibility and influence whether symptoms appear and how severe they become (Escobar-Morreale, 2018). Therefore, PCOS develops through a combination of inherited risk and lifestyle or environmental triggers.

ENVIRONMENTAL MODIFIERS IN POLYCYSTIC OVARIAN SYNDROME (PCOS):

Although genetic factors increase susceptibility to Polycystic Ovarian Syndrome (PCOS), environmental factors play a major role in triggering, worsening, or modifying the expression of the disorder. PCOS develops through a complex interaction between inherited risk and external influences such as obesity, diet, physical inactivity, endocrine-disrupting chemicals, stress, and early-life exposures (Escobar-Morreale, 2018; Teede et al., 2018).

Obesity and Excess Weight

Obesity is one of the most important environmental modifiers of PCOS. While PCOS can occur in lean women, excess body weight significantly worsens hormonal imbalance and metabolic dysfunction. Increased adipose tissue contributes to insulin resistance, which leads to compensatory hyperinsulinemia. High insulin levels stimulate ovarian androgen production and reduce sex hormone-binding globulin (SHBG), increasing free testosterone levels (Azziz et al., 2016).

This interaction between obesity and insulin resistance intensifies symptoms such as irregular menstruation, anovulation, hirsutism, and infertility. Moreover, obesity increases the risk of long-term complications such as type 2 diabetes mellitus, hypertension, and cardiovascular disease (Teede et al., 2018). Weight reduction of even 5–10% has been shown to improve ovulatory function and metabolic parameters in women with PCOS.

Diet and Nutritional Patterns

Dietary habits significantly influence the metabolic profile of women with PCOS. Diets high in refined carbohydrates, saturated fats, and processed foods may worsen insulin resistance and inflammation. Chronic low-grade inflammation is commonly observed in PCOS and contributes to metabolic and reproductive dysfunction (Escobar-Morreale, 2018).

Conversely, balanced diets rich in whole grains, fruits, vegetables, lean proteins, and healthy fats may improve insulin sensitivity and reduce androgen levels. Nutritional modification is therefore considered a cornerstone of PCOS management (Teede et al., 2018).

Physical Inactivity

Sedentary lifestyle is another important environmental factor. Lack of physical activity contributes to weight gain, insulin resistance, and metabolic syndrome. Regular exercise improves insulin sensitivity, supports weight management, and may restore ovulatory cycles in some women with PCOS (Azziz et al., 2016).

Lifestyle interventions combining diet and exercise are recommended as first-line therapy in the international evidence-based guidelines for PCOS (Teede et al., 2018).

Endocrine-Disrupting Chemicals (EDCs)

Exposure to environmental pollutants and endocrine-disrupting chemicals (EDCs) has been increasingly studied in relation to PCOS. Substances such as bisphenol A (BPA), phthalates, and pesticides can interfere with hormonal signalling and reproductive function. Some studies suggest that elevated BPA levels are associated with higher androgen levels and insulin resistance in women with PCOS (Barrea et al., 2021).

Although causal relationships are still under investigation, chronic exposure to environmental toxins may act as a contributing factor in genetically predisposed individuals.

Psychological Stress

Psychological stress may also modify PCOS expression. Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased cortisol production. Elevated cortisol levels may worsen insulin resistance and hormonal imbalance. Additionally, women with PCOS have higher rates of anxiety, depression, and reduced quality of life, which may further affect lifestyle behaviours and treatment adherence (Teede et al., 2018).

Stress management strategies, including counselling and psychological support, are therefore important components of comprehensive care.

Early-Life and Intrauterine Exposures

Emerging evidence suggests that environmental influences during foetal life may predispose individuals to PCOS later in adulthood. Prenatal exposure to excess androgens, maternal obesity, or gestational diabetes may alter foetal metabolic programming (Dumesic et al., 2015). These early-life exposures may increase susceptibility to insulin resistance and ovarian dysfunction through epigenetic changes.

This concept supports the theory that PCOS may originate from both genetic predisposition and early environmental programming.

CLINICAL IMPLICATIONS OF GENETIC AND ENVIRONMENTAL DETERMINANTS IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

Understanding the genetic risk and environmental modifiers of Polycystic Ovarian Syndrome (PCOS) has important clinical implications for early identification, prevention, and long-term management. As PCOS is a multifactorial disorder influenced by both hereditary and lifestyle factors, a comprehensive and multidisciplinary approach to care is essential (Azziz et al., 2016; Teede et al., 2018).

Early Identification and Risk Screening

Women with a family history of PCOS are at increased risk of developing reproductive and metabolic abnormalities. Therefore, clinicians should take a detailed family history when assessing adolescents and young women presenting with menstrual irregularities, acne, hirsutism, or weight gain (Goodarzi et al., 2011).

Early screening for insulin resistance, impaired glucose tolerance, dyslipidaemia, and obesity is recommended, particularly in high-risk individuals. According to the international evidence-based guideline developed by the International PCOS Network (2018), metabolic risk assessment should be part of routine PCOS management.

Early detection allows timely lifestyle interventions, which may reduce the severity of symptoms and prevent long-term complications.

Reproductive Health Implications

PCOS is one of the leading causes of anovulatory infertility. Hormonal imbalance and disrupted follicular development result in irregular ovulation or absence of ovulation. Early recognition of PCOS in reproductive-aged women allows appropriate fertility counselling and treatment options such as ovulation induction therapy (Azziz et al., 2016).

In addition, women with PCOS are at increased risk of pregnancy complications, including gestational diabetes, hypertensive disorders, and preterm birth (Teede et al., 2018). Preconception counselling and metabolic optimisation are therefore important components of care.

Metabolic and Cardiovascular Risks

Genetic predisposition combined with environmental factors such as obesity and sedentary lifestyle increases the risk of long-term metabolic complications. Women with PCOS have a higher prevalence of:

- Type 2 diabetes mellitus
- Dyslipidaemia
- Hypertension
- Metabolic syndrome

Insulin resistance plays a central role in these complications (Escobar-Morreale, 2018). Regular monitoring of blood glucose levels, lipid profiles, blood pressure, and body mass index (BMI) is therefore recommended.

Early lifestyle modification, including diet and physical activity, is considered first-line therapy and has been shown to improve both reproductive and metabolic outcomes (Teede et al., 2018).

Psychological and Quality-of-Life Impact

PCOS is associated with increased rates of anxiety, depression, body image concerns, and reduced quality of life. Symptoms such as hirsutism, acne, infertility, and weight gain can significantly affect emotional well-being (Azziz et al., 2016).

Routine mental health screening and referral for psychological support should be integrated into clinical management. Holistic care addressing both physical and psychological aspects improves overall patient outcomes.

Implications for Nursing Practice

From a nursing perspective, understanding the determinants of PCOS supports:

- Early health education in adolescents
- Counselling on weight management and healthy lifestyle
- Monitoring for metabolic risk factors
- Providing emotional support and patient-centred care
- Promoting adherence to treatment plans

Nurses play a key role in community awareness, lifestyle counselling, and long-term follow-up care. Since environmental modifiers are largely preventable, health promotion strategies can significantly reduce disease burden.

Personalized and Preventive Approach

Although genetic testing is not routinely recommended due to the polygenic nature of PCOS, awareness of hereditary risk allows clinicians to adopt a preventive approach. Women with strong family history may benefit from early lifestyle interventions and regular metabolic screening.

Future research may lead to personalised medicine strategies based on genetic risk profiling. However, at present, integrated management focusing on modifiable environmental factors remains the most effective clinical strategy.

CONCLUSION

Polycystic ovary syndrome is a complex and heterogeneous disorder arising from the interaction between genetic susceptibility and environmental modifiers. While genetic factors contribute significantly to disease vulnerability, lifestyle and environmental influences determine phenotypic expression and severity. The interplay between insulin resistance, hyperandrogenism, obesity, and environmental exposures underscores the multifactorial nature of PCOS. Clinically, this condition extends beyond reproductive dysfunction to include substantial metabolic and psychological consequences. Therefore, early identification of at-risk individuals, comprehensive metabolic screening, lifestyle intervention, and multidisciplinary care are essential. Future research should focus on gene–environment interactions and personalised management strategies to optimise patient outcomes. A holistic, evidence-based approach is crucial for improving the long-term health and quality of life of women with PCOS.

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