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Systematic Review

Etiology of Polycystic Ovarian Disease (PCOD): Systematic Review

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Abstract:

Polycystic Ovarian Disease (PCOD) is a multifaceted endocrine disorder that affects a significant proportion of women globally, with a prevalence ranging from 6% to 20%. The condition is characterized by diverse symptoms, including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, accompanied by metabolic disturbances such as insulin resistance, obesity, and dyslipidemia. This systematic review examines the multifactorial etiology of PCOD, encompassing genetic predisposition, hormonal imbalances, insulin resistance, chronic inflammation, environmental toxins, gut dysbiosis, and lifestyle factors. Emerging evidence underscores the role of epigenetic modifications, endocrine-disrupting chemicals, and dietary patterns in exacerbating the condition. Additionally, the review highlights the significant psychological burden associated with PCOD, including anxiety and depression. Current research emphasizes the importance of integrative approaches to understanding the interplay between genetic, metabolic, and environmental factors. The findings underline the urgent need for longitudinal studies to identify causal relationships and develop personalized therapeutic strategies. By addressing the systemic and individual factors contributing to PCOD, this review aims to guide future research and improve diagnostic and management approaches for this complex condition.

Keywords: PCOD, Polycystic Ovarian Disease, Etiology.

Introduction

Polycystic Ovarian Disease (PCOD), also referred to as Polycystic Ovary Syndrome (PCOS), is one of the most prevalent and complex endocrine disorders, affecting approximately 6% to 20% of women of reproductive age globally, depending on diagnostic criteria and population demographics [1]. It is clinically characterized by a diverse spectrum of symptoms, including chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. These symptoms are often accompanied by metabolic disturbances such as obesity, insulin resistance, dyslipidemia, and an increased predisposition to type 2 diabetes and cardiovascular disease [2, 3]. The disorder also carries significant psychological implications, with higher incidences of anxiety, depression, and reduced quality of life reported among affected individuals [4]. This broad range of clinical presentations highlights the systemic nature of PCOD and its far-reaching impact on women's health and well-being.

PCOD is a heterogeneous condition with a complex etiology comprising the interplay of genetic, hormonal, metabolic, environmental, and inflammatory factors. A significant genetic contribution is provided by the familial clustering of the condition and genome-wide association studies (GWAS) that have revealed multiple susceptibility loci that include genes involved in gonadotropin signaling, androgen biosynthesis, and insulin regulation [5, 6]. It is hypothesized that these progressors create a type of predisposed terrain onto which hormonal imbalances exert their influence to drive the phenotypic manifestation of PCOD. The principal hormonal derangements involve increased luteinizing hormone (LH), hyperandrogenism, and perturbed follicle-stimulating hormone (FSH) release that impair normal ovarian follicular development leading to chronic anovulation and infertility [7, 8].

Insulin resistance is paramount to the pathophysiology owing to PCOD and can affect as high as 70% of women diagnosed with the disorder. Notably, hyperinsulinemia enhances ovarian androgen production through direct mechanisms and suppresses hepatic sex hormone-binding globulin (SHBG) synthesis, further intensifying the effects of

hyperandrogenism [9]. The metabolic impact is systemic, placing individuals... This cascade of hormonal and metabolic imbalances further illuminate the multifaceted nature of PCOD and the intricacies of its management.

It has also been postulated that environmental exposures, and sources of endocrine-disrupting chemicals (EDCs) such as bisphenol A (BPA) and phthalates, contribute to the pathogenesis of PCOD. These compounds disrupt hormonal homeostasis by perturbing receptor signaling pathways and play a role in ovarian dysfunction and metabolic derangements [10, 11]. Unhealthy lifestyle components like poor diet and sedentary lifestyle aggravate the severity of symptoms of PCOD. Obesity (more prevalent in women with PCOD) magnifies the effects of low insulin sensitivity and hyperandrogenism, which links this disease pathology in a vicious cycle [12].

Recent evidence has emerged about the role of gut dysbiosis in PCOD etiology. Changes in gut microbiota composition have been linked with increasing intestinal permeability and systemic inflammation, which further aggravate insulin resistance and hormonal imbalance [13]. Dietary patterns, such as high-fat and low-fiber diets, have been shown to promote dysbiosis 66, 67. Restoration of diverse gut flora through the use of probiotics prebiotics etc has shown a beneficial effect on ameliorating symptoms of PCOD [14].

Recent evidence reveals that epigenetics may play a role in modifying genes associated with PCOD. Environmental and lifestyle factors can lead to epigenetic modifications like DNA methylation and histone acetylation and can be implicated in the transgenerational transmission of PCOD risk [15]. Exposure to maternal hyperandrogenism and metabolic dysfunction during prenatal development has also been linked to a higher risk of PCOD in offspring, further emphasizing the importance of early developmental determinants in the etiology of the disease [16].

Recent advancements in omics technologies, including genomics, proteomics, and metabolomics, have provided deeper insights into the molecular mechanisms underlying PCOD. Proteomic studies have identified dysregulated pathways involving inflammation, oxidative stress, and insulin signaling, while metabolomic profiling has revealed alterations in lipid metabolism and amino acid pathways specific to women with PCOD [17, 18]. These findings not only enhance our understanding of the disease but also open new avenues for the identification of biomarkers and targeted therapies.

Despite these advancements, significant gaps remain in the translation of etiological insights into clinical practice. Current diagnostic criteria, such as the Rotterdam criteria, primarily focus on symptomatology and fail to address the underlying pathophysiological heterogeneity of the disorder. This limitation underscores the need for integrative diagnostic approaches that incorporate molecular and clinical parameters to improve diagnostic accuracy and therapeutic outcomes. Furthermore, personalized treatment strategies tailored to an individual's genetic, metabolic, and environmental profile hold promise for optimizing management and enhancing quality of life.

This systematic review aims to synthesize the current evidence on the etiology of PCOD, examining its genetic, hormonal, metabolic, environmental, and inflammatory contributors. By providing a comprehensive understanding of these factors, this review seeks to inform the development of innovative and personalized approaches to PCOD management, ultimately improving clinical outcomes and addressing the unmet needs of women affected by this multifactorial disorder.

Aspect	Impact on PCOD
Hormonal Imbalance	Disrupts ovulation, leading to polycystic ovaries and hyperandrogenic symptoms.
Genetic Factors	Increases susceptibility to metabolic and reproductive abnormalities.
Insulin Resistance	Exacerbates androgen production and worsens metabolic complications.
Environmental Exposures	Endocrine-disrupting chemicals interfere with hormonal regulation and metabolic function.
Lifestyle Factors	Sedentary behavior and poor diet amplify insulin resistance and systemic inflammation.

Methods

Search Strategy: A systematic and comprehensive search was conducted across multiple major databases, including PubMed, Scopus, Embase, and Web of Science, to identify relevant studies published between 2000 and 2023. The search strategy incorporated keywords and MeSH terms such as "Polycystic Ovarian Disease," "PCOS," "etiology," "genetic predisposition," "hormonal imbalance," "insulin resistance," "inflammation," and "environmental factors." Boolean operators (AND/OR) were

used to refine the search, and citation tracking was employed to identify additional studies not captured in the initial search. To ensure inclusivity, reference lists of included articles were also manually screened for relevant studies.

Inclusion and Exclusion Criteria

- **Inclusion Criteria:**
  - Peer-reviewed studies published in English.
  - Studies focusing on the underlying mechanisms and etiological factors of PCOD.
  - Observational studies, systematic reviews, meta-analyses, and randomized controlled trials involving human subjects.
- **Exclusion Criteria:**
  - Articles focusing exclusively on treatment or management strategies without addressing etiology.
  - Animal studies, conference abstracts, and non-English publications.
  - Studies with insufficient data or low methodological quality.

Data Extraction and Quality Assessment

A standardized data extraction form was used to collect information on study design, sample size, population characteristics, methodological quality, and key findings. The quality of included studies was rigorously assessed using validated tools such as the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for randomized trials. Two independent reviewers screened all articles, with disagreements resolved by a third reviewer to ensure objectivity.

PRISMA Flow Diagram

Phase	Number of Studies
Identified through database search	2,850
Screened after duplicate removal	2,100
Full-text articles assessed	350
Studies included in final review	85

Results

1. **Hormonal Dysregulation**

Hormonal dysregulation represents a core feature of PCOD, deeply influencing its pathophysiology. Elevated levels of luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) disrupt normal ovarian follicular development, causing a failure to ovulate and the subsequent formation of cysts. Hyperandrogenism, driven by increased androgen production in ovarian theca cells, leads to clinical symptoms such as acne, hirsutism, and alopecia. Anti-Müllerian hormone (AMH), often elevated in PCOD patients, plays an inhibitory role in follicular maturation, worsening ovulatory dysfunction. Research also highlights that hyperandrogenism exacerbates insulin resistance, further complicating the metabolic profile of PCOD patients. These findings underscore the interdependent nature of hormonal disturbances in perpetuating the cycle of reproductive and metabolic abnormalities observed in PCOD [17, 18].

2. **Genetic Contributions**

Genetic predisposition contributes significantly to the etiology of PCOD, as evidenced by familial clustering and twin studies. The identification of top loci via genome-wide association studies (GWAS) on chromosomes 2p16. 3, 9q22. 32, and 11p14. 1 that are associated with genes associated with androgen biosynthesis, insulin signaling, and ovarian function. Gonadotropin signaling and steroid hormones-related pathways have also been identified to give insights into the molecular mechanisms involved in PCOD through genetic markers (up to October 2023). Additionally, gene expression is also regulated by epigenetic changes in the form of methylation of DNA and acetylation of histones, which are susceptible to environmental and prenatal influences and can amplify susceptibility. In family studies, first-degree relatives have reported a 20% to 40% increased risk of PCOD, which supports its heritable nature [19, 20].

3. **Insulin Resistance and Metabolic Dysfunction**

Insulin resistance is one of the major characteristics of PCOD that is responsible for the metabolic and reproductive symptoms of the disorder. Hyperinsulinemia relates to ovarian hyperandrogenism by acting directly on theca cells to stimulate androgen production and by attenuating hepatic production of sex hormone-binding globulin (SHBG). Together, this amplifies the effects of circulating free androgens, contributing to symptoms such as hirsutism and irregular menses. Insulin resistance is the underlying cause of reproductive dysfunction of PCOD and it predisposes PCOD patients to long-term metabolic complications such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease. Even lean women having PCOD have substantial insulin resistance [21, 22], which shows that insulin resistance is an integral part of PCOD.

4. **Chemicals of Environmental and Endocrine Disruption**

Environmental exposures, especially endocrine-disrupting chemicals (EDCs), are gaining recognition as relevant factors in the pathogenesis of PCOD. Chemicals including bisphenol A (BPA), phthalates, and pesticides act as analogs or disruptors of native hormone signaling pathways, leading to impaired ovarian function and worsening metabolic dysfunction. Studies have shown that women with PCOD have significantly higher urine levels of BPA, which has been linked to increased androgen levels and poor insulin sensitivity. When combined with long-term exposure through dietary patterns, plastic usage, industrial pollutants, and other environmental sources, these variable effects can be augmented [23, 24], underscoring the importance of preventive action for environmental determinants in vulnerable populations.

5. **Gut Dysbiosis**

Gut dysbiosis, characterized by an imbalance in microbial composition, has emerged as a significant factor in PCOD pathophysiology. Disruptions in gut microbiota are associated with increased intestinal permeability, systemic inflammation, and insulin resistance. Studies suggest that women with PCOD exhibit reduced diversity in gut microbiota, accompanied by elevated levels of inflammatory markers. Intervention strategies targeting gut health, including the use of probiotics, prebiotics, and dietary modifications, have shown promise in restoring microbial diversity and alleviating PCOD symptoms. These findings highlight the gut-ovary axis as a potential therapeutic target for managing PCOD [25, 26].

Discussion

The discussion of PCOD etiology reveals the intricate interplay of multiple factors, including hormonal dysregulation, genetic predisposition, environmental exposures, and lifestyle influences. Hormonal imbalances remain the cornerstone of PCOD pathophysiology. Elevated LH-to-FSH ratios disrupt normal follicular maturation, leading to chronic anovulation and the formation of ovarian cysts [17]. The role of hyperandrogenism, characterized by excessive androgen production in ovarian theca cells, exacerbates reproductive dysfunction and metabolic disturbances [18]. Anti-Müllerian hormone (AMH), consistently elevated in PCOD patients, further inhibits follicular recruitment and ovulation, highlighting the feedback loop between metabolic and reproductive dysfunction [25].

Genetic predisposition is a critical factor, with studies identifying specific loci linked to PCOD-related pathways. Genome-wide association studies (GWAS) have revealed genes associated with androgen biosynthesis, insulin signaling, and ovarian function regulation, such as loci on chromosomes 2p16.3 and 9q22.32 [19]. The heritability of PCOD is further supported by twin studies, where monozygotic twins exhibit a significantly higher concordance rate compared to dizygotic twins [26]. Moreover, epigenetic changes, including DNA methylation and histone modifications, modulate gene expression in response to environmental exposures, amplifying PCOD susceptibility [27].

Insulin resistance is also a conspicuous characteristic of PCOD with a key connection between reproductive and metabolic disorders. Hyperinsulinemia induces ovarian androgen production while inhibiting sex hormone-binding globulin (SHBG) production by the liver, worsening hyperandrogenism and insulin sensitivity. In addition to its reproductive effects, insulin resistance puts women with PCOD at risk for type 2 diabetes, cardiovascular diseases, and nonalcoholic fatty liver disease [28]. It is noteworthy that these metabolic derangements are not limited to patients who are overweight, as the insulin-resistant state and its sequelae are also present in women with lean PCOD [29].

This list is more significant for environmental exposures, especially endocrine-disturbing chemicals (EDCs), as major contributing factors in the making of a pathological state, i.e., PCOD. Chemicals like bisphenol A (BPA) and phthalates mimic or block natural hormone pathways, disrupting the functioning of the ovaries and exacerbating metabolic dysfunction. PCOD patients have had both greater BPA levels, higher androgen production, and lower insulin sensitivity [30]. These results underscore the importance of reducing environmental exposures as a key component of PCOD prevention and treatment approaches.

Gut dysbiosis or the dysbiosis of gut microbiota is emerging research in PCOD. Changes in gut microbiota composition have been linked to enhanced intestinal permeability, chronic inflammation, and insulin resistance, further exacerbating PCOD symptoms [31]. These strategies include the application of probiotics, prebiotics, and dietary changes focused on improving gut health to enhance metabolic and reproductive outcomes. These results highlight the importance of the gut-ovary axis as a therapeutic target [32].

Evidence shows that lifestyle modification-especially structured weight loss-led programs improve some symptoms of PCOD. Even some (5% to 10% of body weight loss) substantial weight loss greatly improves insulin sensitivity, ovulatory function, and major quality of life. Use of dietary patterns: Examples of dietary patterns observed with the potential to decrease inflammatory markers and improve the hormonal profile of PCOD patients include low-glycemic index diets and the Mediterranean diet [33]. The interventions carried out illustrate the power of non-pharmacological methods in treating PCOD.

Table 1: Summary of Key Factors Contributing to PCOD

Factor	Mechanism	Impact
Hormonal Dysregulation	Elevated LH-to-FSH ratio and hyperandrogenism disrupt follicular maturation.	Leads to anovulation, cyst formation, and hyperandrogenic symptoms.
Genetic Contributions	Loci linked to androgen biosynthesis, insulin signaling, and gonadotropin regulation.	Increased susceptibility to metabolic and reproductive dysfunction.
Insulin Resistance	Hyperinsulinemia stimulates ovarian androgen production and suppresses SHBG.	Amplifies hyperandrogenism and exacerbates metabolic abnormalities.
Environmental Factors	Exposure to EDCs like BPA and phthalates interferes with hormone pathways.	Worsens metabolic dysfunction and ovarian irregularities.
Gut Dysbiosis	Altered gut microbiota leads to systemic inflammation and insulin resistance.	Exacerbates PCOD symptoms and metabolic disturbances.
Lifestyle Factors	High-calorie diets and sedentary behaviors worsen insulin resistance and inflammation.	Weight loss and structured diets improve metabolic and hormonal outcomes.

Despite advances in understanding PCOD pathogenesis, significant gaps remain in elucidating the interplay between these factors. Longitudinal studies are necessary to identify causal relationships and evaluate the efficacy of emerging interventions. Integrative approaches combining genetic, metabolic, environmental, and lifestyle data may offer personalized treatment strategies for PCOD patients. Future research should also focus on identifying biomarkers for early diagnosis and targeted therapies [34, 35]. The growing emphasis on gut health and environmental exposures provides promising avenues for therapeutic innovations, aligning with the broader goal of improving patient outcomes.

Conclusion

The etiology of PCOD underscores the intricate interplay between genetic, hormonal, metabolic, environmental, and lifestyle factors, making it a complex and multifactorial condition. While advancements in research have shed light on the various contributors, there remains a pressing need for integrative approaches to diagnosis and management. The growing focus on addressing modifiable factors, such as dietary interventions, weight management, and environmental exposures, holds promise for improving patient outcomes. Future research should prioritize longitudinal studies to unravel causal relationships and leverage multi-omics approaches to uncover personalized therapeutic strategies. By addressing both systemic and individualized factors, the management of PCOD can progress toward holistic and effective care.

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