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Polycystic Ovary Syndrome: A Comprehensive Review Of Pathophysiology, Genetics, Diagnostic Criteria, and Emerging Management Approaches

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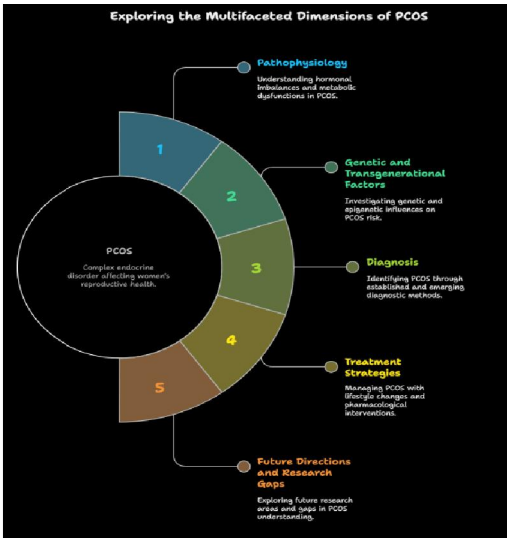
Abstract: *Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder that occurs in 8-13% of women of reproductive age. PCOS is defined as hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, and presents with uncertain and diverse diagnoses and treatments. This review describes the updated recommendations from recently published international guidelines, with newly reported data in the literature, and provides a robust summary of the multidimensional pathophysiology, associated genetics, and diagnostic challenges. In particular, we describe the transgenerational developmental effects of the syndrome, insulin resistance associated with this disorder, and a discussion of the limits of Anti-Müllerian Hormone (AMH) as a diagnostic measure. We relate treatment options (both pharmacological and lifestyle) and describe several practice gaps that further research might address to optimize person-centred care across the lifespan.*

Keywords: PCOS, pathophysiology, diagnosis, AMH, insulin resistance, genetics, lifestyle interventions

Graphical Abstract:



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I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complicated endocrine and metabolic disorder affecting 8% to 13% of women worldwide of reproductive age. It is the most common endocrine disorder in reproductive aged women. Although it is common, there is often misdiagnosis and under-recognition associated with PCOS, largely due to the varied clinical phenotype, complexity of pathophysiology, and the lack of standardization in criteria for diagnosis. The syndrome is defined by a combination of features often referred to as a triad; these include hyperandrogenism (clinical or biochemical), ovulatory dysfunction, and polycystic ovarian morphology. Yet, not all women have all three, and there is variation based on not only ethnic group but also stage of life, likely leading to delays in timely and accurate diagnosis.

PCOS is not only a condition that relates to reproductive health. PCOS has been linked to a multitude of metabolic conditions as well, such as insulin resistance, obesity, dyslipidemia, and increased incidence of type 2 diabetes mellitus. There are also implications for psychological health; women with PCOS have increased rates of depression and anxiety as compared to women without PCOS, and have quality of life scores that fall below that of women without PCOS as well, denoting that there is a large psychological aspect to this issue. Taken together, PCOS impacts systemic health for girls and women, has implications for ongoing chronic health issues, and requires a concerted cross-disciplinary diagnostic, management, and follow-up approach [1].

Medical training and practice do not have an inclusive approach to the complexity of polycystic ovarian syndrome (PCOS). Even in studies of healthcare provider groups, including OBGYN residents, the knowledge of diagnostic criteria are inconsistent with Rotterdam, NIH, and AE-PCOS guidelines. This educational ignorance results in no cohesion in treatment plans and poor patient satisfaction. Furthermore, the symptoms, diagnosis, treatment, and care of PCOS patients are complicated by the overlapping and associating symptoms of other hormonal or metabolic disorders – especially when considering the potential for the variability of presentations in adolescents and perimenopausal women [2].

In the last five years, research progress has contributed to a greater understanding of the mechanisms of PCOS, particularly in regards to genetic predisposition, epigenetics, insulin resistance, or inflammation. Although less emphasized, high maternal levels of hyperandrogenism and prenatal exposure to hormones may have transgenerational influences as well. While some biomarkers including anti-Müllerian hormone (AMH) have demonstrated the ability to garner a reflection of follicle-restricting hormones that impact ovarian dysfunction, using any of the biomarkers as a clinical diagnostic is still controversial [3].

In response to the complexity surrounding PCOS, this review will provide an updated and integrated view of the pathophysiology, genetics, diagnostic controversy, and management options within PCOS. It will describe gaps in knowledge and set future directions for research helping to improve the care of women afflicted with PCOS, since it is very common and often unnoticed.

PATHOPHYSIOLOGY

PCOS has complex pathophysiology in which hypothalamic-pituitary-ovarian (HPO) axis dysregulations, hyperandrogenism, and insulin resistance act as contributors to anovulation and metabolic dysfunction. Elevated insulin levels stimulate increased ovarian androgen levels which result in anovulation and metabolic dysfunction. Environmental antecedents and obesity both provide added layers of insulin resistance and lipotoxicity. The overlap in psychological and reproductive pathology can often occur simultaneously and can contribute to the broad range of clinical presentations [4].

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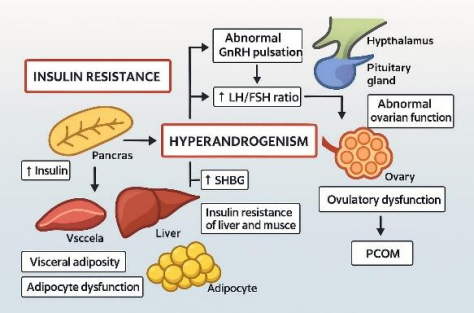

Fig. 1. Pathophysiological Mechanisms Underlying PCOS

GENETIC AND TRANSGENERATIONAL FACTORS

The earliest studies on PCOS were focusing on its inherited nature and family association; now we are starting to see more genetic data emerge, and it is clear that PCOS has a multigenetic nature. 19 risk gene loci for PCOS have been found across multiple genome-wide association studies in genes related to neuroendocrine, metabolic and reproductive pathways. Most recently, unsupervised clustering analysis showed that the two populations, metabolic and reproductive, segregated but suggested in advance of the study. Mendelian randomization analysis showed that there may be causal uncertainties in respect to variations linked to BMI, fasting insulin, timing of menopause, depression, and male-pattern baldness that may link with PCOS. Among all the genes of interest (THADA, FSHR, INS-VNTR, and DENND1A), some gene loci appear to have the most promise, but more validation is needed [5].

It is remarkable that the genetic profiles of both the clinically certified PCOS cases and the self-reported cases were similar, allowing for future data gathering using a less time encumbering and expensive methodology. Basically, the origins of the syndrome PCOS are transgenerational, and the risk of the syndrome is increased by five-fold for daughters born to mothers with PCOS, based on evidence from human and animal research. Excess androgen during pregnancy alone was sufficient for transmission of the syndrome PCOS between generations. If exposure to androgens at a young age has an inductive impact on the syndrome potential, it is reasonable to think one is more likely to develop "PCOS" [6].

It has been shown that infant girls born to mothers with PCOS have longer anogenital distance (AGD), and daughters of PCOS mothers are at greater risk, for metabolic and androgen issues. When maternal testosterone was measured in PCOS affected women, it was found to be predictive of baby AGD. While AMH may be relate to mechanisms, it is still not clear how the daughters were exposed to hyperandrogenism. In a recent study, it was shown that mice exposed to high levels of AMH in late pregnancy gave birth to offspring with PCOS who had increased androgen levels and high luteinizing hormone pulsativity. It was believed that AMH acted to promote hyperandrogenism by mediating aromatase functionality in the placenta. It sounds as if AMH had a role in facilitating the transgenerational transfer of a hyperandrogenic condition. There are reports of elevated AMH levels in second and third trimestral PCOS women and further work is needed to investigate how this relates to human transgenerational effects via AMH [7].

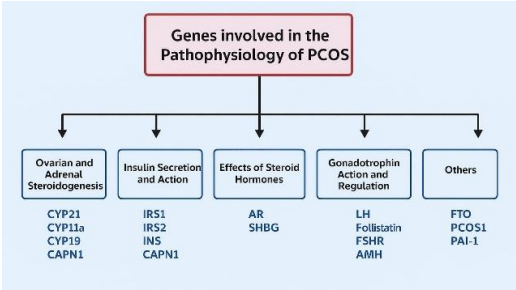

Fig. 2. Genetic and Epigenetic Contributors to PCOS

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DIAGNOSIS

PCOS diagnosis hinges on the presence of two out of three criteria:
Oligo/anovulation,
Hyperandrogenism (clinical or biochemical)
Polycystic ovaries on ultrasound.
The Rotterdam criteria are widely accepted but can yield varied phenotypes. While AMH is typically elevated in PCOS, it is not yet a recommended diagnostic tool due to overlapping values in healthy individuals.

Table. 1. Comparative Diagnostic Criteria for PCOS

Criteria	NIH (1990)	Rotterdam (2003)	AE-PCOS (2006)
Ovulatory Dysfunction	Required	Required or optional	Required
Hyperandrogenism	Required	Required or optional	Required
Polycystic Ovaries	Not considered	Required or optional	Not sufficient alone
Diagnosis Requirement	Both criteria required	Any two of three features	Hyperandrogenism + either ovarian dysfunction or morphology

Challenges in Adolescents:
It is suggested to make the diagnosis after at least 2 years after the start of menarche to avoid diagnosis overlapping with natural physiological changes associated with puberty. Ultrasound should not be performed before 8 years after the start of menarche. While AMH is often elevated in PCOS, it is not recommended to use AMH as the sole and standalone diagnostic tool as there will be an overlap with the normal reproductive ranges [8].
Emerging Approaches:
Biomarkers such as kisspeptin, inhibin B, leptin, and adiponectin are being explored for enhanced diagnostic accuracy.
Artificial Intelligence (AI) and machine learning models are under development to integrate clinical, biochemical, and imaging data to assist with earlier and more accurate diagnosis.
Metabolomic and proteomic profiling, as well as liquid biopsy technologies, may offer future opportunities for personalized diagnosis [9].

TREATMENT STRATEGIES

Lifestyle Modifications (First-Line):
Weight loss (5–10%) improves ovulation and insulin sensitivity.
Exercise and dietary changes improve metabolic parameters [10, 11].

Table. 2. Pharmacologic Therapies

Treatment	Mechanism	Indications
Metformin	Insulin sensitizer	Metabolic dysfunction, ovulation induction
Combined Oral Contraceptives (COCs)	Suppress LH/FSH, reduce androgens	Menstrual irregularity, hirsutism, acne
Spironolactone	Anti-androgen	Hirsutism
Myo-inositol/D-chiro-inositol	Insulin sensitizer	Ovulation support, metabolic improvement
Clomiphene/Letrozole	Ovulation induction	Infertility
GLP-1 Receptor Agonists	Promote weight loss, insulin	Under investigation in PCOS treatment

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Treatment	Mechanism	Indications
	sensitivity	

FUTURE DIRECTIONS AND RESEARCH GAPS

Role of Anti-Müllerian Hormone (AMH) in Pathogenesis and Diagnosis

Although AMH levels are usually elevated in women with PCOS based on the presence of greater than normal antral follicles, the exact role of AMH in the pathogenesis and clinical characterization of PCOS is still not fully understood. Recent studies have proposed the idea that AMH may program the development of PCOS in early life by its influence on placental aromatase activity and/or fetal exposure to androgens. However, it must be noted that AMH levels overlap significantly with that of normal ovulating women making it less reliable as a stand-alone diagnostic biomarker. Additional research is required to determine standard cut-off values of AMH; better characterization of AMH's dynamic behavior and an assessment of its utility for post-treatment monitoring [12].

Cardiovascular Risk in PCOS

Although PCOS is closely associated with metabolic disturbances such as insulin resistance, dyslipidemias, and obesity, the long-term risk for cardiovascular-related health has not been fully defined. New evidence suggests an increased risk of subclinical atherosclerosis, endothelial dysfunction, and hypertension from the larger cohort studies. However, consensus has not been reached in large studies with "hard outcomes" such as myocardial infarction or stroke, and there are no long-term outcome studies in population-based cohorts, so a definitive causal link between PCOS and cardiovascular disease is still lacking. Future work should focus on identifying high-risk phenotypes and assess the possible incorporation of screening for cardiovascular disease in the management of PCOS [13].

Psychiatric Comorbidities and Quality of Life

Women with PCOS commonly suffer mood disorders including anxiety, depression, and low self-esteem, which are often accentuated by the physical health conditions of hirsutism, acne, obesity, and infertility. Despite the prevalence of psychological disorders in women with PCOS, mental health appears to be an under-research area for improving care of PCOS. Generally, this will require carefully developed provider evidence-based guidelines for the practice of mental health, and there is a practical urgency to build integrated models of care that includes the mental health assessment as part of the routine process. A dedicated mental health evidenced based program that employed the validated tools used to measure psychological distress responses that are related to PCOS should be included. Similarly, the utility of psychological interventions, including cognitive behavioral therapy and lifestyle coaching employing longitudinal research could be beneficial to assess effects of protocols [14].

Personalized Medicine and Genetic Profiling

As PCOS is genetically heterogeneous, possible treatment paradigms may evolve toward precision medicine. The continued advances in genomics, transcriptomics, and metabolomics might facilitate the discovery of Plasmids and unique molecular signatures in women with PCOS. As new ‘leaders’ in women’s health research when examining other areas such as metabolic, reproductive, or inflammatory profiles, stratification of patients into subgroups might allow for unique individualized treatment protocols. In the future, pharmacogenomics may lead to safer and more effective recommendations on the use of insulin sensitizers, ovulation inducers, and anti-androgens. Funding more multi-omics research studying populations of diverse cohorts in women and medicine would help to ensure the design of applicable therapeutic algorithms designed to be more inclusive, resulting in more effective and efficacious therapeutic recommendations [15].

Transgenerational Impact and Fetal Programming

The evidence is increasing, in both animals and humans, for the idea that the intrauterine environment may shape fetal development, and that maternal hyperandrogenism and higher levels of AMH can place progeny at risk for PCOS-like characteristics. As well, there is evidence that daughters of women with PCOS demonstrate increased anogenital distance, which may be a measure of early androgen exposure. These findings pose essential questions about transgenerational transmission of risk factors and epigenetic changes. Future research should focus on prenatal therapy

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options, placental biology, and any preventative strategies that may limit risk of PCOS in future generations. Developing maternal-fetal health registries may provide long-term data on these outcomes [16].

II. CONCLUSION

PCOS is a complex disorder involving genetic, metabolic, reproductive, and environmental components. Delayed diagnosis and differing treatment plans impede our ability to optimize care. Advancing our understanding of genetic predisposition and hormonal influences (e.g., AMH) is an exciting area of research, but there are still discrepancies in diagnosis, particularly in adolescents. Lifestyle change and pharmacotherapy interventions are the current best practices for management, but future studies should explore personalized medicine and transgenerational prevention. It is essential for clinicians to stay current in bridging these heterogeneous knowledge gaps and improving the outcomes of women affected by PCOS.

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Conflict of Interest

The author/editor has no conflicts of interest, financial or otherwise, to declare.

Statement of Contribution

Sarika Joga [Lead Author]: Conceptualization, Writing – Original Draft, Supervision
Vasanthi A V [Co-author 1]: Writing – Review & Editing, Formal Analysis
Sreekanth M [Co-author 2]: Data Curation, Investigation, Methodology
Medha Gayatri B [Co-author 3]: Editing, Formal Analysis
Thanmai A [Co-author 4]: Critical Reviews
Are.Vanitha [Co-author 5]:Helping hands
Gone. Madhura [Co-author 5]: Helping hands

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