International Journal of Reproduction, Contraception, Obstetrics and Gynecology
*Bashir M et al. Int J Reprod Contracept Obstet Gynecol. 2025 Oct;14(10):3618-3623*
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20253125

**Review Article**

# Polycystic ovary syndrome: a comprehensive review of pathophysiology, diagnosis, and emerging management strategies

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**Received:** 05 July 2025
**Revised:** 13 August 2025
**Accepted:** 14 August 2025

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## ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 6-20% of women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Its pathophysiology involves intricate interactions among genetic, epigenetic, metabolic, and environmental factors, with insulin resistance, gut microbiota dysbiosis, and novel biomarkers like anti-Müllerian hormone (AMH) playing pivotal roles. This review provides an in-depth exploration of PCOS etiology, diagnostic challenges, and management strategies, including lifestyle interventions, pharmacological therapies, and emerging approaches like microbiota modulation and microRNA therapies. We also address long-term health risks, such as cardiovascular disease, type 2 diabetes mellitus (T2DM), and mental health challenges, emphasizing personalized and multidisciplinary treatment strategies.

**Keywords:** Polycystic ovary syndrome, Insulin resistance, Hyperandrogenism, gut microbiota, Anti-Müllerian hormone, Reproductive health

## INTRODUCTION

Polycystic ovary syndrome (PCOS), first described in 1935 by Stein and Leventhal, remains a leading cause of anovulatory infertility and affects millions of women worldwide.[1] Prevalence varies by diagnostic criteria, with estimates ranging from 6% using NIH criteria to 20% using Rotterdam criteria.[2,3] PCOS is associated with reproductive, metabolic, and psychological complications, including infertility, obesity, T2DM, cardiovascular disease (CVD), and mood disorders.[4] The Rotterdam criteria, established in 2003, require two of three features for diagnosis: hyperandrogenism (clinical or biochemical), ovulatory dysfunction (e.g., oligo- or amenorrhea), and polycystic ovarian morphology (PCOM) on ultrasound, after excluding other conditions.[5] This review synthesizes the latest research on PCOS pathophysiology, diagnostic refinements, and management strategies, incorporating recent advances in precision medicine and novel therapeutic targets.

## PATHOPHYSIOLOGY OF PCOS

### *Hormonal and reproductive dysregulation*

PCOS is characterized by disrupted hypothalamic-pituitary-ovarian (HPO) axis function, leading to elevated luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH).[6] This altered LH:FSH ratio promotes theca cell hyperplasia and excessive androgen production, contributing to anovulation and hyperandrogenism.[7] Hyperandrogenism manifests as hirsutism, acne, or androgenic alopecia, affecting 60-80% of PCOS patients.[8] Recent studies highlight the role of AMH, which is

elevated due to increased antral follicle count in PCOS ovaries.[9] AMH inhibits folliculogenesis, exacerbating ovulatory dysfunction, and is being explored as a diagnostic biomarker, though its specificity is limited by variability across age groups.[10]

### *Insulin resistance and metabolic dysfunction*

Insulin resistance (IR) affects 65-95% of PCOS women, regardless of body mass index (BMI), and is a key driver of hyperandrogenism.[11] IR leads to compensatory hyperinsulinemia, which stimulates ovarian androgen production via insulin-like growth factor-1 (IGF-1) pathways and reduces sex hormone-binding globulin (SHBG), increasing free androgen levels.[12] Women with PCOS are at a fourfold higher risk of developing T2DM and exhibit a higher prevalence of metabolic syndrome (30-40%) compared to the general population.[13] Chronic low-grade inflammation, marked by elevated C-reactive protein (CRP) and interleukin-6 (IL-6), further exacerbates IR and cardiovascular risk.[14] Oxidative stress, driven by reactive oxygen species (ROS), also contributes to metabolic dysfunction and ovarian damage.[15]

**Table 1: Diagnostic criteria for PCOS.**

| Diagnostic criteria | Criteria | Description |
|---|---|---|
| **NIH (1990)** | Hyperandrogenism and chronic anovulation | Requires both; excludes PCOM |
| **Rotterdam (2003)** | Two of three: hyperandrogenism, ovulatory dysfunction, PCOM | Most widely used; excludes other causes |
| **AE-PCOS Society (2006)** | Hyperandrogenism with either ovulatory dysfunction or PCOM | Emphasizes hyperandrogenism |

**Table 2: Key metabolic complications in PCOS.**

| Complications | Prevalence (%) | Risk Increase (x) |
|---|---|---|
| **Insulin resistance** | 65-95 | 2–4 |
| **Type 2 diabetes mellitus** | 10-20 | 4 |
| **Metabolic syndrome** | 30-40 | 2–3 |
| **Cardiovascular disease risk** | 20-30 | 1.5–2 |

### *Genetic and epigenetic contributions*

PCOS has a heritability of approximately 70%, with genome-wide association studies (GWAS) identifying susceptibility loci in genes like AR (androgen receptor), FSHR (FSH receptor), and CAPN10 (calpain-10).[16] These genes influence steroidogenesis, gonadotropin signaling, and insulin action.[17] Epigenetic modifications, such as DNA methylation and histone acetylation, are influenced by environmental factors like endocrine-disrupting chemicals (EDCs) and diet, altering gene expression in PCOS.[18] For instance, hypermethylation of PPARG (peroxisome proliferator-activated receptor gamma) is linked to IR in PCOS patients.[19] These findings highlight the need for integrated genetic-epigenetic research to guide precision medicine.

### *Gut microbiota and novel pathways*

Emerging evidence implicates gut microbiota dysbiosis in PCOS pathogenesis.[20,21] Dysbiosis, characterized by reduced microbial testosterone levels.[22] The gut microbiota influences bile acid metabolism, which modulates insulin sensitivity and inflammation via the farnesoid X receptor (FXR) pathway.[23] Novel pathways, such as IL-22 (interleukin-22), which promotes adipose tissue browning, are also being explored for their role in mitigating hyperandrogenism.[24]

## DIAGNOSTIC CHALLENGES

Diagnosing PCOS is complex due to its heterogeneous presentation and overlap with physiological changes, particularly in adolescents.[25] The Rotterdam criteria, while widely adopted, risk over-diagnosis if ultrasound-based PCOM is misinterpreted, as up to 20% of healthy women exhibit PCOM.[5] AMH is a promising diagnostic tool, with levels 2-3 times higher in PCOS patients, but its use is limited by lack of standardized cutoffs and age-related variability.[10] Biochemical hyperandrogenism, measured via free testosterone or free androgen index (FAI), is more reliable than clinical signs like hirsutism, which can be subjective.[26] Machine learning models integrating hormonal, metabolic, and imaging data are being developed to enhance diagnostic precision, with recent algorithms achieving up to 90% accuracy.[27]

**Table 3: Comparison of diagnostic tools for PCOS.**

| Tools | Advantages | Limitations |
|---|---|---|
| **Ultrasound (PCOM)** | Non-invasive, widely available | Over-diagnosis risk in adolescents |
| **AMH Levels** | Reflects antral follicle count | Lack of standardized cutoffs |
| **Free Testosterone/FAI** | Specific for hyperandrogenism | Requires sensitive assays |
| **Machine Learning Models** | High accuracy, integrative | Limited clinical adoption |

## MANAGEMENT STRATEGIES

### *Lifestyle interventions*

Lifestyle modification is the first-line treatment for PCOS, particularly for overweight or obese patients (50–70% of PCOS cases).[28] A 510% weight loss can restore ovulation in 55-70% of women and improve metabolic parameters.[29] Diets like the Mediterranean, DASH, or low-carbohydrate ketogenic diets reduce IR and androgen levels, though no single diet is universally superior.[30] Aerobic exercise (150 minutes/week) and resistance training improve insulin sensitivity and reduce visceral fat, with high-intensity interval training (HIIT) showing superior benefits in recent trials.[31] Behavioral interventions, including cognitive-behavioral therapy (CBT), enhance adherence to lifestyle changes.[32]

### *Pharmacological treatments*

Pharmacological options target specific PCOS symptoms (Table 4).

**Table 4: Pharmacological options target specific PCOS symptoms.**

| Drug class | Indication | Dosage | Side effects |
|---|---|---|---|
| **Combined oral contraceptives** | Menstrual regulation, hirsutism | Varies (e.g., ethinylestradiol 20-35 µg) | Nausea, thrombosis risk |
| **Metformin** | Insulin resistance, ovulation | 1500-2000 mg/day | GI upset, lactic acidosis (rare) |
| **Letrozole** | Ovulation induction | 2.5-7.5 mg/day | Hot flashes, fatigue |
| **Spironolactone** | Hirsutism | 50-100 mg/day | Hyperkalemia, teratogenicity |

### *Combined oral contraceptives (COCs)*

COCs regulate menstrual cycles and reduce hyperandrogenic symptoms by increasing SHBG and suppressing LH.[33] Ethinylestradiol with drospirenone is preferred for its anti-androgenic properties.[34]

### *Insulin sensitizers*

Metformin (1500-2000 mg/day) improves IR, ovulation, and menstrual regularity, particularly in women with BMI >25 kg/m².[35] Thiazolidinediones (e.g., pioglitazone) are less commonly used due to weight gain and cardiovascular risks.[36]

### *Ovulation induction*

Letrozole (2.57.5 mg/day) is now the first-line agent for ovulation induction, with a 20-30% higher live birth rate compared to clomiphene citrate.[37]

### *Anti-androgens*

Spironolactone (50-100 mg/day) and finasteride (5 mg/day) effectively treat hirsutism but require contraception due to teratogenicity.[38]

### *Emerging therapies*

*Innovative treatments are under investigation*

*Gut microbiota modulation*

Probiotics (e.g., *Lactobacillus rhamnosus*) and prebiotics improve IR and reduce androgen levels in small trials.[39] Fecal microbiota transplantation (FMT) shows promise in restoring gut eubiosis, though clinical data are limited.[40]

*Vitamin D supplementation*

Vitamin D (2000-4000 IU/day) improves oxidative stress and AMH levels, but its impact on gonadotropins is inconsistent.[41]

*IL-22 therapy*

Preclinical studies suggest IL-22 reduces hyperandrogenism by enhancing brown adipose tissue activity.[24]

*MicroRNA therapy*

MicroRNAs like miR-155 and miR-29 target steroidogenesis and insulin signaling pathways, offering potential for gene-based therapies.[42]

*GLP-1 receptor agonists*

Liraglutide and semaglutide, originally developed for T2DM, show promise in reducing weight and IR in PCOS, with ongoing trials evaluating fertility outcomes.[43]

## PSYCHOLOGICAL AND LONG-TERM HEALTH CONSIDERATIONS

PCOS is associated with a 2-3-fold increased risk of anxiety and depression, driven by infertility, body image concerns, and metabolic complications.[44] Psychological screening and CBT are critical to improve quality of life and treatment adherence.[45] Long-term, PCOS patients face

elevated risks of CVD (due to dyslipidemia and hypertension), endometrial cancer (from unopposed estrogen), and T2DM.[46] Annual screening for glucose intolerance, lipid profiles, and endometrial health is recommended.[47]

## FUTURE DIRECTIONS

Precision medicine, leveraging genetic profiling and machine learning, could revolutionize PCOS management by identifying patient-specific therapeutic targets.[48] Large-scale studies are needed to validate AMH as a diagnostic biomarker and to standardize its cutoffs. The role of gut microbiota in PCOS warrants further exploration, with randomized controlled trials (RCTs) needed to confirm the efficacy of probiotics and FMT. Emerging therapies like IL-22 and microRNA-based treatments hold promise but require robust clinical validation. Addressing health disparities in PCOS care, particularly in low-resource settings, is critical to improving global outcomes.[49]

## CONCLUSION

PCOS is a multifaceted disorder with significant reproductive, metabolic, and psychological implications. Advances in understanding its pathophysiology, including the roles of insulin resistance, gut microbiota, and genetic factors, have opened new avenues for diagnosis and treatment. A multidisciplinary approach integrating lifestyle interventions, pharmacological therapies, and emerging treatments like microbiota modulation and precision medicine is essential for optimizing patient outcomes. Continued research into novel biomarkers and therapies will further enhance our ability to manage this complex condition.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Bashir M, Amin F, Amin H, Teli TA, Tali TA. Polycystic ovary syndrome: a comprehensive review of pathophysiology, diagnosis, and emerging management strategies. Int J Reprod Contracept Obstet Gynecol 2025;14:3618-23.