# PATHOPROFILE

# POLYCYSTIC OVARIAN SYNDROME

doi: 10.35493/medu.48.04
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## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most frequent hormonal disorder in women of reproductive age.[1] Despite the high prevalence of PCOS, the disorder remains severely underdiagnosed and misunderstood by affected individuals and healthcare professionals. While the exact pathogenesis for PCOS remains unknown, the disorder is largely associated with hormonal imbalances caused by genetic factors such as granulosa cell dysfunction, and environmental factors such as perinatal androgen exposure.[2,3] Symptoms of PCOS include hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM). Recent research emphasizes personalized PCOS management involving a combination of pharmacological therapy and lifestyle changes, with potential enhancements through patient-centered diagnostics.

## PATHOGENESIS

A prospective cohort study found that PCOS begins as an innate ovarian irregularity.[2] Granulosa cells within the small follicles of the ovary typically produce anti-Müllerian hormone (AMH), which regulates the growth of ovarian follicles.[2] Biological females with PCOM, a precursor to PCOS, have both smaller ovarian follicles and increased secretion of AMH per follicle, resulting in an overall excess of AMH.[2] Elevated AMH suppresses follicular growth within the ovaries by inhibiting the activity of follicle-stimulating hormone (FSH). As a result, ovarian follicles are unable to mature and undergo ovulation.[2]

A study on mice found that the pathogenesis of PCOS is largely associated with perinatal androgen exposure, negatively impacting the homeostasis between the gonadotropin-releasing hormone (GnRH) pulse generator, the pituitary gland, and the gonads.[3] The gonadotropin-releasing hormone (GnRH) pulse generator is a network of neurons within the hypothalamus that orchestrates the release of luteinizing hormone (LH) and FSH from the pituitary gland.[4] Typically, an increase in progesterone levels results in a decrease in the frequency of the GnRH pulse generator, a network of neurons within the hypothalamus that mediates LH and FSH release. This achieves a balance of both hormones through a negative feedback loop.[3] However, this loop is modified following fetal exposure to excess androgen, causing the GnRH pulse generator to become less responsive to excess progesterone and remain in a constant pulsating state.[3] The pituitary gland responds by releasing more LH than FSH. This imbalance is a primary biomarker of PCOS. Elevated LH is known to increase AMH, further promoting the cycle of hormonal imbalance characteristic of PCOS.[2]

One biomarker used to predict early development of PCOS is heightened dihydrotestosterone (DHT). Hyperandrogenism is known to cause both preliminary and progressive symptoms associated with the pathogenesis of PCOS.[5] In a study on mice, exogenously given excess DHT is shown to induce symptoms of PCOS within two weeks post-exposure.[5] Mice treated with DHT experienced no menstrual cycles, an increased number of cyst-like follicles in the ovaries, anovulation, and increased body weight by up to 30%.[5]

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

Misdiagnosing PCOS is common as symptoms are subject to heterogeneity. About 80% of PCOS patients demonstrate hyperandrogenism, making it a predominant symptom.[8] Patients with hyperandrogenism display symptoms including hirsutism and acne, which are typically assessed clinically. Physicians assess the degree of hirsutism and distribution of male-pattern hair growth, in clinical settings using the mFG scale. The scale assesses nine body regions and assigns a hair growth score between zero and four to each. This sign of hyperandrogenism is one of the most recognizable clinical features of PCOS.[7,8]

Ovulatory dysfunction is another common manifestation of PCOS. The hormonal imbalance resulting from elevated LH and reduced FSH interrupts follicle development, leading to anovulation and occasionally a prolonged menstrual cycle. To ensure diagnostic accuracy, this criterion is only used for patients three or more years past their first menstrual period, known as menarche.[9]

A third common manifestation of PCOS is PCOM, defined by an ovary containing more than 20 antral follicles or demonstrating an overall volume greater than 10 mL.[10] PCOM should not be used as a diagnostic indicator within eight years of menarche, as ovarian morphology is still in development.[9] Interpretation of PCOM requires clinical caution and must be considered alongside other diagnostic features as PCOM may appear in individuals without PCOS.

If hyperandrogenism or ovulatory dysfunction is present, it is necessary to consider differential diagnoses. Labs are expected to test for thyroid-stimulating hormone, prolactin, and 17-hydroxyprogesterone to rule out other endocrine disorders.[9]

The diagnostic framework of PCOS has evolved with the 2023 International PCOS Guideline as the current international standard. It states that if a patient exhibits any two of the three core features of PCOS stated above, a diagnosis of PCOS can be established. Before this guideline, three distinct diagnostic criteria were used: the 1990 NIH, 2003 Rotterdam, and 2006 AE-PCOS. This posed an issue in diagnosis and research, highlighting the importance of a unified standard that was addressed by the 2023 guideline.[12]

## TREATMENT

PCOS is a complex disorder requiring a multifaceted approach to treatment. The first line of management usually involves lifestyle interventions such as regular exercise, dietary modifications, and weight loss. Studies have shown that for individuals with obesity, losing 5–10% of body weight can significantly improve menstrual regularity, metabolic health, and fertility outcomes.[14,15]

Approximately 70% of women with PCOS experience dysovulation or anovulation. Ovulation induction agents such as letrozole and clomiphene citrate are commonly used as treatments. Letrozole inhibits the conversion of androgens to estrogen, thereby signaling the brain to increase FSH release, promoting the maturation of ovarian follicles and ovulation.[12] Clomiphene citrate inhibits estrogen receptors in the hypothalamus, stimulating the pituitary to release more FSH and LH to promote ovulation. However, clomiphene can result in the thinning of the endometrial lining and the thickening of cervical mucus, making it hostile to sperm.[12]

Clinical trials comparing the two interventions have shown that biological females treated with letrozole achieved higher rates of pregnancy and conception in fewer cycles. Although pregnancy and live birth rates stabilized after crossover to the alternate intervention, letrozole's lack of adverse effects makes it a preferable primary treatment.[12] Another component of treatment is addressing insulin resistance. High insulin levels stimulate the ovaries to produce more androgens, disrupting ovulation and worsening symptoms such as hirsutism and weight gain. One commonly prescribed insulin sensitizer is metformin, which enhances insulin sensitivity by reducing hepatic glucose production, and improving lipid metabolism.[13] Addressing insulin sensitivity restores ovarian function as the ovaries return to baseline testosterone production, allowing for normal follicular development and ovulation.

Finally, hormonal therapies such as oral contraceptives (OCs), particularly those combining estrogen and progestogen, are used to regulate menstrual cycles and reduce androgen-related symptoms. Clinical improvements in these symptoms are typically observed after six months of consistent use.[18] Additionally, antiandrogens such as spironolactone may be used in conjunction with OCs to further reduce hirsutism and acne.[16]

## GLOBAL IMPACT & FUTURE DIRECTIONS

Recent studies estimate that roughly 9.2% of biological females of reproductive age are affected by PCOS. From 1990–2021, incident cases have greatly increased, reflecting an evolving need for research in reproductive health. Recent literature is becoming increasingly focused on personalized and less invasive treatments. One promising treatment is GLP-1 receptor agonists, which have been shown to improve insulin resistance, lower androgen levels, and support reproductive function.[19] Furthermore, emerging studies suggest that circadian rhythm disruptions may also contribute to PCOS symptoms, with studies being done to test melatonin-based therapies.[20] Advances in artificial intelligence, including tools like PCONet and CystNET, are also helping to enhance the precision of PCOS diagnosis by evaluating cyst patterns and ultrasounds more meticulously.[22] These developments highlight the trend towards a more patient-centred approach to addressing and treating PCOS.

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References can be found on our website:
themeducator.org