Original Article

Polycystic Ovary Syndrome: From Pathogenesis to Personalized Management

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age and is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. The global prevalence ranges from 6%–26%, with Indian studies reporting rates between 7%–22.5%. Diagnosis is primarily based on the Rotterdam criteria, requiring the presence of at least two of the following: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology after excluding other causes. PCOS is associated with several reproductive and metabolic complications including infertility, insulin resistance, type 2 diabetes mellitus, cardiovascular risk, and endometrial hyperplasia. Management should be individualized and focused on the patient's symptoms and reproductive goals. Lifestyle modification, including dietary changes and regular physical activity, forms the cornerstone of treatment. Pharmacological options such as combined oral contraceptives, metformin, and anti-androgens help manage menstrual irregularities and hyperandrogenism, while ovulation induction agents like letrozole are preferred in women seeking fertility. Early diagnosis and a multidisciplinary approach are essential to prevent long-term complications and improve quality of life.

Key words: PCOS, Hyperandrogenism, Ovulatory dysfunction, Insulin Resistance, Rotterdam Criteria, DOGMA theory.

Polycystic Ovary Syndrome (PCOS), previously referred to as Stein–Leventhal syndrome, is a common endocrine disorder characterized by a triad of polycystic ovarian morphology, hyperandrogenism, and ovulatory dysfunction. Globally, its prevalence ranges between 6% and 26%, while Indian studies estimate it to be between 7% and 22.5%. A cross-sectional study conducted in Mumbai reported a prevalence of 22.5% based on the Rotterdam criteria and 10.7% using the AE-PCOS criteria. Notably, a significant proportion of affected women remain undiagnosed.

According to the ESHRE/ASRM (Rotterdam 2003) consensus, the diagnosis of PCOS requires the presence of at least two of the following three features: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM), after excluding other etiologies.[1,2]

In women presenting with both menstrual irregularities and hyperandrogenism, ultrasound is not essential for diagnosis, although it may help in identifying the complete phenotype. Ultrasound evaluation is not recommended in individuals less than 8 years post-menarche due to the high prevalence of multifollicular ovaries during adolescence, which may lead to overdiagnosis.

A stepwise diagnostic approach is recommended. If both irregular cycles and clinical hyperandrogenism are present, PCOS can be diagnosed after excluding other causes. In the absence of clinical hyperandrogenism, biochemical testing should be performed. If only one feature (either menstrual irregularity or hyperandrogenism) is present, further evaluation is required. In adolescents, ultrasound is generally avoided, and such individuals are considered "at risk," warranting reassessment over time. In adults, ultrasound may be used to assess for PCOM and aid in diagnosis.[3]

Clinical assessment of hyperandrogenism includes evaluation of hirsutism using standardized tools such as the modified Ferriman–Gallwey score, where a score of ≥8 suggests hirsutism (with variations based on ethnicity). The Ludwig scale is commonly used to assess female pattern hair loss.[4]

On ultrasound, using a transducer frequency of at least 8 MHz, PCOM is defined by either ≥20 follicles per ovary or an ovarian volume ≥10 mL in at least one ovary. These criteria should be applied only when no dominant follicle or corpus luteum is present to avoid misinterpretation.[5]

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Management of PCOS should be individualized, targeting the patient's reproductive, metabolic, and cosmetic concerns.[6] The primary goals include reduction of hyperandrogenic symptoms, management of metabolic abnormalities, prevention of type 2 diabetes and cardiovascular risks, protection against endometrial hyperplasia, and optimization of fertility when desired. Improving overall quality of life is also a key objective. A multidisciplinary approach is often required, incorporating lifestyle modification, nutritional guidance, metabolic screening, fertility counselling, and psychological support.

Non-pharmacological management forms the cornerstone of therapy. Lifestyle interventions include dietary modification with a caloric deficit of approximately 500–750 kcal/day or about 30% reduction in energy intake, tailored to the individual. Referral to a dietitian may be beneficial. Regular physical activity is recommended, with at least 150 minutes of vigorous or 250 minutes of moderate-intensity exercise per week, along with muscle-strengthening activities. Behavioral strategies such as goal setting using the SMART framework (Specific, Measurable, Achievable, Realistic, and Timely), self-monitoring, problem-solving, and relapse prevention are important for long-term adherence.

For women not seeking pregnancy, combined oral contraceptive pills (COCs) are considered first-line therapy for menstrual irregularities and hyperandrogenism. Low-dose formulations containing 20 µg ethinyl estradiol combined with a progestin (commonly norethindrone) are preferred. If contraindicated, cyclic progestins may be used to provide endometrial protection. COCs act by suppressing ovulation, stabilizing the endometrium, increasing sex hormone-binding globulin (SHBG), and reducing ovarian androgen production.

Metformin may be added, particularly in women with BMI >25 kg/m^2, starting at 500 mg and gradually titrated. It improves insulin sensitivity, reduces hepatic glucose production, and may restore ovulation and menstrual regularity in more than half of patients. The usual effective dose ranges from 1500 to 2000 mg per day. Anti-androgens can be considered if there is inadequate response to COCs after 6 months.[7]

Common anti-androgens include spironolactone (50–100 mg twice daily), flutamide (125–250 mg/day, with liver function monitoring), and 5-alpha reductase inhibitors such as finasteride or dutasteride. Cyproterone acetate, a progestin with anti-androgenic properties, may also be used, though it is contraindicated in conditions such as liver disease, thromboembolic disorders, severe depression, malignancy, and certain systemic illnesses.[8]

In women desiring pregnancy, letrozole is the first-line agent for ovulation induction, as it is associated with higher live birth rates and a lower risk of multiple pregnancies compared to clomiphene citrate. Letrozole, an aromatase inhibitor, achieves ovulation rates of approximately 80% and cumulative pregnancy rates of 30–40%. The risk of ovarian hyperstimulation syndrome (OHSS) is minimal. Clomiphene citrate, a selective estrogen receptor modulator (SERM), acts by blocking estrogen receptors at the hypothalamus, thereby increasing GnRH secretion and subsequently elevating FSH and LH levels, leading to follicular development. In selected cases, particularly lean women with PCOS, pulsatile GnRH therapy may be used, achieving ovulation rates of around 56% and pregnancy rates of approximately 40%.[9]

In women who do not respond to first-line ovulation induction therapies, laparoscopic ovarian drilling may be considered as the next step. However, this intervention is reserved for carefully selected patients, particularly those with elevated luteinizing hormone levels and normal body mass index. It has not been shown to be superior to clomiphene citrate, either as an initial treatment or in clomiphene-resistant cases, and is not routinely recommended prior to in vitro fertilization (IVF).

The procedure typically involves creating 3–6 punctures in each ovary using electrocautery at 40 W for approximately four seconds per puncture. This reduces ovarian androgen production and alters intra-ovarian factors, leading to improved regulation of gonadotropins. Consequently, ovarian sensitivity to endogenous gonadotropins improves, promoting dominant follicle development and ovulation. When all other treatment options fail, IVF remains the final therapeutic option.

Newer therapeutic agents such as inositols act as insulin second messengers. Myo-inositol enhances systemic insulin sensitivity, while D-chiro-inositol regulates intra-ovarian insulin activity, thereby improving menstrual cycles, ovulation, and hyperandrogenic features. A combination of these in a 1:40 ratio appears to provide optimal clinical outcomes.

The Dysbiosis of Gut Microbiota (DOGMA) theory suggests that a high-fat, low-fiber diet disrupts the balance of gut microbiota, leading to increased intestinal permeability or "leaky gut." This results in chronic inflammation, insulin resistance, and hyperandrogenism. This concept links gut health with the metabolic, reproductive, and hormonal abnormalities seen in PCOS. Therefore, interventions aimed at improving gut health, including dietary modification and probiotics, may offer therapeutic benefits.[10]

PCOS is strongly associated with insulin resistance and carries an increased risk of developing type 2 diabetes mellitus. Obesity is present in a significant proportion of affected women. Insulin resistance plays a central role in the development of impaired glucose tolerance. Women with PCOS have a markedly higher prevalence of type 2 diabetes compared to the general population. Additionally, pancreatic beta-cell dysfunction may occur even before glucose intolerance develops. This dysfunction is inversely related to sex hormone-binding globulin levels and contributes to hyperandrogenism and prolonged exposure to unopposed estrogen.[11]

Cardiovascular risk in PCOS arises through two main mechanisms: direct atherogenic effects and unfavorable lipid profiles. Women with PCOS commonly exhibit elevated triglycerides, total cholesterol, and low-density lipoprotein levels, along with reduced high-density lipoprotein levels. Increased levels of plasminogen activator inhibitor-1 further impair fibrinolysis, contributing to vascular dysfunction and increasing the risk of coronary artery disease and hypertension.

Chronic anovulation leads to prolonged unopposed estrogen exposure, which significantly increases the risk of endometrial hyperplasia and carcinoma. Women experiencing menstrual

intervals longer than three months are particularly at risk. There has also been concern regarding a possible increased risk of ovarian cancer in women with chronic anovulation, especially with prolonged use of ovulation-inducing agents, although evidence remains inconclusive.[12]

There is a pressing need for further research to better understand the complex pathophysiology and long-term health consequences of PCOS. It should be recognized as a chronic metabolic and reproductive disorder rather than merely a gynecological condition. Since there is no definitive cure, management focuses on symptom control and prevention of long-term complications through a comprehensive, individualized, and multidisciplinary approach.

In conclusion, due to its high prevalence and frequent underdiagnosis, early detection of PCOS is essential to reduce the risk of chronic and potentially serious complications. Lifestyle modification, including a balanced calorie-restricted diet and regular physical activity, remains the cornerstone of management for improving insulin resistance and fertility outcomes.

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