Polycystic Ovarian Syndrome

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KEYWORDS

• Polycystic • Abnormal uterine bleeding • Metabolic syndrome • Hyperandrogenism • Infertility • Oligo/amenorrhea

KEY POINTS

- Polycystic ovarian syndrome (PCOS) is a metabolic condition.
- PCOS is commonly diagnosed using the Rotterdam criteria, which requires the presence of 2 of 3 criteria: androgen excess, ovulatory dysfunction, and polycystic ovarian morphology.
- The pathogenesis of PCOS is influenced by genetic, hormonal, and environmental factors.
- Patients with PCOS experience a higher incidence of type 2 diabetes, hyperlipidemia, early cardiovascular disease, obstructive sleep apnea, adverse pregnancy outcomes, nonalcoholic fatty liver disease, depression, anxiety, low self-esteem (related to issues of body image as well as potential infertility), suboptimal sexual function, and decreased quality of life.
- Lifestyle intervention (weight loss, dietary modification, and increased exercise) is the first line of treatment.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine pathology in females of reproductive age worldwide. The prevalence of PCOS varies between 6% and 13% based on which diagnostic criteria are used: the National Institutes of Health, Rotterdam, or Androgen Excess-PCOS Society.[1]

The Rotterdam criteria, which are the most widely used and accepted, identify 4 phenotypes (**Table 1**). The classic phenotype has hyperandrogenism and abnormal uterine bleeding with (phenotype A) or without (phenotype B) polycystic ovarian morphology on ultrasonography. The "ovulatory phenotype" or phenotype C has features of hyperandrogenism and polycystic ovarian morphology. The

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Table 1
Polycystic ovarian syndrome phenotypes

	Clinical Presentation		
Phenotype	Androgen Excess[a]	Ovulatory Dysfunction	Polycystic Ovarian Morphology[b]
A	✓	✓	✓
B	✓	✓	
C	✓		✓
D		✓	✓

[a] Chemical androgen excess can be diagnosed by: • Calculated free testosterone or free androgen index OR. • Calculated bioavailable testosterone OR. • Consider androstenedione or DHEAS if testosterone is normal and high index of suspicion for hyperandrogenism.
[b] Ultrasound criteria: Ultrasonography should be transvaginal and using high resolution. Follicle count per ovary should be greater than or equal to 25 (2–9 mm) or ovarian volume greater than or equal to 10 mL.

nonhyperandrogenic phenotype" or phenotype D has abnormal uterine bleeding and polycystic ovarian morphology.

PATHOPHYSIOLOGY

PCOS is a metabolic condition. Insulin resistance (IR) is a key feature found in patients with PCOS and is tissue sensitive. Skeletal muscle, adipose tissue, and liver lose their sensitivity to insulin, whereas adrenal glands and ovaries remain sensitive. Insulin plays a vital role in androgen production in ovarian theca cells, stimulating ovarian follicle growth, hormone secretion, and ovarian steroidogenesis. In synergy with insulin-like growth factor (IGF)-1 and luteinizing hormone (LH), hyperinsulinemia increases LH-binding sites and the androgen-producing response of LH. IR independently increases the production of androstenedione and testosterone (T). Hyperinsulinemia reduces hepatic sex hormone-binding globulin (SHBG) and increases free T levels in the blood. Hyperinsulinemia also inhibits IGF-1-binding hormone, which leads to increased levels of IGF-1, causing higher production of androgens in theca cells, accelerating granulosa cell apoptosis, and inhibiting folliculogenesis. Collectively these mechanisms contribute to the menstrual irregularities, anovulatory subfertility, and growth of immature follicles seen in PCOS.[2]

Hyperinsulinemia also contributes to PCOS by affecting the pituitary gland and hypothalamus and increasing the production of LH and gonadotropin-releasing hormone. Hyperinsulinemia affects the adipose tissue by increasing adipogenesis and lipogenesis, inhibiting lipolysis, and increasing visceral and subcutaneous fat accumulation.[2]

Hyperandrogenism reduces SHBG levels, leading to a higher free T concentration. In women with PCOS, higher T levels are converted to estrone in adipose tissue. Increased alternation of estrone and estradiol affects follicle growth and increases LH to follicle-stimulating hormone (FSH) ratio, resulting in ovulatory dysfunction.[2]

The pathogenesis of PCOS is complex and influenced by multiple genetic, environmental, and hormonal factors. Obesity, particularly visceral fat accumulation, which is common in patients with PCOS, causes low-grade chronic inflammation, resulting in hyperinsulinemia, insulin resistance, and hyperandrogenism. However, nonobese patients with PCOS may also develop visceral fat accumulation, which is proinflammatory, thus leading to metabolic irregularities.[2]

Saturated fatty acids and vitamin D have been associated with the pathogenesis of PCOS. Saturated fatty acids reduce insulin sensitivity by triggering the inflammatory

pathway. Vitamin D deficiency exacerbates PCOS and its comorbidities by decreasing insulin sensitivity in adipose tissue and skeletal muscles, downregulating the antimüllerian hormone (AMH) promoter, and increasing insulin resistance via a proinflammatory response.[2]

There may exist a correlation between stress and PCOS. Stress is a proinflammatory process. Chronic stress can alter adipocytes, immune cells, inflammatory cytokines, cortisol levels, gluconeogenesis by the liver, insulin levels, AMH, and sex hormone levels, all of which are significant in the pathogenesis of PCOS.[2]

PCOS has been associated with multiple genetic alternations. Nineteen risk gene loci, including *THADA, ESHR, INS-VNTR,* and *DENND1A,* have been identified in the neuroendocrine, metabolic, and reproductive pathways.[3] There is a causal link between PCOS, and genetic variants associated with body mass index (BMI), fasting insulin, menopause timing, depression, and male pattern baldness. In addition to genetic foci, PCOS has also been linked to epigenetic mechanisms (inheritable alternations in the genome without changes in DNA sequence). Patients with PCOS have (1) an increased expression of LH receptor on the theca cell surface, resulting in increased steroidogenesis; (2) an increased gene expression and overproduction of the enzyme (epoxide hydrolase 1 EPHX1), reducing the transformation of T to estradiol[2]; and (3) alterations in granulosa cell receptors affecting hyperandrogenism and ovarian function.

PCOS has a component of transgenerational transmission. Daughters born to mothers with PCOS have a 5-fold higher risk of developing PCOS, possibly due to prenatal androgen excess and early androgen exposure.[3] The known genetic risk alleles account for less than 10% of PCOS heritability, suggesting that other etiologic risk factors play a role in PCOS development.

DIAGNOSIS

PCOS is a syndrome and not a uniform disease process; therefore, there is no single clinical finding or laboratory test that confirms the diagnosis. The 2003 Rotterdam criteria[4] are widely accepted for evaluating patients with possible PCOS; they consist of 3 criteria: (1) oligomenorrhea or amenorrhea, (2) clinical or biochemical evidence of androgen excess, and (3) polycystic ovaries on transvaginal ultrasonography. Patients designated as having PCOS must have 2 of these 3 criteria. Amenorrhea is usually secondary, defined as menstrual cycles of less than 21 or greater than 35 days 3 years postmenarche. Clinical hyperandrogenism includes hirsutism, acne, and male-pattern alopecia.

The advent of improved ultrasound technology has resulted in a change in the ovarian morphology criteria, previously based on ovarian size and weight, and now specifying the actual number and size of cysts/follicles. Ultrasonography should be transvaginal and use high resolution. For a diagnosis of PCOS, patients should have at least 25 small follicles (2 to 9 mm) in the entire ovary. Ovarian size at 10 mL remains the threshold between normal and increased. **Table 2** reviews a complete differential diagnosis and indications for additional testing.

There is incomplete agreement regarding the optimal biochemical test for androgen excess. Unlike total T, the measurement of free T is unaffected by the level of SHBG. There are recommendations for checking either free T or total T or calculation of the androgen index (total T/SHBG $\times$ 100).[4,5] Additional testing includes dehydroepiandrosterone and androstenedione if suspicion is high for an androgen-secreting tumor. There are strong recommendations *not* to pursue testing for AMH, FSH, or insulin levels.[5]

Table 2
Differential diagnosis of polycystic ovarian syndrome

Diagnosis	Testing	Diagnostic Workup[a]
Congenital adrenal hyperplasia (late-onset) (21-hydroxylase deficiency)	17-Hydroxy-progesterone	• 17-Hydroxy-progesterone • ACTH stimulation test • Genetic testing when biochemical tests are borderline and before conception
Androgen-secreting tumor (adrenal or ovarian)	Serum T and DHEA (markedly elevated)	• Total testosterone • DHEAS • 17-Hydroxy-progesterone • Rule out Cushing syndrome (see later) • IGF-1
Cushing syndrome	24-h UFC or overnight DST	Initial screening test • Late-night salivary cortisol (2 measurements) OR 24-h UFC excretion (2 measurements) OR overnight 1 mg DST Confirmatory tests • ACTH • CRH or desmopressin test • Imaging if indicated
Hypogonadotropic hypogonadism	Diagnosis of exclusion	• Serum testosterone • Pituitary hormone levels • GnRH stimulation test • Genetic testing before conception

Abbreviations: ACTH, Adrenocorticotropic Hormone; CRH, Corticotrophin-releasing hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; GnRH, gonadotropin-releasing hormone; TSH, Thyroid stimulating hormone; UFC, urinary free cortisol.

[a] TSH, prolactin, and, when appropriate, pregnancy test should be done on all patients as initial laboratory screening tests.

The diagnostic criteria for hyperandrogenism, initially limited to clinical findings only, were widened to include biochemical evidence of androgen excess to facilitate the diagnosis, because clinical signs of hyperandrogenism are only seen in 60% of patients with PCOS.[6] In addition, despite a universally accepted visual scoring system for assessing hirsutism (Ferriman-Gallway score[7]), hirsutism is difficult to quantitate, varies by race and ethnicity, and may be masked by procedures patients undergo to treat it (shaving, chemical removal or bleaching, electrolysis, laser removal). There are also visual scores for androgenic alopecia (AA) (the Hamilton-Norwood classification system for male pattern AA and the Ludwig grade system for female pattern AA) but none for acne.[7] Acanthosis nigricans may be seen in PCOS because it is a clinical manifestation of IR and may aid in diagnosis.

In the past, serum LH/FSH ratio was used for the diagnosis of PCOS. Because the LH and FSH hormone levels can vary in women with PCOS and their effects on oocyte maturity and fertilization is uncertain and variable, the Rotterdam European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine (ESHRE/ASRM)-sponsored PCOS consensus panel does not recommend the measurement of serum LH and FSH ratios for the clinical diagnosis of PCOS.[8] LH levels

are useful in basic science research, and additional studies are needed to clarify the clinical relevance of LH in PCOS, which may also pave the way for LH-related treatment options.

The diagnosis of PCOS in adolescents and perimenopausal women is problematic. In the former, menstrual cycles are often anovulatory for the first several years following menarche. In addition, adolescents often have large polycystic ovaries on ultrasonography, so using this criterion for diagnosis is unreliable.[3] Thus, in the absence of adolescent-specific criteria, anovulation should not be considered until greater than 2 years postmenarche, and ultrasound assessment should be delayed until 8 years postmenarche.[1,3,9] For older women, menstrual cycles may become more regular as they approach perimenopause, and women with PCOS may complete menopause at a later age; thus, the diagnosis may be more challenging to make in women in their postreproductive years.[3,9]

Because PCOS is familial and polygenic, the phenotypic expression will vary based on genetic penetrance and environmental factors. Four distinct phenotypes have been identified (see **Table 1**), although the clinical utility of these designations outside the research setting is unclear.[1] Along with the diagnosis of PCOS, screening for its associated diseases should be undertaken and appropriate treatment initiated (see later discussion). The prevalence of phenotypes varies considerably based on population, race, and ethnicity. Phenotypes A and B are seen frequently in obese women and are associated with more hyperandrogenism, insulin resistance, and worse cardiometabolic profiles. The prevalence of metabolic syndrome prevalence is lowest in phenotype D.[1] The different diagnostic criteria and varying phenotypes may contribute to the difficulty in recognizing and diagnosing this disorder.

CLINICAL IMPLICATIONS AND COMORBIDITIES

The most common abnormalities associated with PCOS are menstrual disorders, infertility, obesity, type 2 diabetes mellitus (T2DM), and the metabolic syndrome.[10]

PCOS has been associated with multiple reproductive comorbidities. Women with PCOS experience higher rates of infertility; they have an increased prevalence of adverse pregnancy outcomes, including gestational hypoglycemia, gestational diabetes, perinatal death, preeclampsia, pregnancy-induced hypertension, preterm delivery, cesarean delivery, and miscarriages.[11]

PCOS is a metabolic and not a gynecologic disease. IR is the critical underlying pathology of PCOS, resulting in a significant (3–7 times) increase in the risk of developing T2DM. IR is independent of obesity but may be worsened by it. Overweight or obese adult and adolescent women with PCOS have significantly higher total cholesterol, low-density lipoprotein, and triglyceride levels and significantly lower high-density lipoprotein levels.[11] Pregnant women with PCOS have higher systolic blood pressure when compared with nonpregnant women with PCOS. It is thought that patients with PCOS may have an increased prevalence of cardiovascular disease (CVD) and are at significantly increased risk for coronary heart disease and stroke; further studies are required to establish this association.[11]

Once the diagnosis of PCOS has been made, patients should be screened regularly for the development of T2DM, obesity, and hyperlipidemia. Again, the optimal screening test for T2DM is not agreed upon because the test with the best sensitivity and specificity, the 2-hour oral glucose tolerance test, is not routinely performed in most offices and is more cumbersome for patients. Fasting blood glucose or HbA_{1c} are acceptable options for most patients.[9] Obtaining insulin levels is not recommended in the evaluation of PCOS.

Patients with PCOS have an increased prevalence of metabolic syndrome and nonalcoholic fatty liver disease (NAFLD). Vitamin D deficiency in patients with PCOS worsens fasting blood glucose and fasting insulin; correcting the vitamin D deficiency improves insulin sensitivity. Patients with PCOS also have lower vitamin D levels, further exacerbating insulin resistance.[11]

PCOS negatively influences the quality of life measured by the health-related quality of life (HRQoL) index.[12] Studies have found that hyperandrogenism, menstruation abnormalities, BMI, and body weight issues have the strongest impact on quality of life.[11] Patients with PCOS have significantly higher depressive and anxiety symptoms scores, along with low self-esteem (related to issues of body image as well as potential infertility) and suboptimal sexual function.

In addition, adult women with PCOS have an increased risk of developing obstructive sleep apnea (OSA) compared with reproductive-age women of similar age. The risk for sleep disturbances in PCOS increases with age and adiposity. OSA in PCOS is associated with worsening metabolic parameters, anxiety, and depression.[13]

Finally, due to the relative excess of estrogen over progesterone and the lack of regular uterine lining shedding seen with regular menses, patients with PCOS have a 2.7 times higher risk for developing endometrial cancer, but not breast or ovarian cancer.[11,14]

MANAGEMENT

The management of patients with PCOS is varied and ultimately dictated by the patient's desired clinical outcomes. These outcomes may include weight loss, regression of hirsutism, regulation of menstrual cycles, and obtainment of pregnancy. In addition, attention should be paid to addressing metabolic risks and abnormalities (which vary by phenotype), lowering the risk of endometrial hyperplasia, and improving mental health. Despite the menstrual irregularly, most women with PCOS become pregnant without medical intervention, so the inclusion of contraception in treatment options should not be dismissed.

For all patients with PCOS, regardless of their clinical goals and preferences, lifestyle interventions should be initiated. Weight loss, dietary modification, and increased exercise should be part of first-line therapy for all patients. These interventions result in decreased androgen levels and IR, with as little as 5% to 10% weight loss resulting in improved CVD risk; the effect of lifestyle changes on ovulatory function, menstrual cycles, and fertility is minimal or uncertain.[15]

For hirsutism, many women use mechanical means, including local hair removal via plucking or shaving, bleaching, electrolysis, laser destruction of the follicles (epilation), and regular, long-term application of an ornithine decarboxylase inhibitor/eflornithine cream.[10] These interventions are usually required even when medications are used to achieve the desired cosmetic effect. Spironolactone, an antiandrogen, is explicitly used to target clinical hyperandrogenism features at doses starting at 50 mg daily and increasing to 100 mg twice daily. Because this drug is a known teratogen, it must be used in combination with a reliable method of contraception.[14] Other antiandrogens that may be used include ketoconazole and flutamide.[10]

Acne may be managed as in any other patient, using topical benzoyl, topical or oral antibiotics, and isotretinoin.[16] The use of combined estrogen/progesterone contraceptives, with or without specific acne treatment, will also improve this clinical manifestation of hyperandrogenism.

Menstrual irregularities can be managed with hormonal contraception—oral combination or progestin-only pills, combination patches, cyclic progesterone, or a

progesterone-containing implant or intrauterine device. All these methods will provide endometrial protection, and all except cyclic progesterone will also provide reliable contraception. Only estrogen-containing products will improve hyperandrogenism but may also increase CVD risk via increased risk for venous thromboembolism and adverse effects on cholesterol profiles.[14] Choosing a preparation with a lower dose of ethinylestradiol (30 μg or less) and a progestin with lower androgenic activity (norgestimate, drospirenone) can mitigate some of these effects.[9]

For patients desiring pregnancy, lifestyle modification, especially in women with obesity, may be all that is required. For ovulation induction, letrozole, an aromatase inhibitor, has replaced clomiphene as the first-line treatment, because recent data favor it over clomiphene for live birth and pregnancy rates and reduced time to pregnancy.[17] If letrozole is not available or if the cost is prohibitive, clomiphene is still very effective as a single agent or in combination with metformin. A trial of gonadotrophins may be considered for patients who fail to conceive with these 2 agents. Patients with PCOS who fail to conceive with ovulation induction medications may opt for in vitro fertilization and embryo transfer.

Metformin, a biguanide used in T2DM, has modest effectiveness in improving pregnancy rates in patients with PCOS through its mechanism against IR. Other medications currently being studied that show promise for patients with PCOS are thiazolidinedione, statins, vitamin D, fibroblast growth factor, and glucagonlike peptide (GLP-1) agonists.[10,18]

Bariatric surgery should be considered part of the treatment in morbidly obese patients with PCOS with metabolic syndrome.

SUMMARY

PCOS is a complex, familial, polygenetic metabolic condition. The Rotterdam criteria are commonly used to diagnose PCOS. Lifestyle changes are the first-line treatment of PCOS. Treatment options for menstrual irregularities and hirsutism are based on the clinical goals and preferences of the patient. Along with treating the symptoms of PCOS, it is essential to screen and treat the comorbid conditions commonly associated with PCOS, including T2DM, obesity, NAFLD, hyperlipidemia, OSA, anxiety, depression, infertility, and vitamin D deficiency.

CLINICS CARE POINTS

- PCOS is diagnosed using the Rotterdam criteria.
- Weight loss, dietary modification, and increased exercise is the first-line therapy for all patients.
- The treatment of symptoms, acne, hirsuitism or menstrual irregularities, is based on patients desired clinical outcomes.
- Screen and treat the comorbid conditions commonly associated with PCOS.

DISCLOSURE

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