The Role of Polycystic Ovary Syndrome in Reproductive and Metabolic Health: Overview and Approaches for Treatment

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Polycystic ovary syndrome (PCOS) is a condition with a range of reproductive and metabolic features that affects 4–18% of reproductive-age women, depending on the diagnostic criteria used (1,2). PCOS typically involves hormonal imbalances, insulin resistance, and metabolic abnormalities, which significantly increase the risk of infertility, type 2 diabetes, and cardiovascular disease (CVD) (3) and affect quality of life (4). Women with PCOS suffer from greater body dissatisfaction and are also at increased risk of mood, generalized anxiety, and eating disorders (2,5,6). Despite its prevalence and implications for reproductive, metabolic, and psychological health, PCOS is underdiagnosed, in part because of the diversity of phenotypes manifested by this condition.

PCOS and Reproductive Health

PCOS is the most common cause of anovulatory infertility; ~ 90–95% of anovulatory women seeking treatment for infertility have PCOS (7). Women may learn they have PCOS only after seeking infertility treatment. Most women with PCOS have elevated levels of luteinizing hormone and reduced levels of follicle-stimulating hormone (FSH), coupled with elevated levels of androgens and insulin (8). These imbalances can manifest as oligomenorrhea or amenorrhea (infrequent or lack of menstruation). Underproduction of estrogen and overproduction of androgens (testosterone, dehydroepiandrosterone, and androstenedione) by the ovaries can result in a number of additional clinical features, including tiny cysts on the surface of the ovaries (polycysts) and hair and skin symptoms (9). Women with PCOS who become pregnant are at higher risk than those without PCOS of developing gestational diabetes mellitus or suffering a first-trimester spontaneous abortion (2,9).

PCOS and Metabolic Health

Insulin resistance with compensatory hyperinsulinemia affects ~ 65–70% of women with PCOS (10). An estimated 30–40% of PCOS patients have impaired glucose tolerance (IGT), and 7.5–10% have type 2 diabetes (7,9). Conversely, the prevalence of PCOS is elevated among women who have already been diagnosed with type 1 or type 2 diabetes (2). Studies suggest that the annual progression rate from normal glucose tolerance to IGT and from IGT to type 2 diabetes in women is substantially enhanced among women with PCOS, with the highest risk in women who are also obese and have a family history of type 2 diabetes (9,11). A 2010 systematic review and meta-analysis (12) of 35 studies found that PCOS is associated with a 2.5-fold increased prevalence of IGT and a fourfold increased prevalence of type 2 diabetes. Insulin resistance, which occurs independently of obesity in PCOS (2), may affect ovulation and fertility by interfering with hepatic production of sex hormone–binding globulin

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(SHBG) (13). Reduced SHBG levels lead to an increase in free testosterone levels (14). Women with PCOS who have chronic anovulation but normal androgen levels tend to not be insulin resistant (15). The combination of anovulation and hyperinsulinemia can promote endometrial cell proliferation, increasing the risk of endometrial carcinomas and other abnormalities (16).

In addition to glucose and insulin abnormalities, CVD risk factors (hypertension, hyperlipidemia, impaired blood vessel function) often accompany PCOS (1,2). In the United States, 33–47% of women with PCOS have metabolic syndrome, a rate two to three times higher than that of age-matched healthy women without PCOS (16). Women with PCOS also have a four- to sevenfold higher risk of having a heart attack than women of the same age who do not have PCOS (17). Between 35 and 60% of women with PCOS are obese (15), which appears to worsen both the metabolic and reproductive features of the condition, particularly in cases of visceral adiposity (18). PCOS and metabolic syndrome have many anthropometric and metabolic abnormalities in common, and hyperinsulinemia may be a crucial link between the two conditions (14). Women who have PCOS and metabolic syndrome or type 2 diabetes are at the highest risk of CVD (19). Production of androgens tends to decrease in the years leading to menopause, so the menstrual cycles of women with PCOS often become more regular, with corresponding improvement in reproductive functioning (20,21). However, research on the impact of PCOS on cardiovascular risk in the postmenopausal years is inconclusive and lacking (22,23).

Etiology of PCOS

Although the exact cause of PCOS is unknown, it is understood to be a multifactorial condition with a genetic component. Approximately 20–40% of first-degree female relatives of women with PCOS go on to develop PCOS themselves, compared to an estimated 4–6% prevalence in the general population (16). Many women with PCOS have female relatives with PCOS, even if it was never diagnosed (2). As with type 2 diabetes, it is likely that numerous genes each make a small contribution to the etiology of PCOS; and recent genome-wide association studies have identified candidate genes (2,3,16). Any underlying genetic predisposition is likely complicated by epigenetic and environmental factors such as an unhealthy diet and lack of physical activity (3,16).

Diagnosing PCOS

Diagnosing and treating PCOS is important to preserve or restore fertility, reduce symptoms, and prevent complications that can develop in women with PCOS from adolescence to the postmenopausal period. Obstacles to timely diagnosis include the presence of multiple PCOS phenotypes and significant individual variation in clinical features, as well as competing diagnostic criteria from the National Institutes of Health (NIH), the European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM Rotterdam), and the Androgen Excess and PCOS Society (AE-PCOS) (Table 1) (3,15). To be diagnosed with PCOS under the ESHRE/ASRM Rotterdam criteria, which are considered to be a compromise between those of NIH and AE-PCOS, a woman must have at least two of three criteria after other related health conditions are ruled out: oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries visible by ultrasound (24,25). Although approximately three out of four women with PCOS have polycysts on their ovaries, this clinical feature is no longer deemed necessary or sufficient for diagnosis. One recommendation from the NIH Evidence-Based Methodology Workshop on Polycystic Ovary Syndrome held in December 2012 was that PCOS be renamed to more accurately reflect the complex nature of this syndrome and its implications for women's reproductive and metabolic health (3).

Clinically, PCOS may manifest as a mild menstrual disorder or a severe disturbance of reproductive and metabolic functions (15). Most visible signs are caused by excessive production of insulin or androgens. Hirsutism (excess hair growth on the face and body) is present in ~ 70% of women with PCOS and is considered to be a good marker for hyperandrogenism but should be evaluated biochemically (20). Alopecia (thinning scalp hair), acne, and other skin symptoms are less common and are not good markers (20). Oral contra-

TABLE 1. Diagnostic Criteria for PCOS

NIH, 1990	ESHRE/ASRM Rotterdam, 2003	AE-PCOS Society, 2006
Both criteria needed: • Chronic anovulation • Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies)	Two of three criteria needed: • Oligo-ovulation and/or anovulation • Clinical and/or biochemical signs of hyperandrogenism • Polycystic ovaries	Both criteria needed: • Clinical and/or biochemical signs of hyperandrogenism • Ovarian dysfunction (oligo-anovulation and/or polycystic ovaries)

ceptive use can temporarily "hide" PCOS by lowering androgen levels, preventing visual signs, and helping to regulate the menstrual cycle, and some women with PCOS have normal androgen levels. Because acne is common in adolescence and the menstrual cycle is often irregular for the first few years of menstruation, progressive hirsutism may be the most consistent marker for PCOS in the teenage years (20,21). It has been suggested that a definitive diagnosis be deferred until at least 2 years after onset of menstruation to assess whether other diagnostic criteria are met (26,27). As with adult PCOS phenotypes, obesity can exacerbate symptoms of hyperandrogenism and hyperinsulinemia in the adolescent phenotypes, and these issues can be treated before a PCOS diagnosis is confirmed (16,26,27).

Insulin resistance can cause acanthosis nigricans, which presents as "dirty looking" raised velvety areas on the skin, often in body folds around the neck, armpits, groin, and breasts. It can also cause skin tags, rough elbows, and rough, reddened hair follicles on the upper arms. Women with PCOS who have insulin resistance may experience hyperglycemia and hypoglycemia and report having intense cravings for carbohydrates. The AE-PCOS Society recommends that all women with PCOS be screened for IGT with a 2-hour oral glucose tolerance test and that women with normal glucose tolerance at baseline be screened at least once every 2 years, or earlier if they have additional risk factors for type 2 diabetes such as obesity or family history of diabetes or metabolic syndrome (9,11).

Other important information to aid diagnosis include weight history, results of previous blood tests and ultrasounds, and menstrual history. Prolonged anovulation may lead to dysfunctional uterine bleeding that mimics menstrual bleeding, and women with oligo-ovulation may experience heavy bleeding when they do menstruate (24). Patients may not know if they have a family history of PCOS; asking about a history of irregular periods or infertility among first-degree female family members can be useful.

Treating PCOS: Lifestyle Interventions

Because the underlying pathophysiology of PCOS has not been fully determined yet, treatment plans typically focus on specific symptoms. Lifestyle change (dietary, exercise, or behavioral interventions) is considered the first-line treatment for management of infertility and metabolic complications in women with PCOS, including reduction of the conversion rate from IGT to type 2 diabetes (2,9,28) and CVD risk (19). Intensive lifestyle modification and weight reduction has been shown to reduce circulating insulin and androgen levels and improve lipid and FSH levels, which can reduce many of the physical symptoms, normalize menstrual cycles, induce ovulation, and improve general health (1,8,15,16). For women with PCOS who are overweight or obese, weight loss of as little as 5–10% has been associated with significant clinical benefits in improving reproductive, metabolic, and psychological features of the condition (2,7).

No specific dietary composition has been demonstrated to be most beneficial, in part because of clinical heterogeneity and methodological problems with the current body of research (29,30). A recent systematic review (30) found that subtle but inconclusive improvements were observed with a low-glycemic diet but that further research is needed. This review did find that a nutritionally adequate weight loss diet based on healthy food choices was of clinical benefit in overweight and obese women with PCOS regardless of the diet composition.

Along with a healthful eating plan, regular physical activity can help with many of the issues and health concerns that surround PCOS by increasing SHBG and decreasing androgen levels, improving insulin sensitivity, assisting with weight management, improving lipid levels, and lowering blood pressure (31). Regular physical activity can also improve mood and body image and help reduce chronic stress and stress-related eating, although women with PCOS should also be screened for mood and anxiety disorders and treated using established therapies (6). Vitamin D deficiency is common in women with PCOS, and there is limited evidence that vitamin D supplementation may improve reproductive function and insulin sensitivity (32). Although more randomized controlled trials are needed, vitamin D levels should be tested, and supplementation may be warranted to increase low levels, especially in women undergoing in vitro fertilization (33).

Medical nutrition therapy (MNT) can help women with PCOS make and maintain the lifestyle changes needed to help reduce symptoms and prevent complications. MNT is based on an assessment of lifestyle changes that would help a patient with PCOS achieve and maintain clinical goals. The Academy of Nutrition and Dietetics' evidence-based nutrition practice guidelines (34) recommend the following structure for the implementation of MNT for adults with PCOS:

- Thorough nutrition assessment to help prioritize MNT
- Nutrition diagnosis, which includes the presence of, risk of, or potential for developing a nutritional deficit that can be addressed by nutrition therapy
- Nutrition interventions, which are specific actions to remedy the nutrition diagnosis; these can include clinical and behavioral goals collaboratively agreed upon with the patient, as well as specific nutrition interventions such as selecting a meal-planning strategy or education on controlling

portion sizes or making healthy choices when dining out
- Nutrition monitoring and evaluation with ongoing follow-up to support long-term lifestyle changes, evaluate outcomes, and modify interventions as needed

The following case study demonstrates how MNT can effectively facilitate lifestyle changes that lead to improved health outcomes.

Case Study: MNT in PCOS

Patient

The patient, Gita, is a 27-year-old South-Asian female referred for MNT with diagnoses of PCOS and infertility.

Food- and Nutrition-Related History

Gita is a lacto-vegetarian who consumes no eggs because of her religious beliefs. She typically skips breakfast; eats a granola bar or orange juice for lunch; snacks on chocolate candy bars, juice, or fruit smoothies; and then enjoys a full supper of vegetarian curry, basmati rice, vegetables, and lentils. She reports having gained 20 lb since moving to the United States from India 1 year ago.

Nutrient Intake

- Most calories consumed at night
- Diet high in carbohydrates

Activity

- Very minimal physical activity

Anthropometrics

- Height: 5 feet, 3 inches
- Weight: 162 lb
- BMI: 28.7 kg/m^2
- Waist circumference: 38.4 inches

Biochemical Data

- A1C: 5.5% (normal 4.5–6%) (1)
- Fasting blood glucose: 90 mg/dL (normal 70–100 mg/dL)
- Vitamin D: 6 ng/mL (normal 30.0–74.0 ng/mL)
- Cholesterol: 188 mg/dL (normal <200 mg/dL)
- HDL cholesterol: 34 mg/dL (normal ≥60 mg/dL)

Nutrition Diagnoses

- Diagnosis 1: Excessive carbohydrate intake related to knowledge deficit as evidenced by diet history and BMI
- Diagnosis 2: Physical inactivity related to knowledge deficit as evidenced by current physical activity level

Nutrition Intervention

Gita agreed to eat three meals and two snacks daily, distributing carbohydrates with fat and protein throughout the day. She can now identify the carbohydrate content of Indian dishes and knows how to balance carbohydrate portions. She understands how to add protein sources to meals and snacks by adding servings of soy milk and yogurt and by using lentils, beans, edamame, and quinoa to provide protein and low-glycemic carbohydrates. She will increase her intake of omega-3 fatty acids through food sources such as nuts, flax, and chia seeds. She also agreed to include the following supplements in her routine: vitamin D (50,000 IU weekly for 8 weeks), ground flax, and a prenatal multivitamin and mineral. In terms of physical activity, she will begin with 15 minutes of walking daily and gradually work up to 45 minutes daily.

Monitoring/Evaluation

- Record dietary intake, including carbohydrate servings, and e-mail them directly to the registered dietitian every week
- Meet for in-person MNT sessions every 3–4 weeks

Outcomes

Gita lost 12 lb (8% of baseline body weight) over 6 months and successfully conceived a healthy son through the use of timed intercourse. She met with the dietitian for an additional nutrition session during pregnancy, and her glucose tolerance test result was normal.

Treating PCOS: Pharmaceutical Interventions

When lifestyle treatment does not result in desired outcomes, pharmacotherapy may be added. In premenopausal patients not currently trying to become pregnant, the Endocrine Society recommends hormonal contraceptives as the first-line therapy to manage menstrual abnormalities and reduce hirsutism and acne (2,35). Metformin helps to improve insulin sensitivity in both women and adolescents with PCOS, which in turn can decrease circulating androgen levels and normalize the menstrual cycle and ovulation (2,15,36). Clomiphene citrate, an estrogen receptor antagonist, is the drug of first choice for induction of ovulation in women with PCOS (2). However, most published, randomized, controlled trials that used medications such as clomiphene citrate or metformin failed to find significant differences in menstrual function between lifestyle intervention and pharmacotherapy. For that reason, in infertile overweight or obese adults with PCOS, evidence does not support treatment with these drugs ahead of either lifestyle intervention alone or starting lifestyle treatment in combination with these drugs (29,37,38). The Endocrine Society recommends metformin for adult PCOS patients with IGT or type 2 diabetes when lifestyle interventions alone are not sufficient and for adolescent patients who have IGT or metabolic syndrome (35).

Summary

Although PCOS is treatable with lifestyle changes and medication, many of the estimated 1 in 10 women with this condition go without adequate treatment because of underdiagnosis. To facilitate accurate diagnosis and timely treatment, clinicians who see female patients need to be familiar with the diversity of PCOS phenotypes that may be encountered in a clinical setting. The adverse effects of PCOS on ovulation and fertility understandably garner much attention, but this condition has broader implications for a woman's metabolic and

psychological health before, during, and after her reproductive years, and treatment interventions should reflect that fact.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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