



Clinical Presentation and Diagnosis of Polycystic Ovarian Syndrome

JESSICA A. LENTSCHER, MD,
and ALAN H. DECHERNEY, MD

Program of Reproductive Endocrinology and Infertility, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Abstract: Polycystic ovarian syndrome (PCOS) is a common endocrinopathy with many clinical manifestations. The effects on women's lives start at puberty and can last throughout her lifetime. Women frequently experience anovulatory menstrual cycles, infertility, hirsutism, obesity and increased risk of diabetes mellitus, hypertension, lipid abnormalities, and metabolic syndrome. PCOS is a heterogenous disorder, and a diagnosis of exclusion. In general, women afflicted will have menstrual irregularities, ultrasound findings of abnormal ovarian size and morphology, and clinical or laboratory evidence of hyperandrogenism. This chapter reviews the current understanding of PCOS, associated metabolic abnormalities, and diagnosis in reproductive-aged women, as well as adolescents.

Key words: polycystic ovarian syndrome, diagnosis, infertility, hirsutism

Introduction

Polycystic ovarian syndrome (PCOS) is a complex, enigmatic, and common disease. It is the most common endocrinopathy faced by

reproductive-aged women, and affects up to 1 in 5 women.¹ Women frequently have anovulatory menstrual cycles, hirsutism, obesity, and are at risk for diabetes mellitus, hypertension, lipid abnormalities, sleep disorders, depression, and metabolic syndrome. Persistent anovulation also increases risk of endometrial cancer.

History of PCOS

Current understanding of PCOS has advanced in the past 170 years. In 1844, the first description of enlarged, polycystic ovaries surrounded by a smooth capsule was reported in France.² In 1935, Stein and Leventhal³ described a symptom collection to include amenorrhea and polycystic ovaries. They noted ovaries in women with these symptoms had a thickened ovarian capsule. Their initial work described 7 patients with amenorrhea, hirsutism, and polycystic ovaries that were notably enlarged. After observing several patients resume menses following

Correspondence: Jessica A. Lentscher, MD, 9000 Rockville Pike, Bethesda, MD. E-mail: jess.lentscher@gmail.com

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an ovarian biopsy, they subjected these patients to an ovarian wedge resection. They reported that all 7 resumed regular menses and that 2 became pregnant after bilateral ovarian wedge resection, involving the removal of one half to three fourths of each ovary. The disease was initially named for the first 2 physicians to link infertility, amenorrhea and polycystic ovaries, “Stein-Leventhal syndrome,” but as new studies have been published, and more information regarding the pathophysiology has come to light, a gradual change in nomenclature to “Polycystic Ovarian Syndrome” generally has become accepted.

Current Understanding of PCOS

Current understanding has developed significantly in the past few decades; however, the etiology of this syndrome is still not well known. PCOS is a likely a complex, multigenic disorder with epigenetic and environmental influences, to include a patient’s diet, exercise and lifestyle features.⁴ The principal clinical manifestations are menstrual irregularities and hyperandrogenism. There are many causes of anovulation, so many conditions may lead to the development of PCOS. PCOS is a heterogeneous disorder, and is a diagnosis of exclusion. In general, women afflicted will have menstrual irregularities, ultrasound findings of abnormal ovarian size and morphology, and clinical or laboratory evidence of hyperandrogenism. The later frequently is associated with metabolic dysfunction with associated insulin resistance, dyslipidemia, obesity, and cardiovascular risk factors.

Many women go undiagnosed throughout adolescence, although the disease is thought to start having manifestations perhaps even before puberty. As such, many women do not seek care until they are trying to achieve pregnancy. Early diagnosis and intervention can allow for life-changing effects in these young women’s lives, and allows for unique opportunities for the Obstetrician and Gynecologist to intervene.

Pathophysiology of PCOS

The exact mechanism of PCOS development is not yet completely elucidated, however there are several hallmarks of abnormal function in women with PCOS. Pathophysiological abnormalities in gonadotropin secretion, and ovarian folliculogenesis are well-known, however, steroidogenesis, abnormal or impaired insulin secretion or action, and abnormal adipose tissue function, have also been described in PCOS. In the hypothalamus and pituitary, women with PCOS have increased gonadotrophin secretion of luteinizing hormone (LH), as well as increased LH pulse amplitude and frequency.⁵ In his recent review, Azziz notes that increased LH pulses and overall increased daytime secretion of LH is observed early during puberty in girls with hyperandrogenism, which may indicate that abnormalities of LH may be a primary defect in PCOS. This increased LH secretion leads to stimulate increased androgen production in the ovarian theca cells, which leads to hyperandrogenism in these females.⁵ Follicles within the ovary have also been noted to have increased resistance to follicle stimulating hormone (FSH), which may contribute to the pathophysiology of PCOS. Ultimately in most women with PCOS, LH to FSH ratios are inverted from normal, with LH increasing, usually 3 times that of FSH. In addition, the ovaries excrete high levels of anti-Mullerian hormone, a glycoprotein made in granulosa cells by preantral follicles, which may contribute to the disorder.⁶

Clinical Presentation

PCOS presents in women in a myriad of ways, as this condition is a spectrum of clinical signs and symptoms. Clinical or biochemical hyperandrogenism, oligoanovulation and polycystic morphology are the generally accepted diagnostic criteria. In general, women with PCOS have 2 main phenotypes: lean and obese.

A small portion of patients with PCOS present with a normal body mass index (BMI; $\leq 25 \text{ kg/m}^2$), and are classified as “lean PCOS.” Recent research suggests that metabolic, hormonal, and hematological abnormalities are similar to women with “obese PCOS,” however they are usually more subtle and less-severe.⁷

Ovarian dysfunction typically results in oligomenorrhea or amenorrhea due to chronic oligo-ovulation or anovulation. Oligo-ovulation is defined as a menstrual cycle > 35 days in length; although some prefer to define oligo-ovulation as < 8 menstrual cycles a year, or cycles > 45 days in length. Approximately 70% to 80% of women with PCOS present with oligomenorrhea or amenorrhea.¹ Up to 40% of hirsute women who claim to be eumenorrheic are actually oligo-anovulatory.⁸ Menstrual irregularity usually begins in adolescence, but is frequently masked with oral contraceptive pill treatments. It is not until they attempt to reproduce and discontinue the hormonal treatment that they seek medical evaluation and treatment. Women may initially present to their provider complaining of infertility, as absence of ovulation leads to infertility. PCOS is the most common cause of anovulatory infertility, and accounts for 90% to 95% of women in infertility clinics.¹

Hyperandrogenism typically presents with hirsutism, which is the presence of unwanted terminal hair growth in a male-like pattern. Terminal hairs grow beyond 5 mm in length, are medullated, and often have both pigment and shape. In contrast, vellus hairs are unmedullated, softer, < 5 mm in length, are uniform in shape and may or may not be pigmented. Traditionally the amount of hirsutism is graded visually using the modified Ferriman-Gallwey (mFG) score. Nine areas of the body (upper lip, chin and neck, upper chest, upper abdomen, lower abdomen, lower abdomen or male escutcheon, upper back, lower back, upper arms, and thighs) are graded each a score of 0 (no visible terminal hair) to 4 (terminal hair growth consistent with normal adult male),

and summed, with a possible total score of 36. A total mFG score > 3 is defined as abnormal body hair, and a score of 6 or more is significant hirsutism.⁵ There are limitations to the mFG scoring system: there are ethnic differences in hair growth and distribution, women typically treat unsightly hair with removal or shaving, and adolescents may not fully exhibit hair growth until later in development. When evaluating for biochemical hyperandrogenism, a total and free testosterone should be assessed.⁵ Acne and alopecia are additional clinical signs of hyperandrogenism, however independently both acne and female alopecia are not specific to hyperandrogenism, especially in the absence of hirsutism.

Ovarian morphology is typically assessed with transvaginal ultrasonography. Polycystic ovarian morphology is defined as an abnormal ovary(ies) with a volume $> 10 \text{ mL}^3$ and/or > 12 follicles measuring between 2 and 9 mm in size in at least 1 ovary.

Diagnosis

PCOS is a syndromic disease and patients are on a clinical spectrum; as such it historically has been difficult to agree on diagnostic criteria. There have been 3 prior efforts to classify and diagnose PCOS (Table 1). In 1990, The National Institute of Child Health and Human Development (NICHD) concluded that the major criteria of diagnosis of PCOS were (1) hyperandrogenism and/or hyperandrogenemia, (2) menstrual dysfunction, and (3) exclusion of other endocrinopathies.⁹

Later, in 2003, the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) held a co-conference in Rotterdam, the Netherlands. Thusly coined the “Rotterdam Criteria,” they concluded that a diagnosis of PCOS should include 2 of the 3 criteria: (1) oligo-anovulation, (2) clinical or biochemical evidence of hyperandrogenism,

TABLE 1. Diagnostic Criteria for Polycystic Ovarian Syndrome

*All Criteria require exclusion of other endocrinopathies

1990 National Institute of Child Health and Human Development (NICHD)⁹ (both criteria needed for diagnosis)

1. Hyperandrogenism and/or hyperandrogenemia
2. Oligo-anovulation

2003 Rotterdam Criteria¹⁰ (minimum of 2 of 3 criteria needed for diagnosis)

1. Clinical or biochemical hyperandrogenism
2. Oligo-anovulation
3. Polycystic ovaries

2006 Androgen Excess-Polycystic ovary syndrome Society Criteria (AE-PCOS)¹¹ (both criteria needed for diagnosis)

1. Hyperandrogenism (clinical and/or biochemical)
 2. Ovarian dysfunction (oligo-anovulation and/or polycystic ovaries)
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and (3) polycystic-appearing ovaries on ultrasound. Ultrasound findings of an abnormal ovary(ies) was described as an ovarian volume $> 10 \text{ mL}^3$ and/or > 12 follicles measuring between 2 and 9 mm in size in at least 1 ovary. The Rotterdam criteria also state exclusion of other endocrinopathies with a similar presentation is necessary for diagnosis of PCOS.¹⁰

The most recent effort was a task force appointed by the Androgen Excess and PCOS Society (AE-PCOS) in 2006. This meeting led to the conclusion of PCOS needing (1) hyperandrogenism (hirsutism and/or hyperandrogenemia), (2) ovarian dysfunction (oligo-anovulation or polycystic ovary), and (3) exclusion of other androgen excess or related disorders.¹¹

The Rotterdam criteria was the first to account for the large spectrum of disorders that women may face, and allow for inclusion of many. Under the Rotterdam criteria, a woman only needs 2 of the 3 criteria, so she need not have polycystic ovaries, or hyperandrogenism, or menstrual abnormalities. Now the Rotterdam criteria are the most commonly accepted and used. Because of the clinical variation seen in patients, there is a desire for an evidence-based criteria, however, there is not currently an existing epidemiologic or basic research basis robust enough to support a more conclusive diagnostic criteria.¹² All 3 of the currently used criteria are based on expert opinion alone.

This serves a point of contention for many, as some experts declare that PCOS is predominantly a disorder of androgen excess¹³ and others maintain that the disease has a broader spectrum of presentation.¹⁴

Women meeting inclusion of PCOS by the NICHD criteria have an increased risk of metabolic and reproductive disorders, such as type 2 diabetes mellitus, obesity and dyslipidemia.¹⁵ Oligo/anovulatory women without clinical or biochemical evidence of hyperandrogenism tend to be the least affected by the sequela of PCOS,¹⁶ so the accurately diagnosing women may assist clinicians in predicting life-long risks and interventions to patients on a more individualized basis.

Diagnosis in Adolescents

Diagnosing PCOS in adolescents presents unique challenges, as menstrual cycles have physiologic variability during this period, and women normally have reproductive and hormonal fluctuations. As such, there is no general consensus for diagnosis in adolescents. Multifollicular ovaries are found in 26% of adolescents, and not specific to those with PCOS. In addition, ovarian volume is typically larger in adolescents compared with adults. Interestingly, after a period of 2 years after menarche, typically age 14 to 19, a period of prolonged oligomenorrhea has been found to be predictive

of persistent ovarian dysfunction later in life.¹² ESHRE/ASRM published diagnostic criteria for adolescents, and when these young patients do not clearly meet criteria by the adult female standards, the diagnosis of PCOS should be considered on the basis of increased serum androgen levels and/or progressive hirsutism, in association with persistent oligo/amenorrhea for at least 2 years after menarche and/or primary amenorrhea by the age 16 years, and/or an ovarian volume $> 10 \text{ cm}^3$, after exclusion of secondary causes.¹⁷

Diagnosis in Menopausal Transition

Diagnosing PCOS in the perimenopause and postmenopause period is difficult, as menstrual cycles, by definition, are changing to different cycle lengths, more infrequent or ceasing altogether. Some women may gain menstrual cyclicality during this period, have a decrease in ovarian volume and number of follicles, and maintain serum androgen levels, which can mask the clinical presentation of PCOS. There is limited data regarding the normative ranges of androgens during the perimenopause period, however there is a general trend toward higher levels in androgen levels in women with PCOS.¹²

Additional Evaluation

In addition to a history, physical examination, and pelvic ultrasonography, laboratory evaluation is also appropriate in a woman presenting with complaints consistent with PCOS. Before diagnosing patients with PCOS, it is important to rule out other mechanisms for anovulation, as they frequently present with similar clinical symptoms. Conditions to be evaluated include hyperprolactinemia, thyroid disease, pituitary tumors inhibiting gonadotropin secretion, central inhibition (stress, weight loss, physical stress,

TABLE 2. Hormonal Testing in Women With Suspected Polycystic Ovarian Syndrome

Hyperandrogenism:
Total and free testosterone
DHEA-S
Ovulatory dysfunction:
Progesterone cycle day 22-24
AMH
Excluding similar disorders:
TSH
Prolactin
17-OHP
Oral GTT
Lipid panel
24-h urine free cortisol

AMH indicates anti-Mullerian hormone; DHEA-S, dehydroepiandrosterone-sulfate; GTT, glucose tolerance test; TSH, thyroid-stimulating hormone; 17-OHP, 17-hydroxyprogesterone.

eating disorders—these conditions typically result in amenorrhea, but lesser degrees of insult may result in intermittent anovulation). A general evaluation should include a prolactin level, thyroid-stimulating hormone level, dehydroepiandrosterone-sulfate, lipid panel, testosterone panel, glucose tolerance test and if clinically indicated, 24-hour urine free-cortisol screen for Cushing disease and 17-hydroxyprogesterone for nonclassic Congenital Hyperplasia (Table 2).⁵ Documentation of ovulation with a serum progesterone level cycle day 22 to 24 is useful. Rarely, severe insulin-resistance syndrome may present with similar symptoms, in which case consultation with a specialist is recommended as well as an insulin level screen. An anti-Mullerian hormone level may be drawn as a surrogate for antral follicle, but is not necessary for diagnosing PCOS.

ENDOMETRIAL BIOPSY

Prolonged oligo-amenorrhea or amenorrhea as well as the presence of hyperinsulinemia puts women with PCOS at increased risk of endometrial hyperplasia and carcinoma, especially if obesity is present. As such, an evaluation of the

endometrial tissue with an endometrial biopsy should be considered in women with a long history of untreated oligo-amenorrhea, particularly if an increased endometrial thickness is noted on ultrasound.⁵

Common Associated Abnormalities

Many factors may also contribute to the syndrome of polycystic ovary, and affect many systems within the body. Insulin acts upon adipocytes, skeletal and cardiac muscle to stimulate glucose uptake, and suppresses hepatic cell glucose production, as well as lipolysis. Insulin resistance is a decreased ability of insulin to have these physiologic effects, and leads to increased circulating levels of insulin in response to a glucose load.¹⁸ Insulin resistance leads to hyperinsulinemia, which acts with LH to stimulate androgen production in ovarian theca cells. This excess androgen works with insulin to decrease sex hormone-binding globin, which further acts to increase free androgens and leads to hirsutism. Decreased insulin sensitivity is likely multifactorial, with multiple genetic and epigenetic abnormalities altering function in the principal cellular transporter for glucose, glucose transporter 4 and insulin-mediated glucose disposal.^{5,18}

INSULIN RESISTANCE

Insulin resistance plays a large role in the pathophysiology of PCOS and associated conditions, such as metabolic syndrome and cardiovascular disease. The pathogenesis of insulin resistance in PCOS is incompletely understood, however in their 2012 update on PCOS mechanisms, Diamanti-Kandarakis and Dunaif¹⁸ suggest there is a postbinding defect in insulin receptor signaling. Prevalence rates of insulin resistance have been reported between 44% and 85%.¹⁹ The gold-standard test for insulin resistance is the euglycemic insulin clamp

test, however cost and logistics limit its clinical use.²⁰ Women with PCOS primarily have postprandial dysglycemia, as opposed to fasting dysglycemia, which suits the alternative test of the oral glucose challenge test to detecting abnormalities.¹⁸

OBESITY

Obesity is commonly seen in women with PCOS, although not all women with PCOS are obese. Obesity has shown to contribute to PCOS symptoms, and the amount of visceral fat, in particular, has been shown to play a key role. Visceral adipose tissue releases several adipokines, including adiponectin. Adiponectin has decreased expression in obesity, and has been linked to insulin resistance. Adiponectin is an insulin-sensitizing, anti-inflammatory molecule.¹⁹ A meta-analysis in 2014 noted lower total adiponectin levels in PCOS women compared with normal controls, independent of BMI.²¹ Visceral fat likely contributes largely to insulin resistance, which leads to the development of impaired glucose tolerance and type 2 diabetes mellitus.¹⁹ The conversion rate of insulin-resistance to diabetes mellitus is estimated to range from 2.5% to 3.6% annually over a period of 3 to 8 years.¹⁸

DYSLIPIDEMIA

Dyslipidemia is common in women with PCOS compared with weight-matched controls.¹ Typically women have higher levels of triglycerides and lower high density lipoprotein levels.²² This association is independent of BMI, however obesity has been shown to worsen lipid profiles.¹ Insulin resistance appears to also play a role in hyperlipidemia, by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase.²²

SLEEP DISTURBANCES

Beyond insulin and lipid abnormalities, the ramifications of PCOS reach to psychological, behavioral and other metabolic health. In the past 15 years, new evidence has

been published demonstrating a link between PCOS and sleep disorders. Women with PCOS have increased incidence of obstructive sleep apnea and excessive daytime sleepiness. Obesity is more common in women with PCOS, but in their review, Fernandez and colleagues note that obesity only partially accounts for sleep disturbances. After adjusting for BMI, women with PCOS were found to have a higher incidence, including women who had normal weights.²³ As the endocrine system plays an important role in governing the sleep wake cycle, it is likely that PCOS independently disrupts the natural arousal and sleep mechanisms. Interestingly, several studies have demonstrated a link between sleep disruption and sleep restriction worsening insulin resistance, and sleep disorders may play a role in the development of insulin resistance.²⁴

METABOLIC SYNDROME

Metabolic syndrome comprises of multiple metabolic disorders that directly increase the risk of diabetes mellitus type 2, cardiovascular disease and coronary artery disease. International Diabetes Federation diagnosis includes 3 of the 5 abnormal criteria in women: hypertension (blood pressure $\geq 130/85$ mm Hg, triglycerides ≥ 150 mg/dL, waist circumference ≥ 88 cm, fasting glucose ≥ 100 mg/dL, and high density lipoprotein <50 mg/dL). Pharmacologic treatment for hypertension, abnormal glucose, or dyslipidemia counts for one of the diagnostic criteria. There is an increased risk of metabolic syndrome in women with PCOS. A recent study noted the risk of metabolic syndrome is 11-fold higher in women with PCOS compared with age-matched controls.²⁵

CARDIOVASCULAR RISK

In combination with increased incidence of diabetes mellitus, obesity, obstructive sleep apnea, women with PCOS have an independent risk of cardiovascular disease. There is an increase in inflammation,

oxidative stress and impaired fibrinolysis in women with PCOS.²⁶ In a 2018 study, Glintborg and colleagues investigated cardiovascular disease risk in a population study of Danish women with PCOS compared with controls without PCOS. They found the hazard ratio (95% confidence interval) for developing cardiovascular disease was 1.7 in women with PCOS. Obesity, diabetes, infertility, and previous oral contraceptive use was associated with an increased risk of cardiovascular disease. Outcomes included hypertension and dyslipidemia.²⁷

PSYCHOLOGICAL EFFECTS

Women with PCOS are more prone to have depression, anxiety, low self-esteem, a negative body image and psychosexual dysfunction.¹ There are concerns with feminine identity and body image, largely thought to be attributed to increased prevalence of obesity, acne, excessive male-pattern hair, infertility, and long-term health consequences. These are thought to lead to poor body image, mood disturbances and reduced psychological wellbeing. In 2019, Damone and colleagues evaluated the symptoms of depression, anxiety, and perceived stress in women reporting PCOS and women without PCOS. They found that even after adjusting for BMI, infertility diagnosis, sociodemographic factors, women with PCOS were still more likely to be depressed, anxious and have a higher level of perceived stress.²⁸ Unfortunately, evidence also suggests that the negative impact of these mood disturbances lead to decreased motivation and ability to implement and sustain lifestyle modifications needed to manage these conditions.²⁹

Conclusions

PCOS is a frequently-encountered condition by the Obstetrician and Gynecologist. Women may present with a spectrum of symptoms, linked to ovulatory dysfunction, insulin resistance and need

complete evaluation. A thorough evaluation should exclude secondary causes for oligo-ovulation and hyperandrogenism. Women may present in adolescence, and this provides a unique opportunity to inform the patient of PCOS and the associated risks. Patients need counseling regarding risk of obesity, metabolic syndrome, and life-long risk of development of cardiovascular disease, coronary artery disease, diabetes mellitus type 2, obesity, infertility, depression, anxiety, sleep disorders, and endometrial cancer. Early education and counseling allow for women to make health lifestyle interventions and modifications.

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