

Polycystic ovary syndrome: diagnostic issues

by Dr M. Hunter

Recent diagnostic challenges have focused renewed attention on polycystic ovary syndrome (PCOS). Clinical features of the syndrome include anovulation, hyperandrogenism and menstrual dysfunction, but several other abnormalities occur, including hyperinsulinaemia, luteinising hormone hypersecretion, elevated testosterone levels and acyclic oestrogen production. Accompanying obesity and lipid abnormalities point to a form of metabolic syndrome, and create long-term risks for the development of diabetes mellitus and cardiovascular disease. Chronic anovulation also places patients at risk for endometrial cancer. Because of these risks, it is of utmost importance to identify such patients early in the course of disease, using both clinical, radiologic and laboratory testing. This article will focus on the diagnostic laboratory evaluation for PCOS.

Polycystic ovary syndrome (PCOS), one of the most common endocrine disorders, affects approximately 6 percent of women of reproductive age [1]. PCOS is the most frequent cause of anovulatory infertility, with its underlying aetiology unknown. The classic description of the syndrome, which includes clinical findings of amenorrhea, hirsutism and bilaterally enlarged ovaries, is representative of more advanced cases. PCOS is now recognised as a heterogeneous and progressive syndrome, with its onset in peripubertal years. Affected women often have signs and symptoms of elevated androgen levels, menstrual irregularity and amenorrhea, without a well-defined cause of androgen excess.

Recent developments in pelvic ultrasonography have enabled more detailed descriptions of bilaterally enlarged cystic ovaries. Studies concerning treatment of underlying metabolic disturbances associated with PCOS are presently ongoing. Currently, treatment approaches are directed at ameliorating the signs and symptoms that PCOS patients experience, preventing potential long-term consequences of chronic anovulation, and treating the underlying metabolic disturbances often associated with the syndrome.

Pathophysiology

Underlying defects in PCOS remain unknown, but there is a growing consensus that the key features include insulin resistance, androgen excess and abnormal gonadotropin dynamics [2]. Recent evidence suggests that the principal underlying disorder is one of insulin resistance, with resulting hyperinsulinaemia stimulating excess ovarian androgen production. PCOS is further defined as an accumulation of many incompletely developed follicles in the ovaries due to chronic anovulation with increase in ovarian androgen production, excluding secondary causes such as androgen producing neoplasms, hyperprolactinaemia, and adult onset congenital adrenal hyperplasia (CAH) [3].

Based on the two-cell two-gonadotropin theory of ovarian steroidogenesis, androgens produced by luteinising hormone (LH)-stimulated theca cells normally undergo aromatisation to oestrogens by follicle-stimulating hormone (FSH) stimulated granulosa aromatase. This shift from an androgenic to an oestrogenic environment follows an increase in aromatase activity within the developing follicle, and ovulation usually ensues. In PCOS, the ratio of follicular androstenedione to oestradiol is high, suggesting an aromatisation defect; a recent P450 aromatase gene mutation has been found to cause a form of the syndrome. This increase in intraovarian androgens is believed to play a significant role in the anovulatory process. Classic ultrasound findings of bilaterally enlarged polycystic ovaries are present in more than 90 percent of women with PCOS, but they may present in up to 25 percent of normal women [4].

Clinical signs and symptoms

Although anovulation, obesity, hirsutism and bilateral polycystic ovaries are considered classic manifestations, PCOS is perhaps best viewed as a

spectrum of symptoms, pathologic findings and laboratory abnormalities. In 1990, the United States National Institutes of Health (NIH) proposed new diagnostic criteria for this disorder- hyperandrogenism and chronic anovulation- excluding other causes such as adult-onset CAH, hyperprolactinaemia and androgen-secreting neoplasms [5]. Criteria, revised in 2003, include two out of three of the following: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries and exclusion of other aetiologies [3].

Women with PCOS may display a wide range of clinical symptoms but usually present for three primary reasons: menstrual irregularities, infertility and symptoms of androgen excess (e.g., hirsutism and acne). In one study 70 percent of affected women reported menstrual dysfunction [6]. Most women with the syndrome experience menarche at a normal age but have irregular menstrual periods that gradually become more abnormal, often leading to amenorrhea. Smaller percentages of women with PCOS actually have normal cycles.

Clinical signs include those associated with a hyperandrogenic anovulatory state. Hirsutism and acne occur in up to 70 percent of women with

	Follicle-stimulating hormone (FSH)	Luteinising hormone (LH)	Prolactin	Testosterone
Extreme exertion or rapid weight changes	Normal	Normal	Normal	Normal
Polycystic ovary syndrome	Normal to mildly reduced	Generally moderately elevated	Normal to mildly elevated	Normal to moderately elevated
Pituitary adenoma	Mildly reduced	Mildly reduced	Moderately elevated	Normal
Progestational agents	Mildly reduced	Mildly reduced	Normal	Normal
Eating disorders	Moderately reduced	Moderately reduced	Normal	Normal
Congenital adrenal hyperplasia	Normal	Normal	Normal	Normal to mildly elevated
Hyperthyroidism or hypothyroidism	Normal	Normal	Normal to mildly elevated	Normal
Premature ovarian failure	Significantly elevated	Moderately elevated	Normal	Normal

Table 1. Differential diagnosis of anovulatory disorders and serum laboratory findings. Adapted from [8].

Urine human chorionic gonadotropin level
Prolactin level
Testosterone level
Luteinising hormone level (LH)
Follicle-stimulating hormone level (FSH)
Fasting glucose level
Lipid profile, including total, low-density lipoprotein and high-density lipoprotein
Dehydroepiandrosterone sulphate level*
17-hydroxyprogesterone level*
Dexamethasone suppression test*

Table 2. Suggested laboratory evaluation of chronic hyperandrogenic anovulatory women [6]. * Suggested only in selected patients.

toromegaly, deepening of the voice, temporal balding or masculinisation of body habitus. Ovarian enlargement may be unilateral or absent [2]. The dermatological disorder acanthosis nigricans may also be present. Obesity is present in up to 70 percent of patients, and upper body obesity is also frequently seen with a waist-to-hip ratio > 0.85.

In recent years, it has become apparent that PCOS is also associated with insulin resistance independent of obesity and an increased risk for the development of impaired glucose tolerance (IGT) or type 2 diabetes mellitus [1, 2]. Although not always recognised early, hyperinsulinaemia and insulin resistance occur at higher rates in women with PCOS than in weight-matched control subjects. Hyperinsulinaemia is also believed to be a key factor leading to hyperproduction of ovarian androgens.

Long term health risks

Insulin resistance may contribute to metabolic dysfunction in PCOS, including an increased likelihood of lipid abnormalities and risk of cardiovascular disease. The prevalence of IGT and development of diabetes

PCOS. Patients usually retain normal secondary sexual characteristics and rarely exhibit virilising signs such as cli-

toromegaly, deepening of the voice, temporal balding or masculinisation of body habitus. Ovarian enlargement may be unilateral or absent [2]. The dermatological disorder acanthosis nigricans may also be present. Obesity is present in up to 70 percent of patients, and upper body obesity is also frequently seen with a waist-to-hip ratio > 0.85.

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mellitus is reported to be as high as 31% and 7.5% respectively [7]. Because this syndrome is also associated with lipid abnormalities, affected women could potentially benefit from measures to prevent cardiovascular disease and other sequelae of long-standing metabolic dysfunction.

Other long-term effects of PCOS are related to the clinical consequences of persistent anovulation, including infertility, menstrual irregularities ranging from amenorrhea to dysfunctional uterine bleeding, hirsutism and acne. Additional long-term effects of unopposed oestrogen place women at considerable risk for endometrial cancer, endometrial hyperplasia and, perhaps, breast cancer. Although no evidence shows improved outcomes, mammography and endometrial sampling to search for underlying oestrogen-stimulated cancer should be considered in high-risk women with dysfunctional uterine bleeding.

Differential diagnosis

PCOS is one of the most common endocrine disorders in women of reproductive age. However, anovulation in the reproductive years may also be due to rapid fluctuations in weight or extreme physical exertion, eating disorders, premature ovarian failure, CAH, use of medications (progestational agents), pituitary adenoma with elevated prolactin levels, or thyroid disorders [Table 1] [8]. Other potential causes of androgen excess and menstrual irregularities include conditions unique to pregnancy, such as luteoma and a hyperactive luteal body. Although as many as 20 percent of healthy eumenorrheic patients have morphologic features consistent with PCOS, only a fraction of these women have endocrinologic abnormalities of menstrual irregularity and hyperandrogenism [4].

Laboratory studies

In the absence of pregnancy and when amenorrhea or oligomenorrhea has persisted for six months or more without a diagnosis, a careful history and physical examination should be undertaken, with particular attention to patterns of hair distribution and a search for acanthosis nigricans. Suggested laboratory and radiologic evaluation of women with chronic hyperandrogenic anovulation is presented in Table 2 [6]. Urine human chorionic gonadotropin (hCG) levels should be measured to exclude pregnancy. In the absence of pregnancy-related conditions, hCG is low or absent in patients with PCOS.

While some attention has been given to ovarian morphology as a primary distinguishing characteristic, more recent attention and discussion has focused on laboratory parameters that can be used to diagnose PCOS. Like clinical symptoms, the laboratory biochemical findings in PCOS lack uniformity, and continued controversy exists concerning diagnostic criteria used to identify the disorder [Table 3] [5]. PCOS is primarily a clinical diagnosis, but laboratory evaluation should be tailored to the clinical presentation. Compared with healthy control subjects, many women with this syndrome have elevated levels of testosterone, androstenedione, LH, oestradiol, oestrone and fasting insulin, an elevated LH-to-FSH ratio, and reduced levels of sex hormone binding globulin (SHBG).

With respect to hyperandrogenism, some debate exists concerning whether the diagnosis should be based on assays of circulating androgens or on clinical signs and symptoms of peripheral hyperandrogenism such as hirsutism and/or acne. It remains uncertain which androgen when the level is elevated is most indicative of PCOS, although some studies advocate testosterone or androstenedione levels as being most consistently elevated in women with PCOS. Testosterone is the most easily assayed parameter of the two. Measurements of free testosterone or free androgen index (FAI) are more sensitive methods of assessing hyperandrogenaemia. Recommended methods for assessment of free testosterone include equilibrium dialysis, calculation of free testosterone from SHBG levels and total testosterone, or ammonium sulphate precipitation [3]. Additional assays of androstenedione add little informational value to evaluation of PCOS. It was found that levels of unbound testosterone provided the best measure of differentiation between controls and PCOS patients, while also providing the best correlation with hirsutism. Use of clinical assays of elevated testosterone has also been advocated because a substantial number of women with PCOS have no overt clinical signs of androgen excess [6]. Although serum testosterone levels are usually mildly to moderately elevated in women with PCOS, testosterone levels are generally measured to rule out virilising tumours. More specifically, virilising tumours should be suspected when hirsutism is rapidly progressive, and are strongly suggested when the mean of three separate serum testosterone measurements is greater than 150 to 200 ng per dL.

Clinical features

Amenorrhea, Oligomenorrhea or dysfunctional uterine bleeding

Hirsutism and/or acne

Central obesity

Anovulatory infertility

Endocrine Abnormalities on laboratory testing

Elevated androgen levels

Elevated luteinising hormone concentration with normal to low follicle-stimulating hormone levels

Insulin resistance with hyperinsulinaemia

Radiologic abnormalities on ultrasound examination

Increased ovarian stromal density and/or volume

Multiple (>8) subcortical follicular cysts

Exclusion of other aetiologies

Virilising tumours of adrenal or ovarian origin

Prolactinoma

Congenital adrenal hyperplasia

Cushing's syndrome

Table 3. Suggested diagnostic criteria for polycystic ovary syndrome. The diagnosis is based on the presence of some or all common clinical features and is confirmed by the presence of biochemical or radiologic evidence of endocrine abnormality and the exclusion of other aetiologies [5].

Risk Factor	Cut-off Value
Abdominal obesity (waist circumference)	> 88 cm (>35 inches)
HDL-C	<50 mg/dL
Triglycerides	≥ 150 mg/dL
Blood pressure	≥ 130/85 mm Hg
Fasting and 2 hour glucose from OGTT	110-126 mg/dL fasting sample and/or 2 hour glucose 140-199 mg/dL

Table 4. Criteria for the metabolic syndrome in women with PCOS. Three out of five criteria qualify for the syndrome [3]. HDL=High density lipoprotein, OGTT=oral glucose tolerance test.

Consideration should also be given to measuring dehydroepiandrosterone sulphate (DHEAS) levels to screen for a virilising adrenal tumour in women with rapidly progressive hirsutism. DHEAS levels above 700 µg per dL in premenopausal women are suggestive of tumours.

Other groups have suggested the use of inappropriate gonadotropin secretion to diagnose PCOS. The pattern of high levels of luteinising hormone (LH) and low-to-normal levels of follicle stimulating hormone (FSH) has been considered characteristic of PCOS for considerable time. Due to the pulsatile nature of LH secretion and elevations of LH in the face of low to normal FSH levels, many researchers consider an LH/FSH ratio in the range of 3:1 diagnostic of the syndrome. Some concern exists, however, about the reliance on gonadotropin levels due to wide overlap between control subjects and PCOS patients. Due to this overlap, fewer than 50% of women with PCOS have abnormal gonadotropin values, and only 20% of patient with PCOS have an LH:FSH ratio greater than 3.

Some groups have focused on ovarian morphologic characteristics as the primary diagnostic criterion for PCOS. Using a radiologic approach, diagnosis of PCOS is based on the finding of more than eight discrete follicles in the ovary, with the follicles less than 10 mm in diameter and peripherally arrayed around an enlarged hyperechogenic ovarian stroma. Improvements in ultrasound assessment using a transvaginal approach have allowed better delineation of multiple follicular cysts.

In women with androgen excess, prolactin levels should also be measured to exclude a possible prolactinoma. Although up to 22 percent of women with PCOS may have mildly elevated prolactin levels, profound prolactinaemia should be investigated further.

Serum 17-hydroxyprogesterone (17-OHP) measurement is a screening test for adult-onset CAH, and should be considered when initial evaluations for PCOS are non-diagnostic in hyperandrogenic anovulatory women. Common signs of hyperandrogenism in postadolescent women with adult-onset CAH are hirsutism, acne and menstrual irregularity. As many as 25 percent of women with adult onset of this disorder also exhibit LH hypersecretion. Serum levels of 17-OHP should be drawn at 8 a.m. in the morning. Basal follicular-phase serum 17-OHP levels above 5 ng per mL suggest adult-onset CAH caused by 21-hydroxylase deficiency. In contrast, serum 17-OHP levels are normal in women with PCOS.

An overnight dexamethasone suppression test should be performed in women with physical features of cortisol excess. For this test, 1 mg of dexamethasone is administered orally at 11 p.m., and serum cortisol measurements are taken at 8 a.m. the following morning. Serum cortisol levels below 5 µg per dL (140 nmol per L) make the diagnosis of Cushing's syndrome unlikely but are routinely present in women with PCOS.

Additional considerations

While not diagnostic for PCOS, consideration for screening of insulin resistance should be entertained in obese hyperandrogenic anovulatory women because of the association of glucose intolerance with PCOS. While there is currently no validated clinical test for detecting insulin resistance in the general population, fasting glucose measurement is a reasonable screening test for diabetes mellitus. If fasting glucose levels are less than 110 mg per dL (6.1 mmol per L), the patient probably has normal glucose metabolism, whereas fasting glucose values greater than 126

mg per dL (7.0 mmol per L) on two separate occasions is diagnostic of diabetes mellitus. Fasting glucose levels between 110 and 126 mg per dL indicate some degree of glucose intolerance

Most consensus conferences to date do not recommend screening for insulin resistance in the general population and high-risk groups due to concerns regarding the value of these parameters to predict clinical events. Instead, criteria have been developed for defining a metabolic syndrome including components associated with insulin resistance such as centripetal obesity, hypertension, dyslipidaemia and fasting hyperglycaemia [Table 4] [3]. To aid in the possible prevention of cardiovascular disease, consideration should also be given to screening for lipid abnormalities and monitoring blood pressure annually. Identified abnormalities should be treated appropriately with dietary and pharmacologic interventions.

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- Additional references are available from the author.

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