Polycystic Ovary Syndrome: Diagnosis and Treatment

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ABSTRACT

Polycystic ovary syndrome affects 6%-7% of reproductive-aged women, making it the most common endocrine disorder in this population. It is characterized by chronic anovulation and hyperandrogenism. Affected women may present with reproductive manifestations such as irregular menses or infertility, or cutaneous manifestations, including hirsutism, acne, or male-pattern hair loss. Over the past decade, several serious metabolic complications also have been associated with polycystic ovary syndrome including type 2 diabetes mellitus, metabolic syndrome, sleep apnea, and possibly cardiovascular disease and nonalcoholic fatty liver disease. In addition to treating symptoms by regulating menstrual cycles and improving hyperandrogenism, it is imperative that clinicians recognize and treat metabolic complications. Lifestyle therapies are first-line treatment in women with polycystic ovary syndrome, particularly if they are overweight. Pharmacological therapies are also available and should be tailored on an individual basis. This article reviews the diagnosis, clinical manifestations, metabolic complications, and treatment of the syndrome. A table summarizing treatment recommendations is provided. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Polycystic ovary syndrome; PCOS; Anovulation; Hirsutism; Insulin resistance; Type 2 diabetes; Treatment

Although up to 5 million women in the United States may be affected by polycystic ovary syndrome, it is frequently not recognized. Because affected women may not view their symptoms of irregular menses and hirsutism as “medical” complaints, they may not bring them up to their provider. Thus, active provider inquiry may be required to uncover the diagnosis.

DIAGNOSIS

Experts at a 1990 National Institutes of Health conference proposed the following diagnostic criteria: oligo- or anovulation and biochemical or clinical signs of hyperandrogenism, such as hirsutism, acne, or male-pattern hair loss.

POSTEROS

Recently, an international consensus group broadened the definition by also including ovarian morphology. They proposed that the diagnosis requires 2 of the following 3 criteria: oligo- or anovulation, biochemical or clinical signs of hyperandrogenism, and polycystic ovaries. In both definitions, hyperandrogenism can be documented with either clinical or biochemical data. This is important because some women have mild or no clinical evidence of hyperandrogenism but have elevated serum androgen levels. Although insulin resistance and obesity are common, neither is part of the diagnostic criteria.

Both definitions require that other causes of menstrual irregularity and hyperandrogenism are excluded. These causes are listed in Table 1 and can be evaluated through a detailed history, physical examination, and supplemental laboratory tests.

PATHOGENESIS

Although the etiology of polycystic ovary syndrome is unknown, 3 main hypotheses have been proposed (Table 2).
Several candidate genes including those related to insulin resistance and androgen biosynthesis or action have been associated with the syndrome. Additionally, environmental factors are thought to play an important role.

**PATIENT EVALUATION**

Evaluation should include a detailed menstrual history and information about the onset and duration of hyperandrogenism symptoms. Polycystic ovary syndrome is typically characterized by chronic menstrual irregularity and slowly progressive symptoms of hyperandrogenism. Abrupt changes in the menstrual pattern or hyperandrogenism symptoms should alert the provider to other possible etiologies. Other important historical information includes personal or family history of late-onset congenital adrenal hyperplasia and metabolic diseases. The physical examination should include assessment of blood pressure, body mass index, and waist circumference. Skin should be examined for evidence of insulin resistance (acanthosis nigricans, skin tags) and hyperandrogenism (hirsutism, acne, and male-pattern hair loss). Laboratory tests to exclude other etiologies and assess for metabolic complications are summarized in Tables 1 and 3.

**Table 1** Laboratory Testing to Exclude Other Causes of Irregular Menses and Hyperandrogenism*

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Evaluation for:</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total or bio-available testosterone</td>
<td>Androgen-secreting tumor</td>
<td>Testosterone levels should be checked if there are symptoms consistent with an androgen-secreting tumor or if biochemical evidence of hyperandrogenism is needed to make the diagnosis of polycystic ovary syndrome. A total testosterone &gt;200 ng/dL should prompt a work-up for an androgen-secreting tumor.</td>
</tr>
<tr>
<td>Dehydroepiandrosterone Sulfate</td>
<td>Androgen-secreting tumor of the adrenal gland</td>
<td>Dehydroepiandrosterone sulfate should be checked if there are symptoms consistent with an androgen-secreting tumor. Although modest elevations in dehydroepiandrosterone sulfate can be seen in polycystic ovary syndrome, greater elevations should prompt a work-up for an adrenal androgen-secreting tumor.</td>
</tr>
<tr>
<td>Morning 17-hydroxyprogesterone</td>
<td>Late-onset congenital adrenal hyperplasia</td>
<td>Late-onset congenital adrenal hyperplasia is caused by a partial adrenal enzyme defect that leads to impaired cortisol production, compensatory elevation in adrenocorticotropic hormone, and subsequent excess androgen production. Screening for this should be considered in women who are Ashkenazi Jews or have a positive family history.</td>
</tr>
<tr>
<td>24-hour urine for cortisol and creatinine</td>
<td>Cushing’s Syndrome</td>
<td>Cushing’s Syndrome should be considered in women with an abrupt change in menstrual pattern, later-onset hirsutism, or other evidence of cortisol excess such as hypertension, supraclavicular fullness, abdominal striae, and fragile skin.</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Hyperprolactinemia</td>
<td>Hyperprolactinemia is a relatively common cause of oligo-menorrhea that may be accompanied by galactorrhea. Consider obtaining prolactin in all women with irregular menstrual cycles.</td>
</tr>
<tr>
<td>Thyroid function studies</td>
<td>Hyper- or hypothyroidism</td>
<td>Thyroid dysfunction can cause oligo-menorrhea and should be evaluated in all women with irregular menstrual cycles.</td>
</tr>
</tbody>
</table>

*Data from Setji and Brown.*

**Table 2** Possible Pathogenesis of Polycystic Ovary Syndrome*

1) Hypothalamic-pituitary axis abnormalities cause abnormal secretion of gonadotropin releasing hormone and luteinizing hormone, resulting in increased ovarian androgen production.
2) An enzymatic defect of ovarian (± adrenal) steroidogenesis favors excess androgen production.
3) Insulin resistance drives the metabolic and reproductive abnormalities in polycystic ovary syndrome.

*Data from Polycystic Ovary Syndrome Writing Committee.*

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*Setji and Brown Polycystic Ovary Syndrome Update*
COMPLICATIONS

Reproductive
The oligo- or anovulation associated with polycystic ovary syndrome can result in reduced fertility. Prolonged absence of ovulation also can result in continuous endometrial stimulation by estrogen, unopposed by progesterone. Thus, women have an increased risk of endometrial hyperplasia and possibly endometrial cancer. Regulating menstrual cycles to prevent endometrial hyperplasia is one of the major treatment goals. Although an in-depth discussion of infertility is outside the scope of this article, it is important to note that many of the treatments that improve insulin sensitivity, such as weight loss, metformin, and thiazolidinediones, may also increase the frequency of ovulation and, thus, improve fertility.

Metabolic
Women with polycystic ovary syndrome are at a markedly increased risk of type 2 diabetes. Both lean and obese North American women with polycystic ovary syndrome have increased insulin resistance and impaired beta-cell function compared with age- and body mass index-matched controls. By their fourth decade, 31% have impaired glucose tolerance (prediabetes) and 7.5% have type 2 diabetes. Additionally, they may have an increased risk of gestational diabetes.

Polycystic ovary syndrome is associated with several other metabolic complications including central obesity, hypertension, dyslipidemia, nonalcoholic fatty liver disease, and obstructive sleep apnea. Surrogate markers for cardiovascular disease, such as carotid artery intima-media thickness, coronary artery calcification, and C-reactive protein are also abnormal. Despite the presence of these cardiovascular risk factors, it is not known whether affected women are at increased risk of cardiovascular-related morbidity and mortality.

Psychological Issues
Although research of psychological issues is limited, small studies have found that women with polycystic ovary syndrome have high prevalence rates of depression and reductions in health-related quality of life and sexual satisfaction. In addition, eating disorders may be more prevalent.

TREATMENT
Treatment of polycystic ovary syndrome targets the reproductive, cutaneous, metabolic, and psychological complications. Recommendations to treat each of these components are summarized in Table 4.

Lifestyle Interventions
Lifestyle interventions such as diet and exercise are first-line treatment for women with polycystic ovary syndrome, particularly if they are overweight. Several nonrandomized trials have shown that a reduction in body weight through diet and exercise improves insulin sensitivity and ovulation rate. In other populations, weight loss of 5%-7% decreases the conversion from impaired glucose tolerance to type 2 diabetes by 58% over a 3-year period.5 Taken together, these data support lifestyle interventions in this high-risk population.

Hormonal Therapy
If pregnancy is not desired, hormonal contraceptive agents containing estrogen and progestin can be used to provide endometrial protection and treat symptoms of hyperandrogenism. Cyclic therapy, such as oral contraceptives, induces regular withdrawal bleeding, thus preventing endometrial hyperplasia. Estrogen-containing contraceptives improve symptoms of hyperandrogenism by decreasing ovarian androgen production and increasing hepatic production of sex-hormone binding globulin. It is possible that some women experience a worsening of carbohydrate metabolism while taking oral contraceptives. However, until this issue is resolved with larger randomized controlled clinical trials, hormonal contraceptives remain an effective treatment.

In women with contraindications to estrogen-containing therapy, cyclic progestin therapy given every 1 to 3 months can provide endometrial protection by inducing regular en-
DOMESTRIAL SHEDDING. ALTERNATIVELY, A PROGESTIN-ONLY CONTRACEPTIVE CAN BE USED. PROGESTIN-ONLY THERAPY WILL NOT IMPROVE HYPERANDROGENISM SYMPTOMS.

ANTI-ANDROGEN THERAPY
Spironolactone (50-100 mg twice daily) effectively treats hirsutism. Spironolactone is often used in combination with oral contraceptives because of the additive effects of androgen suppression (oral contraceptives) and androgen blockade (spironolactone). Spironolactone is contraindicated during pregnancy because of potential teratogenicity.

OTHER COSMETIC TREATMENTS
In addition to using oral contraceptives and anti-androgens to treat hirsutism, permanent hair reduction can be achieved with laser or electrolysis therapy. Because laser therapy relies on the contrast between light and dark for the best effect, it works best in individuals with light skin and dark hair. For darker skin, the laser instrument should be designed to treat darker skin tones. Other available therapies include enflorane hydrochloride 13.9% cream to slow hair growth and topical minoxidil to treat male pattern hair loss.

METFORMIN
Metformin has become a popular treatment, because it improves ovulation, insulin sensitivity, and possibly hyperandrogenemia. It is commonly used to treat infertility, either alone or in combination with clomiphene-citrate. Because it increases ovulation in some women, it can also increase the frequency of endometrial shedding and may help with cycle control. It is not known whether using metformin to treat insulin resistance in women with normal glucose levels improves long-term outcomes. In other populations, metformin decreases conversion from impaired glucose tolerance to type 2 diabetes. Thus, metformin may be useful in women with polycystic ovary syndrome and hyperglycemia. The decision to prescribe this drug should be made on an individual basis. Patients who do not wish to become pregnant should be counseled about contraception.

THIAZOLIDINEDIONES
In a large randomized controlled trial, troglitazone improved glycemic measures, ovulation, hirsutism, and free testosterone levels in women with polycystic ovary syndrome. Troglitazone was subsequently withdrawn from the market in 2002 secondary to hepatic toxicity seen in other trials. More recently, smaller trials of rosiglitazone and pioglitazone have had promising results. However, these benefits need to be confirmed in larger trials. Because thiazolidinediones are category C drugs, patients should be counseled to use contraception while taking the drug.

SUMMARY
Polycystic ovary syndrome is a common condition characterized by hyperandrogenism and oligo- or anovulation. The recently introduced Rotterdam criteria also incorporate morphologic appearance of the ovaries as one of the possible defining traits of the syndrome. The clinical problems that may arise in the course of caring for affected women include endometrial hyperplasia, reduced fertility, and serious metabolic complications. Lifestyle therapies are first-line treatment for prevention of metabolic complications and can improve fertility. Pharmacological therapies are available to regulate menstrual cycles and treat symptoms of hyperandrogenism. Pharmacological therapies can also improve metabolic parameters such as prediabetes in situations where lifestyle interventions are insufficient.

REFERENCES
1. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term


