The American Journal of Medicine (2007) 120, 128-132

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

UPDATE IN OFFICE MANAGEMENT

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.

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. Recently, an international consensus group broadened the definition by also including ovarian morphology.[1] 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.[2]

PATHOGENESIS

Although the etiology of polycystic ovary syndrome is unknown, 3 main hypotheses have been proposed (Table 2).[3]

Dr. Tracy Setji is supported by Duke University fellowship Grant 5T32-DK-007012. Dr. Ann Brown is supported by K23HL04390-01, National Heart Lung and Blood Institute, National Institutes of Health.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2006.06.029

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

Laboratory Test	Evaluation for:	Comment
Total or bio-available testosterone	Androgen-secreting tumor	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 >200 ng/dL should prompt a work-up for an androgen-secreting tumor.
Dehydroepiandrosterone Sulfate	Androgen-secreting tumor of the adrenal gland	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.
Morning 17-hydroxyprogesterone	Late-onset congenital adrenal hyperplasia	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.
24-hour urine for cortisol and creatinine	Cushing's Syndrome	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.
Prolactin	Hyperprolactinemia	Hyperprolactinemia is a relatively common cause of oligo-amenorrhea that may be accompanied by galactorrhea. Consider obtaining prolactin in all women with irregular menstrual cycles.
Thyroid function studies	Hyper- or hypothyroidism	Thyroid dysfunction can cause oligo-amenorrhea and should be evaluated in all women with irregular menstrual cycles.

*Data from Setji and Brown.[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.

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.[3]

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.[2]

Table 3 Laboratory Testing to Evaluate for Metabolic Complications of Polycystic Ovary Syndrome*

Laboratory Test	Evaluation for:	Comment
2-hr oral glucose tolerance test	Impaired glucose tolerance, type 2 diabetes	Consider this in all women with polycystic ovary syndrome, particularly those with a body mass index >25 kg/m^2 or other risk factors for type 2 diabetes such as a positive family history.
Fasting lipid profile	Dyslipidemia	Hypertriglyceridemia and decreased high-density lipoprotein are relatively common in women with polycystic ovary syndrome. Elevations in low-density lipoprotein have also been noted. Thus, periodic screening is recommended.
Alanine aminotransferase and aspartate aminotransferase	Hepatic steatosis	Consider checking transaminases in women with other risk factors for nonalcoholic fatty liver disease.

*Data from Setji and Brown.[2]

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 thiazolodiniediones, 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.[4] 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.[2]

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-

Table 4 Summary of Recommendations for Addressing Reproductive, Cosmetic, Metabolic, and Psychological Complications of Polycystic Ovary Syndrome: "MY PCOS"*

Metabolic	Assess diabetes and cardiovascular disease risk Assess risk for nonalcoholic fatty liver disease Discuss lifestyle therapies such as nutrition and physical activity
Cycle Control	Assess bleeding pattern and risk for endometrial hyperplasia Provide therapies to prevent endometrial hyperplasia: estrogen-progestin therapy (oral contraceptives, patch, or vaginal ring) or cyclic progestin (every 1-3 months)
Psychosocial	Address body image and eating behaviors Screen for depression Discuss stress management Provide nonjudgmental support
Cosmetic	Discuss use of estrogen-containing oral contraceptives to suppress androgens if no contraindications Consider spironolactone 50-100 mg twice daily for refractory hirsutism or acne Discuss use of enflornithine hydrochloride 13.9% cream, laser therapy, and electrolysis Discuss over-the-counter topical minoxidil for male-pattern scalp hair loss
Ovulation	Discuss fertility goals Discuss therapies to increase ovulation frequency: weight loss, metformin Consider referral to Reproductive Endocrinology for assisted reproductive technologies
Sleep Apnea	Screen for sleep apnea Refer for sleep study if indicated

*Data from Setji and Brown.[2]

dometrial 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.[6] 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.

Thiazolodinediones

In a large randomized controlled trial, troglitazone improved glycemic measures, ovulation, hirsutism, and free testosterone levels in women with polycystic ovary syndrome.[7] 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 thiazolodinediones 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

health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81:19-25.
2. Setji TL, Brown AJ. Polycystic ovary syndrome and type 2 diabetes. In: Feinglos MN, Bethel MA, eds. *Type 2 Diabetes Mellitus: An Evidence-Based Approach to Practical Management.* Totowa, New Jersey: Humana Press; 2006:in press.
3. Polycystic ovary syndrome writing committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. *Endocr Pract.* 2005;11:126-134.
4. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab.* 1999;84:165-169.
5. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393-403.
6. Lord JM, Flight IHK, Norman RJ. Insulin-sensitizing drugs (metformin, troglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev. 2003;3:CD003053.
7. Azziz R, Ehrmann D, Legro RS, et al. 2001 PCOS/Troglitazone Study Group. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multi-center, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2001;86:1626-1632.