Polycystic Ovary Syndrome: Update on the Pros and Cons of Treatment Options

March 01, 2007
By Samantha Butts, MD [1] and Deborah A. Driscoll, MD [2]

ABSTRACT: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among females of reproductive age. In adolescents, PCOS often manifests with irregular menses, hirsutism, and acne. Despite general agreement that the metabolic derangements of PCOS arise during puberty, the condition is diagnosed more often in adults than in adolescents. Treatment is focused on weight loss, menstrual cycle regulation, and amelioration of physical symptoms. Acute symptoms can be managed with combination oral contraceptives and antiandrogens and potentially with insulin-sensitizing drugs. Lifestyle modification, especially in overweight patients, can reduce symptoms and help prevent long-term health consequences.

Adolescents with polycystic ovary syndrome (PCOS) are at risk for such complications as dyslipidemia, hypertension, type 2 diabetes, infertility, and (potentially) coronary artery disease. Prompt diagnosis is crucial, as are therapeutic efforts to establish a healthy diet and exercise habits and to prevent potential health risks.

This is the second of 2 articles on PCOS. In part 1 (Polycystic Ovary Syndrome: When to Suspect, February 2007, page 98), we focused on diagnosis. Here we concentrate on treatment options and outline management strategies that can reduce associated long-term health risks.

MANAGEMENT
Patient education and lifestyle modification are crucial in achieving the goals of addressing the acute presenting symptoms and ameliorating the associated long-term health risks. Acute symptoms of PCOS can be managed with combined oral contraceptives (OCs), antiandrogens, and--potentially--insulin-sensitizing drugs. Given the broad range of symptoms in affected patients, a multidisciplinary approach to treatment is generally required.

Obesity. Weight reduction is the central component of treatment of overweight patients with PCOS. Weight loss ameliorates many of the associated endocrine derangements, including insulin resistance, depressed sex hormone-binding globulin (SHBG) levels, and hyperandrognism. A modest weight reduction of 2% to 5% of total body weight has been shown to improve cycle regularity and reduce free testosterone indices.1,2 The most effective approach appears to be a combination of caloric restriction, exercise, and behavior modification. Low-carbohydrate diets do not appear to confer a distinct metabolic benefit over other types of diets.3 Weight loss should be emphasized, regardless of whether medications are incorporated into treatment.

Hirsutism and acne. Effective treatment of hirsutism in PCOS requires a multimodal approach, including suppression of androgen production, blockage of androgen effect, and adjuvant dermatologic methods. The medications described here for hirsutism do not eliminate established hair, but rather reduce new hair growth. Thus, up to 6 months may pass before a significant change in hair distribution is noted.1,4 The incorporation of mechanical treatments (such as electrolysis, depilatories, and laser hair removal) with medical therapy can be extremely beneficial. All but one of the medications described below (ie, eflornithine) is FDA-approved for the treatment of hirsutism, but all have demonstrated efficacy. The absence of pregnancy must be confirmed before initiation of any medical treatments.

Androgen suppression. Combination OCs are first-line therapy for acne and hirsutism because they safely diminish androgen production through several mechanisms. Specifically, OCs reduce ovarian androgen production by suppressing pituitary gonadotropins and stimulating production of SHBG, which binds free testosterone. Both of these actions reduce the amount of testosterone available to stimulate terminal hair growth and cause acne.1,4,6 In addition, OCs reduce androgen production from the adrenal gland by an as yet unspecified mechanism.4

In addition to cosmetic benefits, OCs regulate menstrual bleeding, reduce the likelihood of...
endometrial hyperplasia, and are highly effective contraception for sexually active teenagers.\(^1,6\) The potential for worsened insulin resistance in adolescents with PCOS using OCs has been suggested. However, to date, a substantial clinical risk has not been confirmed, and the clear benefits of OCs overshadow this possibility.\(^5,7\)

The ideal OC for treatment contains a minimally androgenic progestin, such as norgestimate or desogestrel. Drospirenone, an analogue of spironolactone, is now available in combination OCs and may prove to be of particular benefit in patients with PCOS.\(^5\)

When OCs are contraindicated or declined by the patient, medroxyprogesterone acetate may be used as an alternative to reduce androgen levels. The medication can be administered intramuscularly (depot medroxyprogesterone acetate, 150 mg every 3 months) or orally (10 to 20 mg each day). The efficacy of medroxyprogesterone acetate compared with that of OCs may be limited because it produces a less dramatic reduction in testosterone levels and is associated with diminished SHBG levels.\(^1,8\)

**Androgen blockade.** Medications that block or reduce the action of androgens on terminal hair production are used in combination with OCs to prevent fetal exposure and the risk of ambiguous genitalia in a male fetus.\(^1,9\) Spironolactone is first-line among this class of drugs and has multiple antiandrogenic effects that make it an effective treatment. Most important, spironolactone is an androgen receptor blocker and is believed to have synergistic treatment effects when used with OCs.\(^1,4-6\) Because it is also a potassium-sparing diuretic, patients may be at risk for hyperkalemia, especially if they have underlying renal dysfunction.

Make sure that serum potassium and creatinine levels are normal before you initiate treatment. Although some patients benefit from a daily dose of 100 mg, the optimal dosage appears to be 200 mg/d (divided 100 mg bid).\(^1,4,6\) Common adverse effects, such as polyuria and headaches, are minimized by starting at a dose of 25 mg/d and gradually increasing to the final dose over several weeks.\(^4\)

Flutamide is a powerful antiandrogen that is FDA-approved for adjuvant treatment of prostate cancer and may also be used to treat hirsutism. It is not as widely used as other modalities because of concerns about rare but potentially fatal hepatic toxicity.\(^6\)

Finasteride blocks the conversion of testosterone to the more powerful androgen dihydrotestosterone—the hormone primarily responsible for influencing hair growth. Although finasteride may be less effective than flutamide and spironolactone, it has the best side effect profile of the 3 drugs.\(^8,9\)

**Mechanical and topical treatments.** Eflornithine, a topical ornithine decarboxylase inhibitor that prevents hair growth, is FDA-approved for the treatment of excess facial hair. In clinical trials, the drug has been shown to be highly effective; however, its benefits appear to be short-lived after discontinuation. Adverse effects are limited. Its effect on excess nonfacial hair has not been investigated. In addition, the long-term safety of this drug remains to be determined.\(^4,8,9\) Mechanical treatments of hirsutism have been used as monotherapy and as adjuncts to hormonal therapies. Common approaches include shaving, hair bleaching, and chemical depilation. Waxing or plucking of hair in areas of androgenized skin may increase the risk of folliculitis, ingrown hairs, and skin damage.\(^4\) The objective of electrolysis and laser hair removal is to permanently destroy follicles that produce unwanted hair.\(^4,10\) The best results are achieved when initiated after at least 6 months of medical inhibition of new hair growth.\(^1,10,11\)

Electrolysis produces electrocoagulation of the base of the hair follicle. Laser hair removal causes selective thermal damage of the follicle while sparing adjacent tissues.\(^4,10\) Persons with lighter skin and dark hair obtain best results from laser therapy.\(^3,4,10\) Although both electrolysis and laser therapy aim to permanently destroy hair follicles, repeated treatments are required and complete hair removal is not always achieved. Thus, a description of these methods as "permanently reducing" rather than "permanently removing" unwanted hair has been suggested.\(^10\)

Laser hair removal appears to be a promising adjunct to the medical treatment of hirsutism; more outcomes research is required. Most of the data on this method are from small, uncontrolled, and unblinded studies. To date, no studies have compared laser therapy with electrolysis.\(^1,10\)
Abnormal bleeding. If no contraindications exist, OCs are a highly effective means of achieving cycle regularity in patients with PCOS. Oral medroxyprogesterone acetate, 5 to 10 mg daily, can also be used for the first 10 days of each month. Although this regimen does not provide contraception, it can prevent endometrial hyperplasia and dysfunctional uterine bleeding. Alternatively, depot medroxyprogesterone acetate may be used in patients who desire long-term contraception and in those who cannot take or refuse to take OCs. Insulin resistance and anovulation. Insulin sensitizers—metformin and the thiazolidinediones—have become a significant component of the treatment of PCOS in adults. These drugs have been used far less extensively in adolescents. This may be related to the fact that insulin sensitizers are often used to induce ovulation in infertile women with PCOS. The off-label use of insulin sensitizers in PCOS results in diminished ovarian androgen production via reductions in insulin production.

Metformin. This agent has been shown to increase ovulatory frequency in lean and obese women with PCOS. In a meta-analysis of 13 studies that evaluated the treatment of anovulation, metformin had a pooled odds ratio of 3.88 compared with placebo. In addition, metformin reduced blood pressure and low-density lipoprotein cholesterol levels in patients with PCOS, independent of changes in weight. Treatment of adolescents with metformin is controversial, however. Although a few studies on the effects of metformin in adolescents have demonstrated almost universal improvement in metabolic derangements (including oligomenorrhea, insulin resistance, androgen levels, and lipid profiles) and the drug has been shown to be well tolerated and effective in both lean and obese adolescents, the available data are limited by a lack of randomized controlled trials and long-term follow-up. In addition, the therapeutic benefits of treatment with metformin have been shown to disappear rapidly after the drug is discontinued. This suggests a possible need for treatment throughout adulthood. Further studies with larger numbers of patients and adequate control groups are needed to generate required safety and long-term efficacy data in adolescents. It is premature to recommend metformin as first-line treatment of PCOS in adolescents. It may be reasonable to consider the drug as an adjuvant in select groups, such as those who have difficulty in losing weight or those with multiple metabolic abnormalities. Sexually active adolescents should use some form of contraception after metformin therapy is started.

Thiazolidinediones. Pioglitazone and rosiglitazone reduce androgen levels and increase ovulatory frequency in women with PCOS. Given the limited experience—relative to metformin—with these drugs for PCOS and the concern for potential liver toxicity, they are not recommended for the treatment of PCOS in adolescents.

SCREENING AND MONITORING FOR LONG-TERM HEALTH RISKS

Cardiovascular risk factors. Adolescents with PCOS must be screened and monitored for long-term sequelae associated with the syndrome. Type 2 diabetes mellitus develops in up to 10% of
women with PCOS by the time they reach their thirties.\textsuperscript{25,26} Women with PCOS are also at increased risk for dyslipidemia and vascular dysfunction, which suggests a possible association between PCOS and coronary artery disease. In one study, women with PCOS had increased coronary artery calcification, blood pressure, and levels of plasminogen activator inhibitor-1.\textsuperscript{27} While these data are suggestive, preliminary research on the incidence of coronary artery disease in women with PCOS has yielded conflicting results. Long-term follow-up of patient cohorts should provide some answers. A baseline assessment of risk factors for coronary artery disease and type 2 diabetes mellitus is recommended.\textsuperscript{5,6} Screen all adolescents with newly diagnosed PCOS with a fasting lipid panel and blood pressure measurement; follow-up is dictated by the results of these tests and by cardiovascular risk factors. Given the significant prevalence of glucose intolerance and occult type 2 diabetes mellitus among women with PCOS, adolescents should also be screened with a 2-hour oral glucose tolerance test. The provocative test has better sensitivity for glucose intolerance in PCOS than does a fasting glucose assessment.

We do not recommend evaluation of insulin resistance. The commonly used tests (eg, the fasting glucose to insulin ratio) lack accuracy when compared with the diagnostic gold standard: the euglycemic hyperinsulinemic clamp. Furthermore, assessment of insulin resistance has shown no clinical value in determining the need for treatment or response to insulin-lowering therapies.\textsuperscript{5,28} Adolescents who have PCOS and diabetes can be treated with medical and lifestyle intervention. In those with glucose intolerance, lifestyle modifications can help prevent overt diabetes. The role of insulin sensitizers in the prevention of diabetes in patients with PCOS remains unresolved.

**Follow-up.** Evaluate adolescents with PCOS as frequently as is clinically warranted when active medical issues are being addressed. Otherwise, follow-up twice yearly is prudent to monitor weight, blood pressure, and long-term medical interventions. Screen overweight patients annually for glucose intolerance and type 2 diabetes mellitus. Lifestyle modification, especially in overweight patients, is key to reducing the symptoms of PCOS, the risk of type 2 diabetes, and the development of conditions that could lead to coronary artery disease. Emotional pain and depression associated with the physical stigmata of PCOS may best be addressed by a mental health professional.

**CLINICAL HIGHLIGHTS**

- Combination oral contraceptives (OCs) are first-line therapy for hirsutism and acne in adolescents with PCOS. Combination OCs also regulate menstrual bleeding, reduce the odds of endometrial hyperplasia, and are highly effective contraception for sexually active teenagers.

- Screen all adolescents with newly diagnosed PCOS with a fasting lipid panel and blood pressure measurement; follow-up is dictated by the results of these tests and by the presence of cardiovascular risk factors. Given the significant prevalence of glucose intolerance and occult type 2 diabetes mellitus among women with PCOS, adolescents should also be screened with a 2-hour oral glucose tolerance test.

**References:**


Polycystic Ovary Syndrome: Update on the Pros and Cons of Treatment Options

Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

Gynecol. 2002;100: 1389-1402.


EVIDENCE-BASED MEDICINE

Therapeutic Agents in This Article
Depot medroxyprogesterone acetate (Depo-Provera)
Desogestrel/ethinyl estradiol (multiple trade names)
Drospirenone/ethinyl estradiol (Yasmin)
Efornithine (VANIQA)
Finasteride (Propecia)
Flutamide (Drogenil, Eulexin)
Medroxyprogesterone acetate (Provera)
Metformin (multiple trade names)
Norgestimate/ethinyl estradiol (multiple trade names)
Pioglitazone (Actos)
Rosiglitazone (Avandia)
Spironolactone (Aldactone)

Source URL:

Links: