The treatment of polycystic ovary syndrome (PCOS) is based on the patient's presenting symptoms and any significant abnormal findings. Symptoms can be managed with combined oral contraceptives (OCs), insulin-sensitizing agents, antiandrogens, and medications used to induce ovulation.

Here we detail the various treatment options. We also discuss screening for and monitoring of the long-term health risks associated with PCOS. In *Polycystic Ovary Syndrome: When to Suspect*, we focused on the evaluation of the syndrome.

**MANAGEMENT**

**Hirsutism and acne.** Effective management of hirsutism in PCOS requires a multimodality approach, including androgen suppression, blockage of androgen production, and adjuvant dermatologic methods. The medications described in this section do not eliminate established hair, but rather reduce new hair growth. Thus, 6 months may pass before a significant change in hair distribution is noted. The incorporation of mechanical treatments (such as electrolysis, depilatories, and laser hair removal) with medical therapy can be extremely beneficial. Although all the medications described, except for efollornithine, are not FDA-approved for the treatment of hirsutism, 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 suppress ovarian androgen production and stimulate production of hepatic sex hormone-binding globulin (SHBG), which binds free testosterone. Both of these actions reduce the amount of testosterone available to stimulate terminal hair growth and cause acne. In addition to cosmetic benefits, OCs regulate menstrual bleeding, reduce the odds of endometrial hyperplasia, and are highly effective contraception for sexually active women. The potential for worsened insulin resistance in women with PCOS who use OCs has been suggested. However, to date, a substantial clinical risk has not been confirmed, and the clear benefits of OCs overshadow this possibility.

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

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.

**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. 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 in combination with OCs. Because spironolactone is also a potassium-sparing diuretic, patients who take this agent may be at risk for hyperkalemia, especially if they have underlying renal dysfunction. Before initiation of treatment, make sure that serum potassium and creatinine levels are normal. Although some patients benefit from a daily dose of 100 mg, the optimal dosage appears to be 200 mg/d (divided 100 mg bid).

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.
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.\textsuperscript{6,7}

**Adjuvant dermatologic methods.** Eflorenithine, a topical ornithine decarboxylase inhibitor that prevents hair growth, is the only FDA-approved medication for excess facial hair. In clinical trials, the drug has been highly effective; however, its benefits appear to be short-lived after discontinuation. Side 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.\textsuperscript{2,6,7}

Mechanical treatments of hirsutism have been used as monotherapy and as adjuncts to hormonal therapies. Common approaches include shaving, hair bleaching, and chemical depilation. It has been suggested that waxing or plucking of hairs in areas of androgenized skin increases the risk of folliculitis, ingrown hairs, and skin damage.\textsuperscript{2} The objective of electrolysis and laser hair removal is to permanently destroy follicles that produce unwanted hair.\textsuperscript{2,8} The best results are achieved when initiated after at least 6 months of medical inhibition of new hair growth.\textsuperscript{1,2,8}

Electrolysis produces electrolysis of the base of the hair follicle. Laser hair removal causes selective thermal damage of the follicle while sparing adjacent tissues.\textsuperscript{2,8} Patients with the best results from laser therapy are those with lighter skin and dark hairs.\textsuperscript{1,2,8} 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 hairs has been suggested.\textsuperscript{8}

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 comparing laser removal and electrolysis have been performed.\textsuperscript{1,8}

**Abnormal bleeding.** If no contraindications exist and pregnancy is not desired, OCs are a highly effective means of achieving menstrual cycle regularity in patients with PCOS. Another approach is to use oral medroxyprogesterone acetate, 5 to 10 mg daily, 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.\textsuperscript{1,4}

**Infertility.** The main barriers to conception in women who have PCOS are oligoovulation and anovulation. Weight loss, insulin sensitizers, and ovulation induction medications (such as clomiphene citrate) have all been shown to increase ovulatory frequency in PCOS.\textsuperscript{1,9} Appropriate referral to a reproductive endocrinologist for complete evaluation and treatment is warranted in most cases.\textsuperscript{Insulin resistance and anovulation.} Insulin sensitizers—metformin and the thiazolidinediones—have become a significant component of the management of PCOS. Both drugs reduce insulin production, which results in diminished ovarian androgen production. In PCOS, insulin sensitizers are primarily used (off label) to induce and maintain spontaneous ovulation and to treat glucose intolerance and diabetes when these disorders are present.\textsuperscript{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.\textsuperscript{9} In addition, metformin reduced blood pressure and low-density lipoprotein cholesterol levels in patients with PCOS, independently of changes in weight.\textsuperscript{9,10}

Use of metformin during pregnancy is an active area of research. Although existing data show no evidence of teratogenesis from drug exposure, the optimal timing, duration, and long-term effects of metformin therapy during pregnancy are unknown.\textsuperscript{3,15} Whether metformin can reduce miscarriage rates in women with PCOS who are trying to conceive requires further investigation.\textsuperscript{11,12}

Metformin is associated with GI side effects, such as nausea, vomiting, diarrhea, and abdominal discomfort, especially at the start of therapy.\textsuperscript{13,14} Side effects of the medication are reduced by gradually increasing the dose over several weeks and by administration with meals. An extended-release form of the drug is available that may be better tolerated.\textsuperscript{15} Effective dosages of metformin range from 1500 to 2550 mg/d.\textsuperscript{13}

Metformin is contraindicated in women who have a history of renal disease (creatinine greater than 1.4 mg/dL), liver disease, or heart failure because these comorbidities increase the risk of lactic acidosis during treatment.\textsuperscript{1,13} The odds of lactic acidosis developing in otherwise healthy women who take metformin are extremely low.\textsuperscript{15,16} However, discontinuation of metformin 48 hours before major surgery or a radiologic procedure that requires contrast is recommended to reduce the risk of lactic
acidosis. Metformin may be reinitiated after surgery, when normal fluid intake is reestablished. In general, normal baseline liver and renal function is sufficient for low-risk patients who use metformin. Up to 30% of patients who take metformin have impaired vitamin B<sub>12</sub> absorption and may be at risk for anemia. We recommend a yearly assessment with a complete blood cell count and mean corpuscular volume measurement in women with long-term use of metformin. Treatment of adolescents with metformin is controversial. Early studies suggest that metformin reduces androgen levels and improves menstrual cyclicity and lipid profiles in adolescents, but that these therapeutic benefits disappear rapidly after cessation of treatment. Until further safety and efficacy data become available, it is premature to recommend long-term therapy with metformin for adolescents.\textsuperscript{17,18}

**Thiazolidinediones.** Pioglitazone and rosiglitazone reduce androgen levels and increase ovulatory frequency in women with PCOS.\textsuperscript{19,20} Metformin is more widely used than the thiazolidinediones in this setting because it is considered safer in women who conceive.\textsuperscript{7,21}

**Obesity.** Weight reduction is a central component of treatment of PCOS in overweight patients. Weight loss ameliorates many of the associated endocrine derangements, including insulin resistance, depressed levels of SHBG, and hyperandrogenism. A modest weight reduction of 2% to 5% of total body weight has been shown to improve cycle regularity and reduce free testosterone indices.\textsuperscript{1,21} 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.\textsuperscript{22}

**SCREENING AND MONITORING FOR LONG-TERM HEALTH RISKS**

**Cardiovascular risk factors.** Women who have PCOS must be screened and monitored for long-term sequelae associated with the syndrome. Glucose intolerance remains undiagnosed in 30% to 40% of women with PCOS, and type 2 diabetes mellitus (DM) develops in up to 10% of these women by the time they reach their 30s.\textsuperscript{23,24} 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 were found to have increased coronary artery calcification, blood pressure, and levels of plasminogen activator inhibitor-1.\textsuperscript{1} 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 DM is recommended.\textsuperscript{3,4} Screen all women who have newly diagnosed PCOS by obtaining a 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 DM among women with PCOS, they should also be screened with both a fasting glucose test and a 2-hour oral glucose tolerance test. The provocative test has better sensitivity for glucose intolerance in women with PCOS than a fasting glucose assessment.

We do not recommend evaluation of insulin resistance in women with PCOS. 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{3,26}

Women who have PCOS and diabetes can be treated with medical and lifestyle intervention. In those with glucose intolerance, lifestyle modifications can help prevent the development of overt diabetes. The role of insulin sensitizers in the prevention of diabetes in patients with PCOS remains unresolved.

**Endometrial carcinoma.** Maintain a high index of suspicion for endometrial hyperplasia and carcinoma in women with PCOS who have amenorrhea or abnormal bleeding in the third or fourth decade of life. Chronic anovulation results in long-standing unopposed exposure of the endometrium to the stimulatory effects of estrogen and is a significant risk factor for hyperplasia, which can progress to endometrial carcinoma.\textsuperscript{4,27} An endometrial biopsy (only after pregnancy has been ruled out) is the initial method for assessing endometrial pathology; it should be performed in women older than 35 years with a persistent history of abnormal bleeding caused by chronic oligoovulation.\textsuperscript{27}

Obesity is an independent risk factor for endometrial hyperplasia and carcinoma. Hence, the risk of these disorders is compounded in obese women with PCOS.\textsuperscript{1,4}

**Follow-up.** Evaluate patients with PCOS as frequently as is clinically warranted when active medical issues (ie, infertility, hirsutism) are being addressed. Otherwise, follow-up twice a year is
prudent to monitor weight, blood pressure, and long-term medical interventions. Screen overweight patients annually for glucose intolerance and type 2 DM. Lifestyle modification, especially for overweight patients, is key to reducing the risk of type 2 DM and the development of conditions that could lead to coronary artery disease.

References:

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**Evidence-Based Medicine**


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