OBG MANAGEMENT

COVER ARTICLE

Polycystic ovary syndrome

3 key challenges

BY DALE W. STOVALL, MD

Newer findings have broadened options for medical management of insulin resistance, anovulation, and hyperandrogenism.

An expanded array of pharmacologic combinations and regimens has increased our options for treating women with polycystic ovary syndrome (PCOS).

Managing PCOS has always been a complex process, due to the wide range of troubles experienced by patients with this disorder. An effective treatment strategy should address the 3 clinical challenges typical of the syndrome:

- insulin resistance,
- menstrual irregularities associated with anovulation, and
- hyperandrogenic symptoms such as hirsutism.

Here, I review recent findings—including new data on the use of insulin-sensitizing agents for hyperinsulinemia—and offer a practical guide, complete with algorithm (FIGURE), for managing women with PCOS.

PCOS: A diagnosis of exclusion

PCOS clearly is a common cause of hirsutism and anovulation and is associated with intrinsic insulin resistance in many

women. This disorder affects up to 6% of reproductive-age women and tends to develop shortly after menarche.

Although there is considerable disagreement about diagnostic criteria, most clinicians rely on the 1990 National Institutes of Health (NIH) Consensus Conference guidelines.[1] These include clinical or biochemical evidence of hyperandrogenism and ovulatory dysfunction, and the absence of other causes. Thus, at present, PCOS is a diagnosis of exclusion.

Surprisingly, ultrasound visualization of "polycystic" ovaries is not one of the diagnostic criteria for PCOS. That is because women who have polycystic ovaries are not necessarily anovulatory. Conversely, the ovaries of women who meet the NIH criteria for PCOS may not appear to be polycystic.

1. Treat insulin resistance

Insulin exerts its primary effects in the liver, signaling the organ to reduce glycogenolysis and gluconeogenesis. Insulin also affects muscle, adipose tissue, and other organs, where it increases glucose uptake.

Insulin resistance—a reduction in the tissue response to insulin—affects one third to one half of all women with PCOS and leads to compensatory hyperinsulinemia.[2] Although the obesity associated with PCOS may exacerbate insulin resistance, even lean PCOS patients can be affected.[3]

Insulin augments the stimulating effect of luteinizing hormone on the growth and androgen secretion of ovarian theca cells and inhibits the production of sex hormone binding globulin. For this reason, women with PCOS and insulin resistance are at increased risk for beta-cell dysfunction and subsequent impaired glucose tolerance or diabetes. Thus, it is not surprising that oral hypoglycemic agents have been used to treat these patients. In fact, numerous studies have demonstrated that oral hypoglycemic agents can reduce circulating androgen levels, increase sex hormone binding globulin, facilitate weight loss, and induce ovulation in these women.

Measure tissue response. The "gold standard" for assessing insulin sensitivity is the hyperinsulinemic-euglycemic clamp. Unfortunately, because it requires a constant intravenous infusion of insulin, this technique is not clinically practical.

Fortunately, many other methods are available to assess insulin sensitivity, including the insulin tolerance, oral glucose tolerance, and fasting insulin tests. One method that has gained popularity is the fasting glucose:insulin ratio.[4] However, there are clear ethnic and racial differences in the normal values for this test. Since these values are not available for all subpopulations, the usefulness of this study is limited.[2]

Nevertheless, assessing a woman's fasting plasma glucose helps determine whether she has impaired glucose tolerance. The National Diabetes Association defines diabetes as a fasting plasma glucose level of 126 mg or more per deciliter on 2 separate occasions; impaired glucose tolerance is defined as a fasting plasma glucose level between 110 mg and 126 mg per deciliter. Since impaired glucose tolerance is a

KEY POINTS

- Women with PCOS and insulin resistance are at increased risk for impaired glucose tolerance or diabetes. Hypoglycemic agents can reduce circulating androgen levels, increase sex hormone binding globulin, facilitate weight loss, and induce ovulation.
- Take steps to enhance or induce ovulation. Even women who do not desire fertility stand to gain, because chronic anovulation increases the risk of endometrial cancer.
- Address hirsutism and other hyperandrogenic effects. Treatment of hirsutism is best approached with a combination of medical and mechanical means. Counsel patients that response is likely to be slow and subtle.

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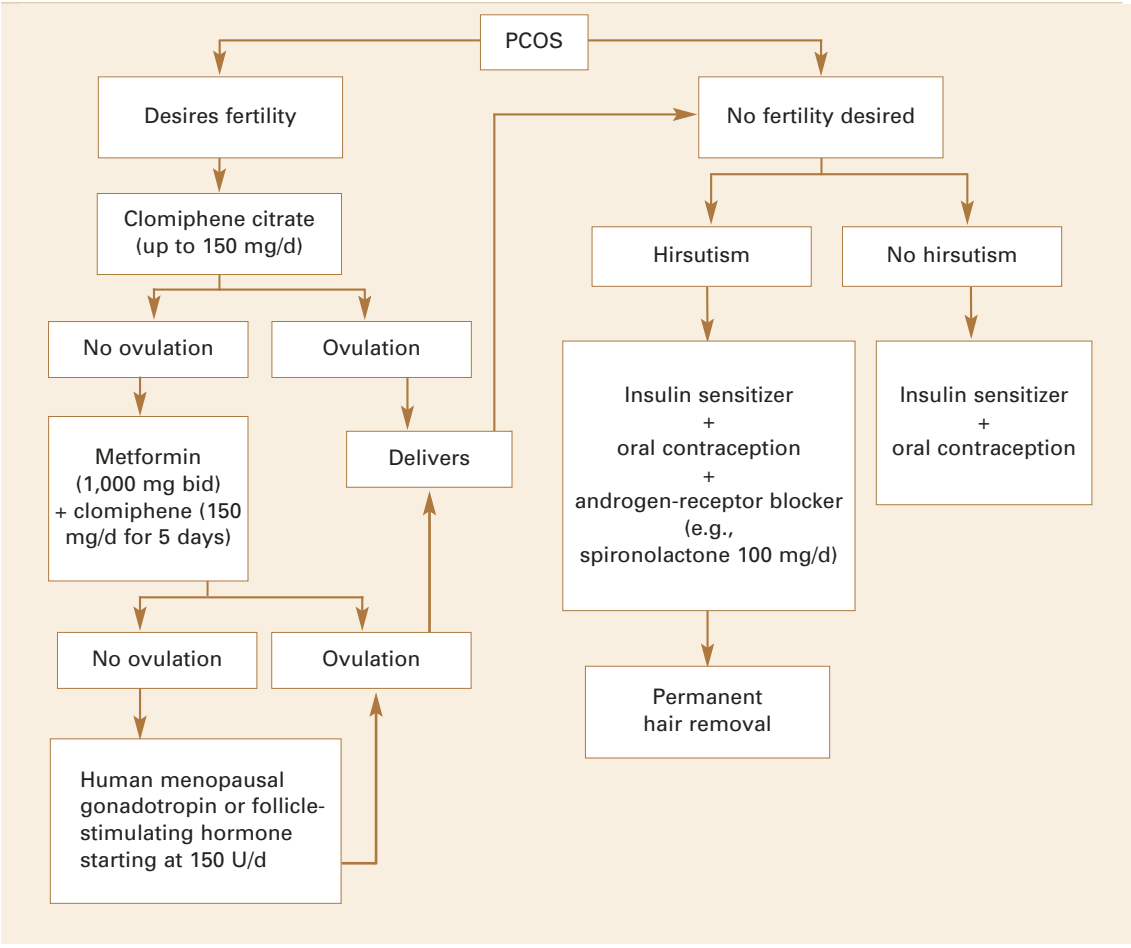
FIGURE

Treatment algorithm for PCOS



risk factor for the development of diabetes, this test is useful in populations at risk.

I use fasting plasma glucose to assess glucose tolerance and screen for diabetes mellitus. However, as neither serum insulin levels nor impaired glucose tolerance are predictive of response to insulin-sensitizing agents, I do not use the results to determine who should receive these drugs.

Metformin's efficacy in improving insulin resistance and enhancing ovulation is overwhelming in nonmorbidly obese and lean women with PCOS.

Choose the appropriate agent. Oral hypoglycemic agents are classified by type, each of which affects a different area in the glucose metabolism scheme.

- **Sulfonylureas,** which have been available since the 1950s, reduce glucose levels by stimulating the release of insulin.[5] Sulfonylureas may cause hypoglycemia and have not been studied in women with PCOS.
- **α-glucosidase inhibitors** slow or block the breakdown of starches and sugars in the gastrointestinal tract, thereby reducing the absorption of glucose.
- **Insulin-sensitizing agents** work through various mechanisms (TABLE 1). Like the α-glucosidase inhibitors, they rarely cause hypoglycemia. Since insulin resistance is likely to

TABLE 1

Insulin-sensitizing agents

AGENT	DOSE	NOTABLE SIDE EFFECTS	MECHANISM OF ACTION	PREGNANCY CATEGORY
Metformin	1,500-2,000 mg/d	Gastrointestinal distress	Reduces glucose production in the liver	B
Thiazolidinediones		Liver toxicity	Increases insulin sensitivity via peroxisome proliferator-activated receptor-γ (PPAR-γ)	C
Rosiglitazone	4-8 mg/d			
Pioglitazone	30-45 mg/d			

lead to impaired glucose tolerance and subsequent type 2 diabetes, insulin-sensitizing agents make good clinical sense.

One such agent is metformin—a biguanide that has been in use for several decades but was not approved by the US Food and Drug Administration (FDA) for type 2 diabetes until 1994. Metformin works primarily by reducing glucose production in the liver.[6]

Its main side effects are gastrointestinal upset and diarrhea. Lactic acidosis has been reported in patients who have renal or liver disease. Of the many studies of metformin use in women with PCOS, most[7-16] but not all[17-20] have demonstrated that a dose of 500 mg 3 times daily lowers circulating androgen levels, reduces weight, improves insulin resistance, or induces ovulation in women with PCOS.

If a patient achieves a 5% to 10% weight loss, I may stop treatment to see if she ovulates without the drug.

In none of the trials was ovulation induced successfully in all women receiving metformin. In other words, certain subpopulations may be metformin-resistant. Nevertheless, metformin's efficacy in improving insulin resistance and enhancing ovulation is overwhelming in nonmorbidly obese and lean women with PCOS. However, this agent may not be efficacious in women who are morbidly obese.[19]

As a first-line therapy, I use metformin in PCOS patients who do not wish to become pregnant and clomiphene citrate if the patient is trying to conceive (FIGURE).

Thiazolidinediones also are insulin-sensitizing agents, but work primarily in muscle and adipose tissue. These compounds stimulate peroxisome proliferator-activated receptor-γ, triggering the production of glucose transporter proteins.[20]

Of the 2 currently marketed thiazolidinediones—pioglitazone and rosiglitazone—only the latter has been evaluated for treatment of women with PCOS.[21,22] Preliminary reports suggest that rosiglitazone may improve insulin sensitivity, reduce serum androgen levels, and induce ovulation in women with PCOS.

Although my experience is limited, I give rosiglitazone when metformin fails to regulate menses or when the patient cannot tolerate metformin's gastrointestinal side effects.

The primary side effect of the thiazolidinediones is liver toxicity. One agent, troglitazone, was removed from the market for this effect.

Extended use of insulin-sensitizing agents. There are no data on the long-term effects of insulin-sensitizing agents in women with PCOS. I reevaluate the patient 1 month after beginning therapy (to assess side effects and tolerability), 6 months later, and then annually.

If a patient achieves a 5% to 10% weight loss, I may stop treatment to see if she ovulates without the drug. I use menstrual history to assess efficacy.

If the patient's baseline testosterone levels

are elevated, I may also measure serum testosterone after 5 to 6 weeks of therapy to see if the levels are decreasing. Although another drug may come on the market at any time, I tend to think of metformin therapy as lasting at least until menopause.

2. Facilitate ovulation

Even women who do not desire fertility stand to gain by ending chronic anovulation, which increases the risk of endometrial cancer. Fortunately, a number of avenues are available.

Weight loss. Up to 70% of women with PCOS are obese and thus at increased risk for diabetes, hypertension, and cardiac disease. Numerous studies have shown that weight loss can lower circulating androgen levels and induce resumption of regular menstrual cycles. Surprisingly, only a modest weight loss—as little as 5% of initial weight—can produce these changes.[23]

Therefore, all obese women with PCOS should be advised to lose weight—not only to improve their chance for spontaneous ovulation, but for the multiple health benefits associated with weight loss itself.

Clomiphene citrate. Even improvements in insulin resistance not accompanied by weight loss can improve ovulation. For decades, clomiphene has been used as first-line therapy to induce ovulation in women with PCOS. It is a selective estrogen receptor modulator, exerting its effects at the level of the hypothalamus and pituitary gland, where it acts as an antagonist to the estrogen receptor. Blocking the negative feedback of estrogen in the hypothalamus and pituitary gland increases the production and release of follicle-stimulating hormone. This increase stimulates the development of secondary ovarian follicles and ultimately results in ovulation.

Clomiphene is not effective in hypoestrogenic women or those who lack a functionally normal hypothalamus and pituitary gland.

For women hoping to conceive, initiate clomiphene treatment in the early follicular phase and continue for 5 days. The starting dose is one 50-mg tablet per day. If ovulation does not occur, increase the dose by 50 mg in the next cycle, to 100 mg/d. If ovulation has not occurred by the time a daily dose of 150 mg is reached, response to higher concentrations is unlikely and the condition should be considered clomiphene-resistant.[24] Approximately 15% of women with PCOS have clomiphene-resistant anovulation.[25]

Note however, that obese women often require higher doses of clomiphene to induce ovulation.[26] Although I give obese patients the same starting dose of clomiphene, I raise daily levels up to 200 mg in this patient population.

Using metformin to enhance ovulation. Pretreatment with metformin may enhance ovulation induction with clomiphene. In a multinational, randomized, placebo-controlled trial, obese women with PCOS were given metformin or placebo for 5 weeks.[27] The ovulation rates were 34% (12/35) in the metformin group and 4% (1/26) in the placebo group. The women who did not ovulate were then given 50 mg of clomiphene per day for 5 days in addition to placebo or metformin. In the clomiphene-metformin group, the ovulation rate was 90% (19/21) versus 8% (2/25) in the placebo-metformin group.

Metformin also appears to be effective in women with clomiphene resistance. One randomized, placebo-controlled trial examined women with PCOS and clomiphene-resistant anovulation at a dosage of 150 mg/d. Participants were given a thrice-daily dose of 500 mg metformin or placebo for 7 weeks, followed by clomiphene, starting at 50 mg/d with increasing doses until ovulation occurred or a dosage of 150 mg/d was

Even modest weight loss can improve insulin resistance and enhance ovulation.

achieved.[28] The rate of ovulation was 75% (9/12) in the metformin-clomiphene group versus 27% (4/15) in the placebo-clomiphene group.

More investigation is needed to determine the effects of combination therapies, including various oral hypoglycemic agents, in the treatment of women with PCOS. An NIH-funded clinical trial is currently comparing the effectiveness of ovulation induction with clomiphene alone, metformin alone, and the two agents in combination.

3. Address hirsutism

Hirsutism is the presence of terminal hair on a woman's face, chest, lower abdomen, suprapubic area, upper arms, thighs, or back. PCOS is the most common cause of hirsutism in women of reproductive age. Most women with PCOS have elevated serum levels of luteinizing hormone and total and free testosterone, which results in hirsutism.

Patients should be counseled that their response to therapy for hirsutism will likely be slow and subtle.

Counsel the patient. Treating this condition is difficult; it is best approached with a combination of medical and mechanical means. Patients should be counseled that their response to therapy will likely be slow and subtle. In fact, noticeable changes may not occur for as long as 6 months.

Unfortunately, there is no accepted method for assessing a patient's response to therapy. Even baseline assessment can be difficult, because many patients camouflage hirsutism with depilatories and cosmetics.

I ask patients if they shave and, if so, how often. I also ask if they use any other method of hair removal. In addition, I use a modified Ferriman-Gallwey scale and a pictogram to document hair growth. At follow-

TABLE 2
Medical therapies for PCOS-associated hirsutism

AGENT	DOSE	MAJOR SIDE EFFECTS	FDA-APPROVED USE
Androgen-receptor antagonists			
Flutamide	250 mg/d	Elevated liver enzymes Dry skin Urine discoloration	Adjuvant for prostate cancer
Spironolactone	25-100 mg/d	Polyuria Orthostatic hypotension Hyperkalemia	Diuretic
Cyproterone acetate	100 mg/d	Adrenal insufficiency Loss of libido	Not available in United States
5α-reductase inhibitor			
Finasteride	1-5 mg/d	Teratogenic in a male fetus	Male alopecia Prostate cancer

up, I ask if they have noticed any changes in their hair growth or if they are shaving less often.

Medical therapy. Begin by treating the patient's anovulation and androgen production. Next, antagonize androgenic effects at the level of the pilosebaceous unit. This can be done using compounds that antagonize the binding of androgen to its receptor or that inhibit the enzyme 5α-reductase, which metabolizes the conversion of testosterone to dihydrotestosterone (TABLE 2).

■ **Androgen-receptor antagonists.** Among the androgen-receptor antagonists is spironolactone, which not only competitively binds to the androgen receptor, but also inhibits the 5α-reductase enzyme. It also has been used in combination with oral contraceptives. Oral contraceptives are helpful because they reduce ovarian androgen production by decreasing luteinizing hormone and stimulating the production of sex-hormone binding globulin, which binds testosterone and reduces free testosterone. Oral contraceptives also ensure effective contraception.

Other androgen-receptor agonists include flutamide, which is FDA-approved for adjuvant treatment of prostate cancer, and cyproterone acetate, a potent progestin that not only antagonizes androgens at the peripheral level, but decreases serum luteinizing hormone levels and androgen production. Unfortunately, the latter agent is not available in the United States.

■ **5α-reductase inhibitors.** The 5α-reductase enzyme exists in 2 forms. Type I occurs predominately in the skin, and type II occurs mainly in the prostate. Finasteride, which inhibits both forms, is approved for the treatment of prostate cancer at a daily dose of 5 mg and male alopecia at a daily dose of 1 mg.

Overall, the literature suggests that both flutamide and finasteride are effective against PCOS-associated hirsutism. One randomized, placebo-controlled clinical trial involving 40 women utilized both the Ferriman-Gallwey score and hair-shaft diameter to assess clinical effectiveness of these agents. In that study, 5 mg/d of finasteride was shown to be as effective as 100 mg/d of spironolactone or 250 mg/d of flutamide.[29] (Note that 5α-reductase inhibitors should not be used during pregnancy.)

After 6 to 12 months of medical therapy, mechanical methods may be very useful in permanently removing hair.

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■ **Eflornithine, a topical agent,** was recently approved for the treatment of facial hair. This compound is available in a cream that the patient applies twice daily. Eflornithine inhibits ornithine decarboxylase, an enzyme that is important in the function of the pilosebaceous unit. In one trial, the first signs of effectiveness were noted after 8 weeks of therapy; one third of patients improved after 24 weeks of use.[30]

■ **As a first-line agent** I rely on spironolactone, simply because it has been on the market longest and I have more clinical experience with it. I also have used finasteride. Unfortunately, there are no data to aid in patient selection.

Mechanical treatments. Once treatment with medical therapy has been maintained for 6 to 12 months, mechanical methods may be very useful in permanently removing hair. These include electrology and lasers. Types of electrology include:

■ **Electrolysis,** the application of a galvanic current to achieve chemical destruction of the hair follicle.

■ **Thermolysis,** which utilizes alternating current and the generation of heat to destroy the hair follicle. ■

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