

Metformin for PCOS symptoms: 5 challenging cases

This inexpensive and versatile drug broadens the choices for treating polycystic ovary syndrome. An expert describes its efficacy for common manifestations of PCOS.

Inducing ovulation. Decreasing insulin resistance. Facilitating weight loss. These are a few of the benefits metformin offers women with polycystic ovary syndrome (PCOS). This article's 5 case histories illustrate a range of major complaints and secondary factors to consider in making prescribing decisions.

The decision to use metformin depends on the patient's major PCOS-related complaint (TABLE 1), as well as other considerations. In some cases, metformin may not be appropriate at all.

(For dosing and common side effects, see "Metformin: The prescribing basics," page 37.¹⁻³)

Metformin, which is an oral biguanide unrelated to the sulfonylureas, has the potential to correct:

- **Anovulatory infertility.** Used alone,

metformin induces ovulatory cycles in many cases. In patients with clomiphene-resistance, it can be added to the regimen to enhance ovulation rates.

- **Oligomenorrhea.** Although oral contraceptives remain the first-line agent, metformin is a second-line agent that restores normal menstruation in about 50% of treated women.

- **Obesity.** Clinical trials indicate that metformin may add helpful pharmacologic support to a diet and exercise program.

- **Gestational diabetes.** Early evidence suggests that use of metformin in pregnancy may reduce the incidence of gestational diabetes and spontaneous abortion, although more study is needed.

More study also will be necessary to understand the role of metformin in the treatment of hirsutism.

Characteristics of PCOS

According to a group of experts working with the National Institutes of Health (NIH), polycystic ovary syndrome is the presence of oligomenorrhea or amenorrhea with clinical or laboratory evidence of hyperandro-

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KEY POINTS

- Metformin's role in treatment of PCOS varies with the patient's chief complaint, clinical characteristics, and lifestyle.

- The primary uses of metformin in treating PCOS are to induce ovulation in women resistant to clomiphene alone and to treat oligomenorrhea in women who can't or won't use oral contraceptives.

- To be a candidate for metformin treatment, a patient must have a serum creatinine lower than 1.4 mg/dL to avoid the risk of developing lactic acidosis.

genism (hirsutism, elevated free testosterone) in the absence of other causes such as a testosterone-producing ovarian tumor or non-classical adrenal hyperplasia (21-hydroxylase deficiency). Using the NIH definition, a diagnosis of PCOS is not appropriate for women with regular ovulatory menses.

Many authorities believe the combination of regular ovulatory menses and hirsutism should be diagnosed as idiopathic hirsutism.

The prevalence of PCOS in women of reproductive age is 4.7% in the southeastern United States; prevalence is similar in several other parts of the world where it has been measured.⁴⁻⁶

Three key endocrine abnormalities characterize PCOS:

- Elevated luteinizing hormone (LH) secretion—seen in almost all women with PCOS.⁷⁻⁹
- Increased circulating insulin caused by insulin resistance, found in many women with PCOS.^{10,11}
- Elevated ovarian androgen production—present in virtually all women with PCOS. Increased androgen production causes hirsutism and, in some women, acne.

These abnormalities prevent growth of a dominant follicle (FIGURE 1), leading to anovulation and oligomenorrhea.

CASE 1

Combating PCOS-related oligomenorrhea

The primary care doctor of a 25-year-old student has established a PCOS diagnosis based on the patient's report of 2 menstrual periods per year and an elevated serum free-testosterone measurement. Her body mass index (BMI) is 24.5, and her main problems are

TABLE 1

First- and second-line therapy for the chief complaints of PCOS

COMPLAINT	FIRST-LINE THERAPY	SECOND-LINE THERAPY
Oligomenorrhea	Oral contraceptive	Metformin
Hirsutism	Oral contraceptive plus an anti-androgen (eg, spironolactone 100mg)	Metformin plus an anti-androgen
Anovulatory infertility	Clomiphene or metformin alone	Clomiphene plus metformin
Obesity	Lifestyle changes: Increased exercise Decreased calorie intake	Metformin plus lifestyle changes

hirsutism, oligomenorrhea, and a propensity for gaining weight. She took the birth control pill and believes it was responsible for a 25-lb weight gain. When the patient discontinued the pill, she lost 20 lb, and she is adamantly opposed to taking it again. The patient's pelvic examination is normal, with no evidence of virilization. She read about metformin on the Internet and asks if you will prescribe it for her oligomenorrhea.

Oral contraceptives remain first-line treatment

Metformin may be effective in some women for the treatment of oligomenorrhea. However, as mentioned earlier, more study is needed into its effects on hirsutism.

Oligomenorrhea. No large-scale clinical trial evaluating the efficacy of metformin for oligomenorrhea in women with PCOS has been reported. However, a number of small-scale clinical trials and case series suggest that metformin restores normal ovulatory menses in some women. For women with PCOS treated with metformin alone, about 25% begin regular menses within 3 months,^{12,13} and about 50%¹⁴ to 95%^{15,16} begin regular menses within 6 months. In my practice, about 50% of women begin having regular ovulatory menses after 6 months of treatment.

Patient characteristics that predict successful induction of regular ovulatory menses are not fully delineated. It appears, however, that women with elevated serum testosterone

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Characteristics of polycystic ovary syndrome (PCOS)

Cascade of events leading to anovulatory infertility

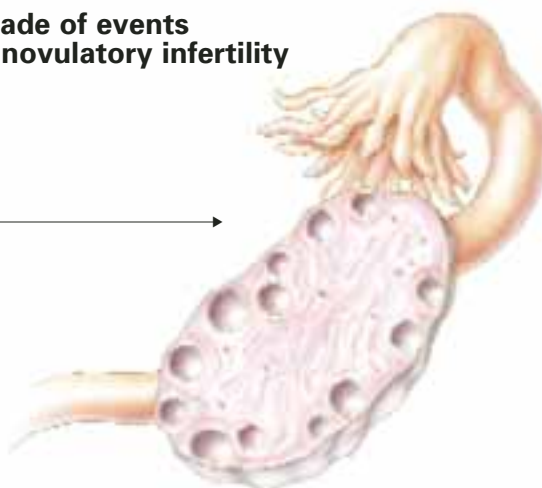
Follicular milieu is disrupted by elevated luteinizing hormone (LH), androgens, and insulin

↓
Arrested follicular growth
(maximum 4 mm to 8 mm)
No follicle is dominant

↓
Anovulation

↓
Oligomenorrhea

↓
Anovulatory infertility



3 key endocrine abnormalities

ABNORMALITY	WHO IS AFFECTED	EFFECTS
Elevated LH secretion	Almost all women with PCOS	Increased ovarian androgen secretion Disruption of normal follicular growth
Elevated circulating insulin caused by insulin resistance	Many women with PCOS	Low hepatic production of SHBG Increased ovarian androgen secretion
Elevated ovarian androgen production	Virtually all women with PCOS	Hirsutism Adiposity Acne, in some women

IMAGE: Maura Flynn

have a greater response to metformin.¹⁷

Many months of treatment may be required to reestablish regular menses when metformin is used as a second-line agent in this context. Some women initially may have increased estrogen production (paralleled by an increase in cervical mucus secretion) without ovulation. Treatment with a progestin to prevent endometrial hyperplasia may be necessary during the initial months of therapy.

Hirsutism. In 1 small-scale clinical trial that directly compared the efficacy of oral contraceptives and metformin, 17 women with PCOS were randomized to receive metformin (500 mg twice daily for 3 months, followed by 1,000 mg twice daily for 3 months) or an oral contraceptive (ethinyl estradiol 35 µg and cyproterone acetate 2 mg daily).¹⁸ Both

regimens produced an approximate 30% decrease in serum testosterone. The OC also decreased the hirsutism score and ovarian volume, as determined by sonography. Metformin did not decrease hirsutism or ovarian volume. Half the women in the metformin group had restoration of menses, and 100% of the women in the OC group had regular withdrawal bleeding.

Clinical course

Trial of metformin, switch to spironolactone, cyclic progestins

Because this patient believes OCs caused her to gain weight, the recommended first-line treatment for oligomenorrhea is not an option. She is started on metformin at a dose of 500 mg 3 times daily. After 4 months

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of therapy, she still does not have regular ovulatory menstrual cycles, and cyclic progestins are instituted to reduce the risk of endometrial hyperplasia and induce withdrawal bleeding.

After 6 months of treatment, the patient reports little reduction in her hirsutism. She discontinues metformin and starts spironolactone (an anti-androgen), taking 100 mg daily and using a barrier contraceptive to prevent pregnancy. The combination of spironolactone and cyclic progestin withdrawal results in satisfactory symptom control.

CASE 2

When renal insufficiency accompanies oligomenorrhea

A 40-year-old woman with PCOS and eczema presents for treatment of oligomenorrhea. She cannot take OCs because she once experienced deep vein thrombosis while using them. Her eczema is being treated with cyclosporine. Her serum creatinine measurement is high—1.8 mg/dL—and her internist believes the cyclosporine caused this renal dysfunction. She asks if she can take metformin for her oligomenorrhea.

Watch for lactic acidosis risks

A serum creatinine of less than 1.4 mg/dL must be demonstrated in all patients before metformin treatment is initiated. In rare instances, metformin causes lactic acidosis, which is fatal in as many as half of patients who develop it.¹⁹ Because the kidney excretes metformin, patients with renal insufficiency (creatinine higher than 1.4 mg/dL) are at increased risk of metformin-induced lactic acidosis.

Other conditions that contraindicate metformin because of increased risk of lactic acidosis include congestive heart failure, sepsis, concurrent liver disease, and a previous history of lactic acidosis.^{20,21} The risk of lactic acidosis with metformin treatment is very low when clinicians follow these prescribing guidelines.²² Unfortunately, physicians often prescribe metformin for patients with contraindications.²³

Surgery. Lactic acidosis also poses a threat at

the time of surgery.²⁴ Therefore, metformin therapy should be suspended temporarily for all major surgical procedures where fluid intake is restricted. Metformin can be reinstated once the patient's fluid intake and renal function are normal.

Clinical course

Cyclosporine reduced, cyclic progestins offered

This patient's elevated creatinine level puts her at increased risk of metformin-induced lactic acidosis. For this reason, metformin is not prescribed at the time of the evaluation, and the cyclosporine dose is reduced in an effort to reduce her creatinine level. She is offered treatment with cyclic progestins for her oligomenorrhea.

CASE 3

A tool for ovulation induction

A 30-year-old woman with PCOS and primary infertility requests a consultation after failing to ovulate with clomiphene. She has a long history of oligomenorrhea, hirsutism, elevated serum free testosterone, and a serum dehydroepiandrosterone (DHEAS) of 2.3 µg/mL (normal range: 0.7 to 3.4 µg/mL). Her BMI is 27.8. The patient's hysterosalpingogram is normal, as is her partner's semen analysis. Her physician prescribed clomiphene 50 mg daily for cycle days 5 to 9, but the patient did not ovulate. She then was given clomiphene 100 mg daily for cycle days 5 to 9, but still did not ovulate. She asks if the next step should be in vitro fertilization (IVF).

Low-cost, low-risk options include metformin

The initial treatment of ovulatory infertility caused by PCOS should focus on interventions that are inexpensive and associated with a low risk of multiple gestation. These include weight loss, clomiphene or metformin monotherapy, and combination treatment such as clomiphene plus metformin or clomiphene plus a glucocorticoid. If these

interventions are ineffective, then treatments such as follicle-stimulating hormone (FSH) injections, ovarian surgery, or IVF may be warranted (TABLE 2).²⁵

The combination of clomiphene and metformin was superior to clomiphene alone in inducing ovulation in women with PCOS, in 3 randomized clinical trials.²⁶⁻²⁸ In 1 trial, 56 infertile women with PCOS, oligo-ovulation, and resistance to clomiphene monotherapy received either metformin 850 mg twice daily or placebo for 1 month.²⁸ The average BMI of the subjects was about 31. Metformin treatment was associated with a significant decrease in serum LH and testosterone concentration.

In the first month of the trial, 1 woman in the metformin group became pregnant. After the initial month, clomiphene citrate 100 mg daily for cycle days 4 to 7 was administered to both groups. In the metformin plus clomiphene group, 21 women (78%) ovulated, compared with 4 women (14%) in the placebo plus clomiphene group.

Early evidence suggests higher pregnancy rates. Data about the impact of metformin plus clomiphene on pregnancy and delivery rates in women with PCOS are limited. In 1 study, investigators reported that the pregnancy rate was 55% in women treated with metformin plus clomiphene compared with 7% in women treated with placebo plus clomiphene.²⁶ In this study, women with PCOS who did not ovulate when treated with clomiphene (150 mg daily for 5 days) received either metformin (1,500 mg daily) or placebo for 7 weeks. During the initial 7-week treatment period, 1 of the 12 women in the metformin group and none of the 15 women in the placebo group ovulated.

After this initial treatment period, all women received clomiphene citrate, beginning at a dose of 50 mg daily for 5 days, with dosage escalation in the absence of ovulation. Nine of the 12 women in the metformin plus clomiphene group ovulated, compared with 4

of the 15 women in the placebo plus clomiphene group. Of the women who completed the clinical trial, 6 of 11 in the metformin plus clomiphene group became pregnant, compared with 1 of 14 in the placebo plus clomiphene group.

Another clinical trial demonstrated the merit of a trial of clomiphene plus metformin when ovulation does not occur with clomiphene alone, before advancing to a resource-intensive regimen such as gonadotropin therapy. Women were given either clomiphene plus metformin or gonadotropin injections.²⁹ Pregnancy rates after both treatments were similar. However, the cost of treatment for the clomiphene plus metformin therapy was 25% that of gonadotropin therapy.

Clinical course

Recommend alternatives to in vitro fertilization

At this point in her care, this patient should not be offered IVF treatment. IVF is a resource-intensive treatment that is associated with a high rate of multiple gestation. This patient could instead be directed to any of the low-resource options that she has not yet tried: weight loss, metformin monotherapy, or clomiphene plus a glucocorticoid or clomiphene plus metformin.³⁰ Even though this patient is only slightly overweight (her BMI of 27.8 is near normal), losing weight sometimes restores ovulatory menses in women with PCOS.³¹⁻³⁵

Several clinical trials have reported that, in women with PCOS with a serum DHEAS higher than 2 $\mu\text{g}/\text{mL}$, clomiphene plus a glucocorticoid is more effective than clomiphene alone for inducing ovulation.³⁶

Metformin plus clomiphene. In this case, you decide it would be helpful to give the patient metformin. The drug is initiated at a dose of 500 mg daily, to be taken with dinner. The metformin dose is increased over a period of weeks to a target dose of 500 mg 3 times

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daily (850 mg twice daily is another option). After 2 months of metformin therapy, you prescribe clomiphene 100 mg daily (50 mg daily is sometimes prescribed) for cycle days 5 to 9. The patient ovulates and becomes pregnant.

CASE 4

Treating PCOS during pregnancy

A 35-year-old woman with PCOS began taking metformin 500 mg 3 times a day for amenorrhea and infertility. She also started a diet and exercise plan, losing 45 lb during the first 6 months. She began to menstruate monthly and became pregnant. She asks if she should continue metformin during pregnancy.

Weigh risk versus benefit

Metformin is a category B drug and is not approved by the US Food and Drug Administration for use in pregnancy. Some clinicians who use metformin to treat diabetes continue the agent during pregnancy.³⁷ However, many authorities recommend insulin as first-line therapy when medication is necessary during pregnancy, while others recommend using an agent that does not cross the placenta, such as glyburide.³⁸

No randomized, prospective clinical trials have been performed to address metformin use in pregnancy in women with PCOS. In 1 cohort study, it was associated with an increased risk of preeclampsia and an increased rate of adverse perinatal outcomes.³⁹ While preliminary reports from case series suggest that met-

TABLE 2

Treatment of anovulatory infertility associated with PCOS: A stepwise approach

STEP	INTERVENTION	COST	RISK OF MULTIPLE GESTATION
1	Weight loss (if baseline weight is elevated)	Low cost	Not increased
2	Clomiphene	Low cost	Modest increase (7% risk of twins, 0.5% risk of triplets)
3	Metformin alone	Low cost	Not increased
4	Clomiphene plus metformin	Low cost	Modest increase
5	Clomiphene plus glucocorticoid	Low cost	Modest increase
6	FSH injections	Resource-intensive	Significantly increased (20% risk of twins, 5% risk of triplets)
7	Ovarian surgery	Resource-intensive	Not increased
8	In vitro fertilization	Resource-intensive	Markedly increased (30% risk of twins, 4% risk of triplets; risk dependent on number of embryos transferred)

FSH = follicle-stimulating hormone

formin treatment in pregnancy may reduce the risk of spontaneous abortion and decrease the risk of gestational diabetes, no randomized, prospective trials have established these effects. The studies that have been performed in these areas are provocative, however.

In 1 study of the effects of metformin on early pregnancy loss in women with PCOS, the spontaneous abortion rate was 9% among women receiving metformin (6 of 68 pregnancies) and 42% in women who did not receive metformin (13 of 31 pregnancies).⁴⁰ Although a similar result was reported by another group,⁴¹ it is not clear if the metformin and control groups were well matched on important clinical variables.

It is highly likely that metformin is effective in reducing elevated blood sugar in pregnant women with gestational diabetes. In a study of pregnancy outcome in 33 nondiabetic women with PCOS taking metformin 2,550 mg daily, CONTINUED

compared with a control group of 39 nondiabetic women with PCOS who were not taking metformin, gestational diabetes was diagnosed in 3% of the women taking metformin and in 23% of the women not taking metformin.⁴²

A clinical trial is needed to confirm these preliminary findings and better characterize the effects of metformin on the fetus. Based on currently available information, 100 pregnant women with PCOS would need to be treated with metformin to prevent gestational diabetes in 20.

More information also is needed about the characteristics of gravidas most likely to benefit from metformin, as well as the effects of metformin on maternal outcomes. Until high-quality trials supply this data, clinicians and patients need to weigh the known relative risks and benefits of metformin in early pregnancy.

Clinical course

Metformin discontinued

After a thorough discussion of the possible risks and benefits of metformin, the patient discontinues her metformin treatment. She has an uneventful pregnancy, does not develop gestational diabetes, and has a vaginal delivery at term.

Her pre-pregnancy weight loss likely helped to normalize her central metabolism and decrease her risk of developing gestational diabetes. Pre-pregnancy exercise and diet are probably the most effective method for reducing the risk of gestational diabetes in women with PCOS.

CASE 5

Facilitating weight loss

A 40-year-old woman with PCOS and a body mass index of 35 (height 5' 6", weight 216 lb) wants to lose weight. The patient has a strong family history of diabetes. In addition, her fasting blood sugar level is 108 mg/dL. She asks if metformin might help her to lose weight.

Metformin is more effective with diet, exercise

Although it is not approved as a weight-loss medication, a number of trials report that metformin plus a low-calorie diet is superior to a low-calorie diet alone in fostering weight loss.¹ Metformin (850 mg twice daily) plus a low-calorie diet (1,200 to 1,400 kcal daily) was superior to a low-calorie diet alone in facilitating weight loss both in women with PCOS and obese women who did not have hirsutism and irregular menses.⁴³ In this study, the pretreatment mean weight was 103 kg in the women taking metformin and following a low-calorie diet, and it was 102 kg in the placebo-low-calorie-diet group. After 7 months of treatment, the mean weight was 94 kg and 97 kg, respectively.

Note, however, that metformin treatment without a low-calorie diet or increased exercise is not likely to be associated with significant weight loss,⁴⁴ although it may decrease hunger and food cravings of patients, especially at daily doses above 1,700 mg.⁴⁵

Obese adolescents may benefit from metformin. In a clinical trial of 24 hyperinsulinemic, nondiabetic obese adolescents who followed a regimen of metformin (850 mg twice daily) plus a low-calorie diet (1,500 kcal daily for females) or a low-calorie diet alone, the group treated with both interventions lost more weight and body fat than the group treated with a low-calorie diet alone.⁴⁶ Other investigators have reported similar results.⁴⁷

The importance of lifestyle interventions in preventing diabetes in high-risk populations—which includes obese women with PCOS—was demonstrated in a large clinical trial.⁴⁸ Nondiabetic men and women (n = 3,234) with impaired fasting glucose (fasting glucose between 110 and 126 mg/dL) received placebo, metformin (850 mg twice daily), or a lifestyle-modification program with a goal of 7% weight loss and 150 minutes of physical activity per week.

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Metformin: The prescribing basics

Generic metformin is available as 500-, 850-, and 1,000-mg tablets. The target dose is in the range of 1,500 mg to 2,550 mg, which can be achieved by doses of 500 mg 3 times daily, 850 mg 2 or 3 times daily, or 1,000 mg 2 times daily. The maximum dose of metformin is 850 mg 3 times daily (2,550 mg daily). Significant responses to metformin are not regularly observed at total doses lower than 1,000 mg daily. The cost of 1,500 mg of generic metformin is about \$1.75.

Metformin is taken with meals to reduce gastrointestinal side effects and is usually initiated at a dose of 500 mg, administered at the largest meal. If the patient tolerates this initial dose, metformin can then be increased to 500 mg at the 2 largest meals and then to 500 mg at breakfast, lunch, and dinner. It may take the patient 1 to 2 weeks to adapt to the gastrointestinal effects of an increase in dose.

Extended-release metformin is available as 500- and 750-mg tablets (Glucophage XR). The

entire daily dose is taken at dinner. The initial dose is 500 mg or 750 mg daily, with escalation to a maximum of approximately 2,250 mg. Many authorities believe that extended-release metformin is associated with fewer gastrointestinal side effects than generic metformin.

Side effects. The most common side effects are diarrhea (10% to 53% of patients), nausea or vomiting (6% to 26%), flatulence (12%), indigestion, and abdominal discomfort. Weakness has been reported in 9% of patients. In 1 clinical trial at a dose of 2,550 mg daily, treatment was associated with diarrhea in 53% of the patients, compared with 12% of patients taking placebo.⁴⁹ In the same study, nausea or vomiting was reported in 26% of those taking metformin and 8% of those taking placebo.

A small percentage of women discontinue the medication because of side effects.^{49,50} Occasionally, the onset of side effects begins well after the patient has begun taking the medication.⁵¹

The mean age of the cohort was 51 years, and the mean BMI was 34. The average follow-up was 2.8 years.

The incidence of newly diagnosed diabetes was 11, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. Compared with placebo, lifestyle changes reduced the risk of developing diabetes by 58%, while metformin reduced it by 31%.

Obese women with PCOS may want to try to achieve the goals established in this study: weight loss of 7% of body weight and at least 150 minutes of exercise weekly. If lifestyle change alone is not effective for achieving a desired target weight, then metformin 500 mg 3 times daily or 850 mg twice daily could be prescribed.

Metformin for hyperglycemia, type 2 diabetes. Metformin also may be helpful in patients with type 2 diabetes; it is approved as

monotherapy for hyperglycemia in patients in whom disease has not been controlled with diet and exercise alone.

Unlike sulfonylureas, metformin does not cause the body to make more insulin and hence does not produce hypoglycemia in normal subjects or patients with type 2 diabetes.

Clinical course

Key element: Lifestyle changes

The patient decides to use metformin plus lifestyle changes in her weight-loss plan, even though you recommend first trying lifestyle changes alone.

Over 6 months she loses 35 lb and reports being satisfied with her treatment. She believes that metformin was largely responsible for her weight loss. However, it is likely that her commitment to diet and exercise were the key to her success. ■

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Dr. Barbieri reports no financial relationship with any companies whose products are mentioned in this article.