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John E. Nestler

Virginia Commonwealth University, Medical College of Virginia, jnestler@mcvh-vcu.edu

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CLINICAL THERAPEUTICS

Metformin for the Treatment of the Polycystic Ovary Syndrome

John E. Nestler, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A 23-year-old woman with known polycystic ovary syndrome visits her family physician. She has taken oral contraceptive pills in the past but did not tolerate them and is not currently receiving any treatment. She has three or four menstrual periods per year and is not interested in becoming pregnant now, but she will be getting married in a year. She has heard that the polycystic ovary syndrome is associated with diabetes and is concerned because both her mother and father have type 2 diabetes. Her body-mass index (the weight in kilograms divided by the square of the height in meters) is 32, her waist circumference is 38 in. (96.5 cm), her serum total testosterone level is elevated at 0.9 ng per milliliter (90 ng per deciliter, or 2.9 nmol per liter), her plasma high-density lipoprotein cholesterol level is 35 mg per deciliter (0.9 mmol per liter), and her triglyceride level is 190 mg per deciliter (2.1 mmol per liter). Her serum glucose level 2 hours after the ingestion of 75 g of dextrose is 138 mg per deciliter (7.7 mmol per liter). The physician wonders whether treatment with metformin would be beneficial and refers the patient to an endocrinologist.

THE CLINICAL PROBLEM

The polycystic ovary syndrome is a clinical diagnosis characterized by the presence of two or more of the following features: chronic oligo-ovulation or anovulation, androgen excess, and polycystic ovaries.¹ It affects 5 to 10% of women of childbearing age^{2,3} and is the most common cause of anovulatory infertility in developed countries. Common clinical manifestations include menstrual irregularities and signs of androgen excess such as hirsutism, acne, and alopecia.

The polycystic ovary syndrome is associated with important metabolic derangements. The prevalence of type 2 diabetes in the United States is 10 times as high among young women with the polycystic ovary syndrome as among normal women,^{4,5} and impaired glucose tolerance or overt type 2 diabetes develops by the age of 30 years in 30 to 50% of obese women with the polycystic ovary syndrome.⁴⁻⁶ The prevalence of the metabolic syndrome is two to three times as high among women with the polycystic ovary syndrome as among normal women matched for age and body-mass index, and 20% of women with the polycystic ovary syndrome who are younger than 20 years of age have the metabolic syndrome.⁷ Although outcome data specifically for women with the polycystic ovary syndrome are lacking, the risk of fatal myocardial infarction is twice as high among women with severe oligomenorrhea, most of whom would be expected to have the polycystic ovary syndrome, as among women with eumenorrhea.⁸

From the Departments of Internal Medicine, Obstetrics and Gynecology, and Pharmacology and Toxicology, Virginia Commonwealth University, Richmond. Address reprint requests to Dr. Nestler at the Division of Endocrinology and Metabolism, Medical College of Virginia, PO Box 980111, Richmond, VA 23298-0111, or at jnestler@mcvh-vcu.edu.

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 PATHOPHYSIOLOGY AND EFFECT
OF THERAPY

The pathophysiological characteristics of the polycystic ovary syndrome are not fully understood but are known to involve complex interactions between the actions of gonadotropins, the ovaries, androgens, and insulin (Fig. 1). An important element of this syndrome is insulin resistance. The majority of women with the polycystic ovary syndrome, regardless of weight, have a form of insulin resistance that is intrinsic to the syndrome and is poorly understood.⁹⁻¹¹ Obese women with the polycystic ovary syndrome have an added burden of insulin resistance related to their adiposity.¹¹

The insulin resistance that is characteristic of the polycystic ovary syndrome appears to be responsible for the association of the disorder with type 2 diabetes.¹² Insulin resistance may also underlie the association of the polycystic ovary syndrome with recognized cardiovascular risk factors such as dyslipidemia and hypertension,¹³ as well as with anatomical¹⁴⁻¹⁷ and functional^{16,18,19} cardiovascular derangements.

Insulin resistance and compensatory hyperinsulinemia also play an important role in other aspects of the polycystic ovary syndrome, including androgen excess and anovulation (Fig. 1). Insulin stimulates the ovarian production of androgen by activating its homologous receptor,^{20,21} and the ovaries of women with the polycystic ovary syndrome appear to remain sensitive to insulin,²² or perhaps hypersensitive to it,²³⁻²⁵ even when classic target tissues such as muscle and fat manifest resistance to insulin action. In addition, hyperinsulinemia inhibits the hepatic production of sex hormone-binding globulin,²⁶ further increasing circulating free testosterone levels. Finally, insulin impedes ovulation, either by directly affecting follicular development or by indirectly increasing intraovarian androgen levels or altering gonadotropin secretion.²⁷ Further evidence of the influence of insulin resistance in the polycystic ovary syndrome is that multiple diverse interventions, which are related to one another only in that they lower circulating insulin levels, result in increased frequency of ovulation or menses, reduced serum testosterone levels, or both. These interventions include the inhibition of insulin release (with the use of diazoxide²⁰ or octreotide²⁸), improvement of insulin sensitivity (with the use of diet-induced weight

loss,²⁹ metformin,^{30,31} troglitazone,³² rosiglitazone,^{23,33} or pioglitazone³⁴), or the reduction of carbohydrate absorption (with the use of acarbose³⁵).

Metformin, a biguanide, is the most widely used drug for the treatment of type 2 diabetes worldwide. Its primary action is to inhibit hepatic glucose production, but it also increases the sensitivity of peripheral tissues to insulin.³⁶ The increase in insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been shown in nondiabetic women with the polycystic ovary syndrome.³⁷ In women with the syndrome, long-term treatment with metformin may increase ovulation, improve menstrual cyclicality, and reduce serum androgen levels^{30,31}; the use of metformin may also improve hirsutism.³⁸ If published data on the effects of metformin in the prevention of diabetes can be extrapolated to women with the polycystic ovary syndrome, then the drug may actually retard progression to glucose intolerance in affected women, as reported in a small, retrospective study.³⁹

 CLINICAL EVIDENCE

In 1996, it was reported that the administration of metformin to women with the polycystic ovary syndrome reduced circulating insulin levels and was associated with decreases in ovarian 17,20-lyase activity and ovarian secretion of androgens.⁴⁰ Most, but not all, subsequent studies confirmed the ability of metformin to lower fasting serum insulin³⁰ and androgen³¹ levels in women with the polycystic ovary syndrome. However, studies specifically assessing the effects of metformin on clinical signs of androgen excess (e.g., hirsutism, acne, and androgenetic alopecia) are limited.³⁸

With regard to ovulation, in results of a randomized clinical trial reported in 1998, pretreatment with metformin, as compared with placebo, increased the incidence of ovulation after subsequent treatment with clomiphene.⁴¹ Subsequently, several studies compared metformin with placebo, metformin with no treatment, metformin plus clomiphene with clomiphene alone, or metformin plus clomiphene with placebo. The most rigorous of these studies were included in a meta-analysis by Lord et al. in 2003.³⁰ The meta-analysis included data from 13 trials and 543

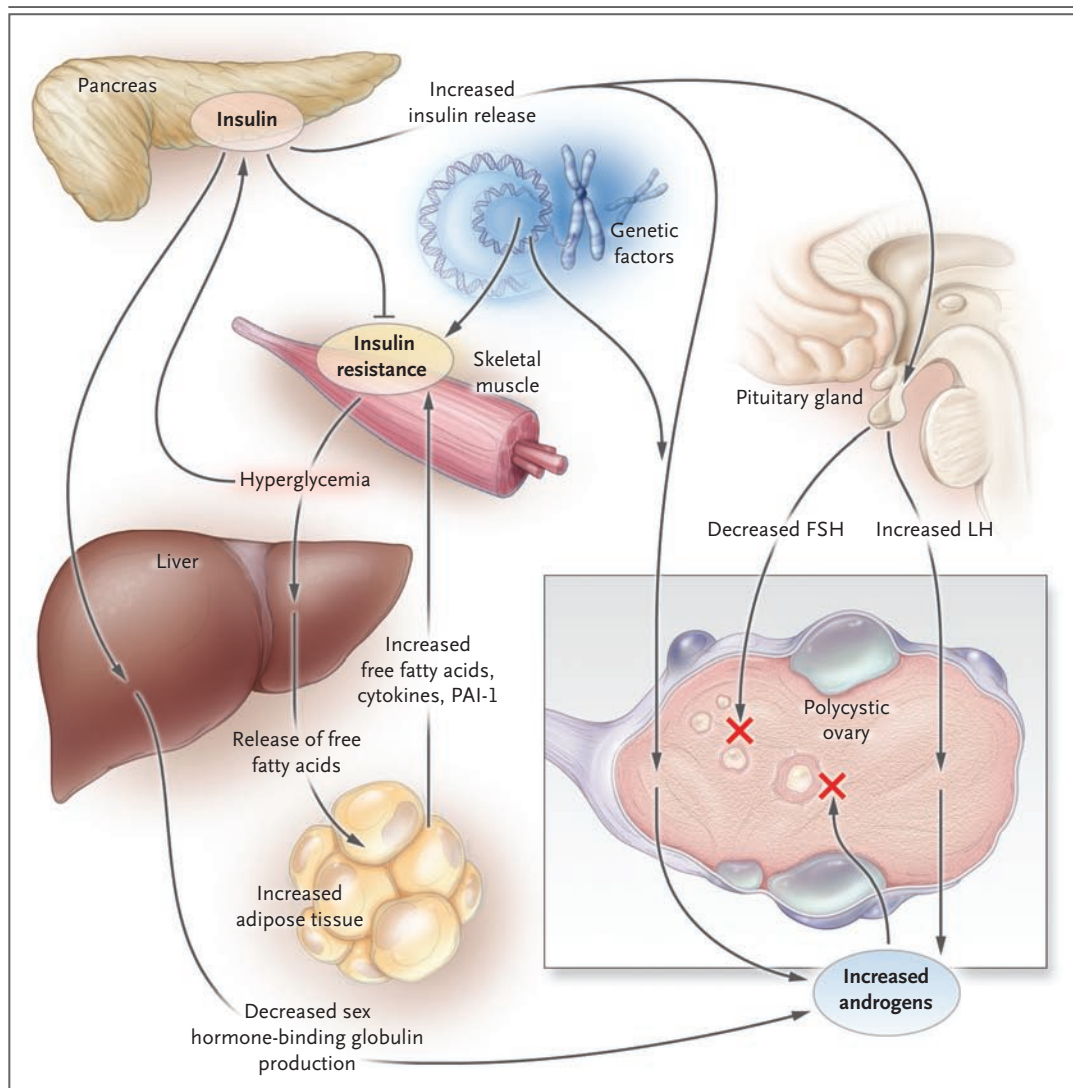


Figure 1. Pathophysiological Characteristics of the Polycystic Ovary Syndrome (PCOS).

Insulin resistance results in a compensatory hyperinsulinemia, which stimulates ovarian androgen production in an ovary genetically predisposed to PCOS. Arrest of follicular development (red "X") and anovulation could be caused by the abnormal secretion of gonadotropins such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH) (perhaps induced by hyperinsulinemia), intraovarian androgen excess, direct effects of insulin, or a combination of these factors. Insulin resistance, in concert with genetic factors, may also lead to hyperglycemia and an adverse profile of cardiovascular risk factors. PAI-1 denotes plasminogen-activator inhibitor type 1.

women with the polycystic ovary syndrome; it was concluded that metformin is effective in increasing the frequency of ovulation (odds ratio, 3.88; 95% confidence interval, 2.25 to 6.69).

Since publication of the meta-analysis, three additional randomized clinical trials have been published.⁴²⁻⁴⁴ They involved head-to-head comparisons of metformin or metformin plus clomiphene with clomiphene for the short-term induction of ovulation in women with the polycystic

ovary syndrome who desire pregnancy, and the trials yielded conflicting results. The largest of these trials, the Pregnancy in Polycystic Ovary Syndrome trial,⁴² included 626 infertile women with the polycystic ovary syndrome. It confirmed that the addition of metformin to clomiphene therapy increased the cumulative ovulation rate as compared with administration of clomiphene alone (60.4% vs. 49.0%, $P=0.003$), but the rate of live birth did not differ between the two groups

(26.8% and 22.5%, respectively; $P=0.31$). In that study, clomiphene was more effective than metformin in inducing ovulation in the short term and producing a live birth.

With regard to diabetes, two major randomized clinical trials, the Indian Diabetes Prevention Programme (IDPP-1)⁴⁵ and the U.S. Diabetes Prevention Program (DPP),⁴⁶ have shown that the use of metformin decreases the relative risk for progression to type 2 diabetes (by 26% and 31%, respectively) among patients with impaired glucose tolerance at baseline. Whether this effect of metformin truly represented the prevention of progression to diabetes, rather than simply the masking of progression by means of lowering blood glucose levels, remains controversial. However, after the discontinuation of metformin in the DPP, diabetes developed in fewer subjects than would have been expected if masking had been the sole effect.⁴⁷ To my knowledge, no randomized clinical trial has assessed the effect of metformin on the progression to type 2 diabetes specifically in patients with the polycystic ovary syndrome. In an uncontrolled, retrospective study of 50 women with the polycystic ovary syndrome treated with metformin for an average of 43 months at an academic medical center, there was no progression to type 2 diabetes, even though 11 women (22.0%) had impaired glucose tolerance at baseline.³⁹ The annual conversion rate from normal glucose tolerance to impaired glucose tolerance was only 1.4%, as compared with 16 to 19% reported in the literature^{4,6} for women with the polycystic ovary syndrome who are not taking metformin.

CLINICAL USE

The approach to the management of the polycystic ovary syndrome depends in part on the patient's and physician's principal therapeutic objectives. For some women, infertility is the principal issue. Such patients are frequently treated in the short term with clomiphene, to induce ovulation. When fertility is not a concern, an estrogen-progestin contraceptive, with or without an antiandrogen such as spironolactone, has been the mainstay of long-term therapy. This approach is effective in achieving the traditional treatment goals in the polycystic ovary syndrome, which include ameliorating the effects of androgen excess (e.g., hir-

sutism, male pattern baldness, and acne) and restoring regular menses, thereby preventing endometrial hyperplasia.

However, given the metabolic derangements associated with the polycystic ovary syndrome, it seems prudent and appropriate to plan long-term therapy that addresses not only management of the consequences of androgen excess and anovulation but also the new goals of ameliorating insulin resistance and reducing the risks of type 2 diabetes and cardiovascular disease. The effect of estrogen-progestin contraceptive agents on glucose tolerance is controversial. Limited evidence from controlled, short-term studies suggests that the use of oral contraceptives aggravates insulin resistance and worsens glucose tolerance in women with the polycystic ovary syndrome.⁴⁸ The use of estrogen-progestin contraceptives is associated with a twofold increase in the relative risk of cardiovascular arterial events in the general female population⁴⁹; the risk among women with the polycystic ovary syndrome in particular is unknown.

Metformin improves insulin sensitivity and, as noted earlier, has been shown to retard or prevent progression to type 2 diabetes in patients with impaired glucose tolerance. Although metformin has not been specifically shown to reduce the risk of cardiovascular events in patients with the polycystic ovary syndrome, the available mechanistic and clinical evidence support the use of metformin as a protective measure against the adverse cardiovascular effects of insulin resistance and insulin excess. In addition, metformin may decrease circulating androgen levels and may improve ovulation and menstrual cyclicity, thus addressing the traditional goals of long-term treatment. For these reasons, although metformin is not approved by the Food and Drug Administration for the treatment of the polycystic ovary syndrome, the drug is commonly used for this purpose.

To minimize side effects, metformin therapy is initiated at a low dose taken with meals, and the dose is then progressively increased. My practice is to have patients take 500 mg of metformin once daily with the largest meal, usually dinner, for 1 week; then increase the dose to 500 mg twice daily, with breakfast and dinner, for 1 week; increase the dose to 500 mg with breakfast and 1000 mg with dinner, for 1 week; and finally,

increase the dose to 1000 mg twice daily, with breakfast and dinner. There is no dose-ranging study of metformin in the polycystic ovary syndrome, but a dose-ranging study of patients with diabetes, using the glycated hemoglobin level as the outcome measure, suggested that a dose of 2000 mg daily is optimal.⁵⁰

Metformin should not be used in women with renal impairment (a serum creatinine level >1.4 mg per deciliter [124 μ mol per liter]), hepatic dysfunction, severe congestive heart failure, or a history of alcohol abuse. Given the young age of women with the polycystic ovary syndrome, these contraindications are rarely an issue. Repeat testing during metformin treatment is not indicated unless an illness or condition (e.g., dehydration) that might affect renal or hepatic function develops.

When metformin is prescribed, advice about a weight-loss diet and a scheduled exercise routine should also be given. Such interventions are beneficial in preventing diabetes.^{45,46} In addition, weight loss increases the likelihood of resuming ovulation, most likely as a result of improved insulin sensitivity.^{29,51}

The patient is asked to maintain a menstrual diary, cautioned that fertility may be rapidly established, and advised to use a barrier method of contraception. Oral contraceptive agents and antiandrogens are not administered at the initial visit, since they might affect menstruation or serum androgen levels and confound the assessment of the efficacy of metformin. Topical eflornithine can be prescribed for the treatment of facial hirsutism.

Follow-up visits are scheduled at 3 and 6 months. Menstrual cyclicity is reviewed and serum total testosterone is determined at each visit. If an improvement in menstrual cyclicity is noted, it is important to document whether the menses are ovulatory. This can be accomplished by measuring the serum progesterone level 7 days before the next onset of menses; a serum progesterone level of more than 4.0 ng per milliliter (12.7 nmol per liter) is consistent with the presence of the luteal phase and ovulation.

After 6 to 9 months of treatment, the efficacy of metformin is assessed. If menstrual cyclicity and ovulation are satisfactorily improved, further treatment is individualized. For some women, treatment with metformin alone might suffice.

Women desiring contraception could be given an oral contraceptive agent while continuing to take metformin. In cases in which hirsutism remains troublesome, an oral contraceptive agent, antiandrogen, or both could be added to metformin.

ADVERSE EFFECTS

Lactic acidosis has been reported with the use of metformin, but this complication is rare (0.3 episode per 10,000 patient-years) in otherwise healthy patients and is confined primarily to patients who should not have received the drug, because they had underlying renal or hepatic disease.

The main limiting side effect of metformin, affecting 10 to 25% of patients, is gastrointestinal distress, namely nausea and diarrhea. If the nausea or diarrhea occurs at a given dose, that dose is either maintained or decreased by 500 mg per day for 2 to 4 weeks until the symptoms abate. Fortunately, the gastrointestinal side effects of metformin are usually transient; however, in a minority of cases, gastrointestinal distress may require the discontinuation of metformin.

Metformin can cause malabsorption of vitamin B₁₂ in some patients receiving long-term therapy. In one analysis, risk factors for the development of this adverse effect included both the daily dose and duration of metformin therapy as well as age.⁵² Although the likelihood of clinical deficiency of vitamin B₁₂ appears to be low, patients should be monitored for signs and symptoms.

Metformin is a category B drug, and no teratogenic effects have been found in animal models. It was administered in South Africa to a limited number of women with type 2 diabetes or gestational diabetes, throughout their pregnancies, and no teratogenic effects or adverse fetal outcomes were reported.³¹

AREAS OF UNCERTAINTY

Although metformin is increasingly used to treat patients with the polycystic ovary syndrome, therapy is guided in part by the results of randomized, controlled trials in populations without the polycystic ovary syndrome, which showed that diabetes was prevented. Similar randomized, controlled trials specifically involving patients with the polycystic ovary syndrome are needed. Strategies for long-term metformin therapy in patients

with the polycystic ovary syndrome are evolving, and the identification of predictors of the response to metformin, possibly even through pharmacogenomic approaches, would improve the utility of this agent in the management of the polycystic ovary syndrome. Although long-term treatment with metformin seems likely to be beneficial in many patients with the polycystic ovary syndrome, less clear is when metformin should be used as monotherapy or in combination with antiandrogens or hormonal therapies. The efficacy of metformin in ameliorating the signs of androgen excess, such as hirsutism, has not been critically assessed.

Metformin has been used for many years in patients with type 2 diabetes. However, we do not have data regarding the potential long-term effects of the drug in patients treated for the polycystic ovary syndrome, in whom therapy, if effective, may be continued for many years. If a woman were to become pregnant, it is unclear whether metformin should be continued during pregnancy and, if so, for how long.

GUIDELINES

The recent position statement of the Androgen Excess Society⁵³ recommends that women with the polycystic ovary syndrome, regardless of weight, be screened for glucose intolerance with the use of a glucose-tolerance test at the initial presentation and every 2 years thereafter. It notes that the use of metformin to treat or prevent progression to impaired glucose tolerance may be considered but should not be mandated until there have been well-designed randomized, controlled trials demonstrating efficacy. A position statement of the American Association of Clinical Endocrinologists⁵⁴ recommends that metformin be considered the initial intervention in most women with the polycystic ovary syndrome, particularly those who are overweight or obese.

RECOMMENDATIONS

The obesity, family history of diabetes, and polycystic ovary syndrome of the patient in the vignette put her at high risk for type 2 diabetes. In addition to obesity, she has several signs of insulin resistance, including a low serum high-density lipoprotein cholesterol level and a high triglyceride level, and her data fulfill the Adult Treatment Panel III criteria of the National Cholesterol Education Program for the metabolic syndrome.^{55,56} Although her glucose tolerance is currently normal, treatment with metformin is reasonable, and a weight-loss diet and exercise are also encouraged.

Although fertility is not an immediate concern, it is likely that metformin will increase the frequency of ovulation, thereby improving menstrual cyclicality. Once menstrual cyclicality has improved, I would determine whether ovulation is occurring by measuring the serum progesterone level during the presumed luteal phase. Since the patient does not tolerate oral contraceptives, a barrier method of contraception could be recommended. When and if the patient desires pregnancy, fertility may be improved if the frequency of ovulation increases during metformin therapy. If not, the patient should be evaluated for causes of infertility unrelated to anovulation, and the addition of clomiphene to her regimen should be discussed.

I would see the patient every 3 months during the first year, not only to monitor the efficacy of metformin but also to reinforce lifestyle changes to reduce weight and increase physical activity. Thereafter, she could be seen every 6 to 12 months, depending on the response to treatment. Given that she is at high risk for diabetes, I would repeat the oral glucose-tolerance test every 2 to 3 years, even if metformin therapy is used.

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