PART 3 OF A 4-PART E-SERIES
Polycystic ovary syndrome: The long-term metabolic risks

Many of my patients with polycystic ovary syndrome (PCOS) have metabolic syndrome and are being treated with metformin. Can metformin be an effective treatment for my patient’s symptoms of PCOS as well as her metabolic syndrome?

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Women with polycystic ovary syndrome (PCOS), compared with women without the condition, have a greater chance of developing metabolic syndrome (also known as syndrome X). Recent data have drawn attention to these long-term metabolic risks of PCOS. What is metabolic syndrome, and how can its first-line treatment, metformin, affect my patient’s symptoms of PCOS, including hyperandrogenism, anovulation, infertility, weight loss, and early pregnancy loss?

We address these questions in part 3 of this four-part series, which will continue to be posted on the OBG MANAGEMENT Web site. [Editor’s note: For readers’ ease of access, all installments of this series will, as they are published, be collected on a single Web page of links.]

Metabolic syndrome

What is metabolic syndrome and what are the criteria for diagnosis?

Metabolic syndrome is a cluster of risk factors for cardiovascular disease that, together, increase a woman’s likelihood of a heart attack or stroke (by fourfold compared with those free of the condition) and increase the chance of her developing diabetes mellitus (DM). According to the American Heart Association, between 20% and 25% of the US adult population (between 58 and 73 million men and women) has metabolic syndrome.1

The diagnostic criteria for metabolic syndrome are presence of at least three of the following:

- abdominal obesity (excessive fat tissue in and around the abdomen)
- atherogenic dyslipidemia (blood fat disorders—including elevated triglyceride level, low high-density lipoprotein cholesterol [HDL-C] level, and elevated low-density cholesterol [LDL-C] level—that foster arterial plaque buildup)
- elevated blood pressure
- insulin resistance or glucose intolerance
- prothrombotic state (which is a high level of fibrinogen or plasminogen activator inhibitor-1 in the blood)
**Metformin**

We know metformin is used to treat insulin resistance…but can it help hyperandrogenism, anovulation, infertility, weight loss, and early pregnancy loss?

Metformin, a biguanide antidiabetic drug, was first described in the scientific literature in 1957. It was first marketed in France in 1979, but it did not receive approval by the US Food and Drug Administration (FDA) for DM until 1994. In contrast to sulfonylurea medications, which work rapidly to control elevated blood glucose levels by increasing pancreatic insulin production, metformin is an insulin-sensitizing agent—it improves peripheral insulin sensitivity and suppresses hepatic gluconeogenesis. Metformin is preferred for initial DM treatment because it does not induce hypoglycemia. Although metformin is not FDA-approved to treat PCOS, it is increasingly being used to treat the syndrome in patients with impaired glucose tolerance and those with no impaired glucose tolerance. More recent research has focused on metformin’s effect on other associated maladies of PCOS, including hirsutism, acne, weight loss, anovulation, pregnancy, and pregnancy loss.

**Metformin and hirsutism**

What is the status of metformin and the treatment of hirsutism?

PCOS and its associated hyperinsulinemic state causes excess ovarian androgen production and reduces hepatic sex hormone binding globulin (SHBG) production. As treatment with metformin results in lower circulating insulin, the net affect is reduced ovarian androgen production and less free testosterone. Thus, it is reasonable to think metformin would be effective in the treatment of hirsutism. However, conflicting results have been reported with respect to this issue.

While some study results suggest an improvement in patients’ hirsutism symptoms with metformin treatment, results of a recent meta-analysis of randomized controlled trials involving treatment with metformin for at least 6 months for hirsutism suggest that insulin sensitizers provide limited or no important benefit for women with hirsutism. Of 348 studies, 16 trials (22 comparisons) that were eligible for inclusion in the meta-analysis showed a small decrease in Ferriman-Gallwey scores in women treated with insulin sensitizers compared with women treated with placebo. There was no significant difference in hirsutism between women treated with insulin sensitizers and women treated with oral contraceptives; metformin was inferior to both spironolactone and flutamide. Further study into metformin’s role in treatment for hirsutism is warranted.

**Metformin and acne**

What is the status of metformin and the treatment of acne?

The use of insulin-sensitizing agents, such as metformin, to treat acne also requires more research. The same mechanism of action that infers metformin’s use in hirsutism also applies to its use in acne treatment. In a Cochrane Review of randomized controlled trials comparing insulin-sensitizing agents to OCs (alone or in combination) for treating acne, limited data demonstrated no evidence of difference in effect between metformin and the OC. This analysis included six trials, four of which compared metformin with an OC (104 participants) and two of which compared an OC combined with metformin with an OC alone (70 participants).

**Metformin and weight loss**

What is the status of metformin and weight loss?

Weight loss leads to greater improvements in overall health, increased fecundity, and improved pregnancy outcome. In spite of the advantages, most patients with PCOS have difficulty losing weight and often regain lost weight over time. Many investigators have raised the question as to whether treatment with insulin-sensitizing drugs contributes to weight loss, compared with diet or a lifestyle that improves peripheral insulin sensitivity, suppresses hepatic gluconeogenesis, and does not induce hypoglycemia.
A meta-analysis showed that metformin improved ovulation, especially in non-clomiphene–resistant women.

In the next installment: The authors address several questions about current opinion and future considerations:

- What is the current opinion concerning how important circulating LH/FSH ratios are to the diagnosis of PCOS?
- Are there any new tests on the horizon that will make the diagnosis of PCOS easier?
- My patient has excessive hair growth and acne and only wants cosmetic results. Other than traditional therapy with oral contraceptives, what medical treatment options does she have?
- We hear a lot about weight loss improving the clinical effects of PCOS. Are there any specific dietary approaches that are more successful than others in PCOS?
There is inadequate evidence to support the use of metformin during pregnancy

outcome, the authors concluded there was no evidence of an increased risk with metformin.8

While it is logical to say that metformin could even be beneficial during pregnancy, given its effect of reducing the risk of developing gestational diabetes, there is inadequate evidence to support the use of metformin during pregnancy at this time.6,8

References