



## 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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**W**omen 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.]

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## Metabolic syndrome

**Q** 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.<sup>1</sup>

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)

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- proinflammatory state (which is elevated plasma C-reactive protein level).

### Metformin

**Q** 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.<sup>2</sup> 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

**Q** 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.<sup>3</sup>

#### Metformin and acne

**Q** 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<sup>4</sup> 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

**Q** 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



**Metformin is an insulin-sensitizing agent—it improves peripheral insulin sensitivity, suppresses hepatic gluconeogenesis, and does not induce hypoglycemia**

modification program.

A systematic search of the literature for randomized controlled trials in women of reproductive age that assessed the effect of insulin-sensitizing drugs on weight loss compared with placebo and diet and/or a lifestyle modification program, revealed 14 trials in the literature, including two in women with PCOS.<sup>5</sup> Treatment with metformin showed a statistically significant decrease in body mass index compared with placebo, with some indication of greater effect with high-dose metformin (>1,500 mg/day) and longer duration of therapy (>8 weeks).

Clearly, a structured lifestyle modification program to achieve weight loss should still be the first-line treatment in obese women with or without PCOS. Further adequately powered studies are necessary to confirm such findings.<sup>2</sup> As new weight loss drugs become available, they should also be considered for treatment of obesity in women with PCOS.

### Metformin and anovulation

**Q** What is the status of metformin and the treatment of anovulation?

While metformin may offer limited assistance with weight loss, especially when combined with diet and lifestyle therapy,

**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?”

and weight loss generally improves ovulation in overweight women with PCOS, there is no evidence that metformin is a powerful ovulatory drug.<sup>6</sup> However, results of a meta-analysis that included 17 studies totaling more than 1,600 women with PCOS, showed that metformin did improve ovulation, especially in non-clomiphene-resistant women.<sup>7</sup> Metformin alone did not increase the odds of pregnancy, but in combination with clomiphene, pregnancy was increased. The combination of metformin and clomiphene was especially beneficial in clomiphene-resistant women.

It is important to note that, in women with PCOS, treatment with metformin alone, and in combination with clomiphene, helps to reduce the number of multiple pregnancies, compared with treatment with clomiphene alone.<sup>9</sup>

### Metformin and early pregnancy loss

**Q** What is the status of metformin and the treatment of early pregnancy loss?

While there is mixed evidence as to metformin's effect on early pregnancy loss, the strongest evidence to date does not indicate a beneficial effect. In a large, randomized, prospective study of 626 infertile women with PCOS, the rate of pregnancy loss was similar between the clomiphene only and clomiphene plus metformin groups, and there was a slight trend for an increase in pregnancy loss in the metformin alone group.<sup>9</sup>

In a comprehensive review of the literature, Mathur and colleagues concludes that, while some studies have found improvements or no difference in the rates of early pregnancy loss with metformin (alone or in combination with clomiphene), there are “no conclusive data to support a beneficial effect of metformin on pregnancy loss.”<sup>6</sup>

### Metformin and pregnancy outcomes

**Q** What is the status of metformin and improving pregnancy outcomes?

In a meta-analysis of eight studies of women with PCOS or DM exposed to metformin during the first trimester of pregnancy with major fetal malformations as the primary



**A meta-analysis showed that metformin improved ovulation, especially in non-clomiphene-resistant women**

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

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.<sup>6,8</sup> ❌

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**There is inadequate evidence to support the use of metformin during pregnancy**