

## Do insulin-sensitizing drugs increase ovulation rates for women with PCOS?

### ■ EVIDENCE-BASED ANSWER

Short-term use of metformin (Glucophage) improves ovulation rates for women with polycystic ovary syndrome (PCOS) (strength of recommendation [SOR]: **A**, based on systematic reviews of randomized controlled trials [RCT]). Metformin also decreases menstrual irregularities (SOR: **B**, extrapolated from a systematic review). When added to clomiphene, metformin increases ovulation and pregnancy rates when compared with clomiphene alone (SOR: **A**, systematic review).

Thiazolidinediones (TZDs) improve ovulation rates as well (SOR: **B**, based on low-quality RCTs). Research of longer duration including the key outcomes of pregnancy and birth rates, is needed to clarify the appropriate use of insulin-sensitizing drugs for PCOS.

### ■ EVIDENCE-BASED SUMMARY

A common female endocrinopathy, PCOS affects 5% to 10% of women. Characterized by anovulation and hyperandrogenism, it often manifests as infertility and irregular menstruation. Metformin and thiazolidinediones are likely effective treatments for these expressions of insulin resistance, but study limitations restrict our ability to clearly define their role.

The most influential systematic review was a meta-analysis that reviewed 13 RCTs including 543 women to determine the effects of metformin on ovarian function in PCOS.<sup>1,2</sup> By selecting RCTs, performing precise statistical analysis according to the Cochrane protocols, and clearly stating lim-

itations, this review gives good evidence that metformin modestly increases the odds of ovulation for women with PCOS (odds ratio [OR]=3.88; 95% confidence interval [CI], 2.25–6.69 for metformin vs placebo) and that metformin with clomiphene (Clomid) effectively increases ovulation (OR=4.41; 95% CI, 2.37–8.22) and pregnancy rates (OR=4.40; 95% CI, 1.96–9.85) when compared with clomiphene use alone. When metformin is used as a sole agent, ovulation is achieved in 46% of recipients compared with 24% in the placebo arm (number needed to treat [NNT]=4.4). When metformin and clomiphene are

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used in combination, 76% of recipients ovulate compared with 42% receiving clomiphene alone (NNT=3.0).

Several problems with recommending metformin as first-line therapy exist: (1) equal or better ovulation rates have been described by using lifestyle interventions to achieve weight loss, (2) there are no long-term studies of the effects of metformin in PCOS patients, and (3) we cannot assess the clinically important outcome of pregnancy rates because the trials did not control for other infertility factors and did not define live births as a primary outcome. In addition, there are no head-to-head trials of metformin vs clomiphene, the standard first-line therapy for ovulation induction. Only 1 study addressed menstrual patterns specifically; they were improved with metformin (OR=12.88; 95% CI, 1.85–89.61).

An additional meta-analysis reports similar results.<sup>3</sup> Eight RCTs addressing the use of metformin or clomiphene for treatment of PCOS were reviewed for ovulation and pregnancy rates. Metformin is 50% better than placebo for ovulation induction among infertile PCOS patients (relative risk [RR]=1.50; 95% CI, 1.31–1.99), but this benefit is not necessarily improved with longer duration (>3 months) of therapy (RR=1.37; 95% CI, 1.05–1.79). Also, metformin is beneficial in regulating cycles for fertile PCOS patients with irregular menses (RR=1.45; 95% CI, 1.11–1.90).

The conclusions regarding pregnancy rates and combined therapy with metformin and clomiphene are limited due to small samples, short follow-up time (2–6 months), and study design. An ongoing randomized trial (Pregnancy in Polycystic Ovarian Syndrome: PPOS study) of 768 infertile PCOS patients is investigating effects of metformin vs clomiphene on ovulation induction and achievement of singleton pregnancies. These outcomes should clarify remaining uncertainties regarding appropriate use of metformin.

Finally, a review of 7 RCTs describes the evidence accumulated by well-designed trials and its

**For PCOS patients seeking cycle regulation, oral contraceptives may remain the better therapy**

clinical relevance.<sup>4</sup> Metformin improves ovulation and menstrual cyclicity but these improvements were variable and modest. On average, 1 additional ovulation is attained in every 5-month interval with metformin treatment; specifically, the baseline of 1 ovulation per 5-month interval increased to 2 ovulations per 5-month interval. Spontaneous ovulation and normal menstruation are achieved rapidly (within 3 months of the start of therapy). These data corroborate the benefits of metformin but place its clinical significance in perspective. For PCOS patients seeking cycle regulation but not pregnancy, oral contraceptives may remain better therapy because metformin does not normalize menses.

Less information exists on the role of TZDs and ovarian function in PCOS. Studies of the most researched drug in the class, troglitazone (Rezulin), report improvements in ovulation rates and metabolic markers of PCOS.<sup>5,6</sup> Troglitazone has been taken off of the market due to hepatotoxicity, but results from a RCT of 40 patients with PCOS reported that the use of pioglitazone (Actos) for 3 months increased normal regular cycles and ovulations over placebo (41.2% vs 5.6%;  $P<.02$ ).<sup>7</sup> No liver effects were noted, but caution must be taken since these drugs are pregnancy class C. Two small RCTs studied the use of rosiglitazone (Avandia) in combination with clomiphene and reported improvements in menstrual regularity<sup>8</sup> (92% with combination therapy achieved improved menstrual cycles vs 68% with rosiglitazone alone; OR=0.185) and both spontaneous and clomiphene-induced ovulation rates (52% of clomiphene-resistant women ovulated after rosiglitazone therapy and 77% vs 33% ovulated with combination therapy vs rosiglitazone alone,  $P=.04$ ).<sup>9</sup> Further research is needed to determine the clinical effects of the thiazolidinediones.

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## ■ RECOMMENDATIONS FROM OTHERS

The American College of Obstetricians and Gynecologists guideline on diagnosis and management of PCOS reports that interventions that improve insulin sensitivity, including weight loss, use of metformin, and use of TZDs are useful for improving ovulatory frequency for women with PCOS.<sup>10</sup> The recommendation is based on good and consistent scientific evidence (SOR: **A**). They also note that insulin-sensitizing agents may improve many risk factors for diabetes and cardiovascular disease, but this recommendation is based on limited evidence (SOR: **B**). Finally, they recommend, based on expert opinion (SOR: **C**), that caution be used with these agents because their effects on early pregnancy are unknown, even though metformin appears to be safe.

The American Association of Clinical Endocrinologists recommends using metformin 850 mg twice daily to treat the hyperandrogenic state of PCOS.<sup>11</sup> The use of TZDs is less clear due to limited evidence and risks of teratogenicity.

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## ■ CLINICAL COMMENTARY

### For those trying to conceive, the tried-and-true medication is clomiphene

I tend to think of women with PCOS as falling into 2 camps, those actively trying to conceive and those who are not. Those who are not can often get benefits for their menstrual cycles and hyperandrogenism with birth control pills. For those trying to conceive, the tried-and-true first-line medication is clomiphene.

Metformin has been figuring prominently in the literature as adjunct or second-line therapy for infertility for women with PCOS. It is also an accepted treatment for hirsutism. So, for women with PCOS, metformin is a treatment that bridges the 2 camps. I look forward to seeing head-to-head trials of metformin, clomiphene, and both therapies for induction of ovulation.

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