

Views 2

Should metformin be used as front-line therapy for fertility in women with PCOS?

View 1

YES! Metformin is a reasonable—and possibly superior—choice as first-line therapy for women with polycystic ovary syndrome (PCOS) who wish to become pregnant. Insulin resistance is a key factor in the pathogenesis of

PCOS. Metformin, an insulin sensitizer commonly used to treat type 2 diabetes, can reduce insulin resistance in women with PCOS and therefore may enhance fertility.

Jean-Patrice Baillargeon, MD, MSc

Assistant Professor, Departments of Medicine and Physiology, University of Sherbrooke, Sherbrooke, Quebec, Canada

View 2

NO! Two large multicenter trials, one conducted in the US and one in the Netherlands, have shown no benefit to metformin either as a single agent or as adjuvant therapy in combination with clomiphene for the treatment of infertility in women with PCOS.

These studies showed that metformin alone or in combination with clomiphene offered no benefit over clomiphene alone with regard to the end point of most clinical relevance, namely, live birth.

Richard S. Legro, MD

Professor, Department of Obstetrics and Gynecology, Penn State Milton S. Hershey College of Medicine, Hershey, Pennsylvania

View 1

Metformin improves ovulation and pregnancy rates

Accumulating evidence has shown that the rationale for metformin use makes sense: 2 meta-analyses of randomized controlled trials (RCTs) have shown that the use of metformin alone improves ovulation and pregnancy rates in women with PCOS.^{1,2} Metformin and clomiphene treatments were compared in a head-to-head clinical trial by Palomba and colleagues.³ In this study of 100 non-obese, anovulatory women with PCOS, patients on metformin had significantly higher pregnancy rates than the clomiphene subjects (15.1% vs 7.2%, $P = .009$). Efficacy rates of metformin increased steadily during the 6 months of the study; in contrast, clomiphene showed higher efficacy initially, but this declined over time. The authors concluded that higher cumulative pregnancy rates showed that

metformin was more effective than clomiphene in treating anovulatory infertility, but that data from a larger sample would be needed to demonstrate a superior effect on the live birth rate.

Metformin reduces spontaneous abortion

Spontaneous abortion is a significant concern when women with PCOS become pregnant; rates of pregnancy loss during the first trimester can be as high as 30% to 50%.^{4,5} Use of metformin during a pregnancy has been shown to reduce pregnancy loss. A retrospective review of pregnancies in women with PCOS revealed that metformin significantly reduced early pregnancy loss (EPL) compared with controls (8.8% vs 41.9%, $P < .001$).⁶ This was confirmed in a prospective study of women with PCOS in which the EPL rate significantly decreased from 62% in 100 previous pregnancies without

metformin to 17% in 84 later pregnancies during which metformin was used.⁷

Insulin resistance usually decreases with metformin

Almost all studies of metformin as a treatment for PCOS have shown that metformin reduces insulin levels and improves insulin sensitivity.^{2,8-14} It has been suggested that insulin lowering is essential for metformin's effect in improving androgen levels and fertility.¹⁵

One very notable result of the recent Pregnancy in Polycystic Ovary Syndrome (PPCOS) study was the absence of any statistically significant effect of metformin on insulin levels or insulin resistance (homeostasis model assessment of insulin resistance [HOMA IR]).¹⁶ This study challenged the results of earlier studies when it showed that the live birth rate achieved with clomiphene was higher for women who received clomiphene alone (22.5%) or

in combination with metformin (26.8%) than the live birth rate for women who received metformin alone (7.2%). PPCOS used a long-acting formulation that demonstrated none of the expected metabolic effects of metformin. The absolute change from baseline in insulin in the metformin group was 2.2 ± 34.0 mcU/mL (95% CI, -2.4 to 6.9; $P = .35$) and the absolute change in HOMA IR was 0.7 ± 10.9 (95% CI, -0.9 to 2.2; $P = .40$), without significant differences as compared with clomiphene ($P = .29$ and $P = .14$, respectively). The change in body mass index (BMI) with metformin was statistically significant at -0.6 ± 2.2 (95% CI, -0.9 to -0.2; $P < .001$) but minor. In the absence of metabolic change, it is not surprising that fertility parameters did not improve, ie, that the cumulative rate of ovulation after 6 months in the metformin group was only 29%, as compared with 63% in the study from Palomba and colleagues³ and 58% after 3 to 6 months in a meta-analysis of 4 RCTs.¹

Extended-release metformin has not previously been studied in women with PCOS. Thus, it has not been ascertained that its efficacy is comparable to regular metformin in this population. For example, the lack of reduced appetite—a known side effect of regular metformin—might cause less weight loss than expected.

In addition to possible problems with the formulation of metformin, body mass may have also had a role in the outcome of PPCOS. Metformin has been shown to be less effective in patients with a high BMI.^{2,17} The women in the metformin group had a baseline BMI of 35.6 kg/m² (± 8.5), which may account, in part, for the poor results in this group.

Metformin does not increase risk of multiple gestation

Metformin induces normal ovulation, and the risk of multiple gestation is no more than that in the general population. Conversely, clomiphene can precipitate the release of multiple eggs in a given menstrual cycle and carries a high risk of multiple gestation: in the PPCOS study, multiple gestation was 6% in the clomiphene group and 0% with metformin.¹⁶

Conclusions

The results of the study by my colleague on the “no” side of this debate might suggest that metformin should not be used as a first-line therapy for enhancing the fertility of women with PCOS. However, based on the concerns outlined above, this

is probably not the definitive study, and the benefit of short-acting metformin as first-line therapy is still unclear. Until this question is resolved, metformin remains a good initial therapeutic option that can be discussed with patients.

Both agents do have side effects, primarily gastrointestinal effects with metformin and hot flashes with clomiphene.¹⁶ Gastrointestinal side effects with metformin are short lived and do not usually cause patients to stop taking the drug.¹⁸ However, when a patient is unable to take one drug, it is valuable to have an effective alternative.

Additionally, the 2 agents differ in the time until efficacy, which can be an important consideration for women. Clomiphene produces higher rates of ovulation and pregnancy in the early months of treatment than does metformin and might be preferable to women who wish to become pregnant quickly.³ However, a patient with more time to become pregnant may benefit from metformin’s metabolic effects. During the 3 to 6 months that it takes for metformin to become maximally effective, the patient can prepare for pregnancy by losing weight through diet and exercise, and possibly as an effect of the metformin. Reducing a patient’s weight might considerably optimize her intended pregnancy.¹⁹

In summary, metformin remains a first-line treatment for infertility that could be offered to women with PCOS after appropriate discussion of the options.

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Metformin does not improve live birth rates

For infertile women, the only

acceptable outcome of treatment is live birth—not biochemical pregnancy or a missed abortion—and pregnancy loss must be tallied in these studies. It is true that the preliminary data showed a benefit of metformin on live birth rates, both alone and in combination with clomiphene.¹ However none of these studies had more than 100 subjects, and none were adequately powered to address live birth as an outcome.

The US study known as Pregnancy in Polycystic Ovary Syndrome (PPCOS) was an NIH-NICHD-sponsored multicenter trial specifically powered to answer the question of benefit on live birth.² PPCOS had a double-blind, double-dummy design and randomized 626 women to 1 of 3 treatment arms: metformin, clomiphene, or the combination of clomiphene and metformin. The live birth rate in the clomiphene-only group was 47/209 (22.5%), 15/208 (7.2%) in the metformin-only group, and 56/209 (26.8%) in the combination therapy group ($P < .001$ metformin vs clomiphene and combined, $P = .307$ clomiphene vs combined) (FIGURE 1).³ There was no placebo arm in the study, so only relative comparisons between treatment groups can be made.

These findings were supported by a Dutch multicenter randomized trial.⁴ Ovulation was the primary outcome of this study, which randomized 228 subjects with PCOS for up to 6 ovulatory cycles to either clomiphene alone or the combination of metformin and clomiphene. They found no benefit on ovulation rates (or pregnancy rates) between the combination of metformin and clomiphene, compared with clomiphene alone (cumulative pregnancy rate: 40% vs 46%; risk difference -6%; 95% CI, -20%–7%).⁴

Overall pregnancy rates were higher in the Dutch study, which had a thinner, less severely affected population of women with PCOS, than in PPCOS. The PPCOS data showed a dose response reduction in pregnancy rates as body mass index (BMI) increases (FIGURE 2). Some have questioned whether obesity blunted the benefits of metformin and have theorized that a thinner population would have performed better as in the study by Palomba et al in Italy.⁵ The design of this study was similar to that of PPCOS, using a double-blind, double-dummy design that randomized infertile women with PCOS to metformin or clomiphene with opposite results.⁵ Their study excluded obese (BMI >30 kg/m²) subjects (71% of the PPCOS subjects were obese), and excluded women older than 34 years (6.23% of PPCOS subjects were >34 years). However, subset analysis of PPCOS for a similar population of women with a BMI less than 30 kg/m² and patients aged 34 years or younger (N = 170) showed the same results as the larger PPCOS study. Live birth rates were 20/53 (37.7%) in the clomiphene-only group, 5/57 (8.8%) in the metformin-only group, and 24/60 (40%) in the combination therapy group.³ The reasons for the differences among these studies are unknown.

Clomiphene may significantly enhance risk of multiple pregnancy

There is some truth to the statement that metformin protects against multiple pregnancy; all multiple pregnancies in the PPCOS study occurred in clomiphene-containing arms, including 1 triplet pregnancy. The multiple pregnancy rate in the clomiphene-only group was 6.4% (N = 3, 1 triplet pregnancy), 0% in the metformin-only group, and 3.3% in the combination therapy group (N = 2).³ This rate (~5%) is at or below what has been reported from large series of women conceiving on clomiphene citrate⁶ and well below the expectations of many of an enhanced

multiple pregnancy rate in response to clomiphene in women with PCOS.⁷ However, given the low number of multiple pregnancies overall, there was no statistical difference in multiple pregnancy rates between treatment groups. The Dutch study reported 1 triplet pregnancy (none survived) and 1 twin pregnancy on clomiphene therapy.⁴ Further research is needed, because preventing multiple pregnancies should be a prime concern for caregivers and patients alike.

It is unknown whether metformin prevents pregnancy loss

Studying pregnancy loss prevention was not an aim of the PPCOS trial, because all medication, including metformin, was stopped at the first positive pregnancy test. Therefore the trial cannot answer whether continuing metformin would have lowered pregnancy loss rates. What is concerning from the trial is the relatively high miscarriage rate in the metformin group: 10/25 (40%) compared with clomiphene-only (14/62 [22.6%]) and combination therapy (20/80 [25%]). Although this was not statistically significant—again, due to the low numbers—this is potentially an area of concern and one worthy of further study.

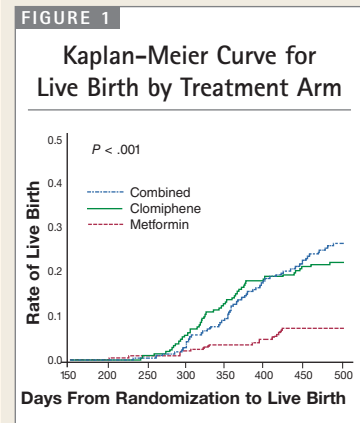
Conclusions

No one doubts that metformin increases ovulation rates. In fact, the PPCOS trial clearly upheld the previous landmark trial by Nestler et al⁸ showing an improved ovulation rate of clomiphene and metformin compared with single-agent treatment, although no benefit to the addition of metformin was found in the Dutch study.² But PPCOS also clearly demonstrated that all ovulations are not alike. Fecundity as determined by conception per ovulated patient was significantly lower in the metformin-only group (21.7% [25/115]) compared with the clomiphene-only (62/157 [39.5%]; $P = .002$) or combination therapy groups (80/174 [46.0%]; $P < .001$).³ The goal of infertility therapy in anovulatory women is not restoration of ovulation—it is a live birth,⁹ and this should be the outcome of interest in infertility trials. ■

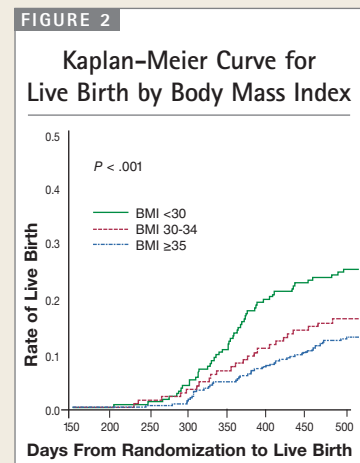
Dr Legro reports that he receives grants/research support from Pfizer; serves as a consultant to Ferring and QuatRx; and is on the speakers' bureau of Serono.

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