Will insulin sensitizers treat infertility associated with polycystic ovary syndrome (PCOS)?

**Evidence-Based Answer**

Metformin does not appear to be any more effective than clomiphene as a single agent for treating infertility in PCOS (SOR: B, conflicting systematic reviews). However, metformin used in combination with clomiphene may improve fertility rates over clomiphene alone, particularly in obese women (SOR: B, systematic review of RCTs).

A 2012 systematic review examined the effectiveness of metformin for fertility in PCOS. The review included 4 RCTs (766 patients) comparing clomiphene and metformin and 6 RCTs (969 patients) comparing clomiphene monotherapy with combination treatment of clomiphene plus metformin. No statistically significant difference was noted in the pregnancy rate associated with clomiphene compared with metformin (OR 0.94; 95% CI, 0.3–3.4). Combination treatment with metformin plus clomiphene achieved a higher clinical pregnancy rate than clomiphene alone (Peto OR 1.6; 95% CI, 1.2–2.1).

Another 2012 systematic review evaluated live birth rate in patients with PCOS. It included 4 RCTs comparing clomiphene with metformin (3 of which were included in the above systematic review, 612 patients) and 4 RCTs comparing clomiphene with combination therapy of clomiphene plus metformin (790 patients). Treatment with metformin led to a lower live birth rate than treatment with clomiphene (Peto OR 0.48; 95% CI, 0.31–0.73). No significant difference was noted in live birth rate between clomiphene and combination therapy (Peto OR 1.1; 95% CI, 0.78–1.5).

A 2008 systematic review of 17 RCTs evaluated the efficacy of metformin (1,500–2,000 mg/d) on ovulation or early pregnancy in 1,639 patients with PCOS. Compared with placebo, metformin led to a statistically significant increase in the rate of ovulation (9 trials, N=504; OR 2.9; 95% CI, 1.4–6.0) but not early pregnancy (6 trials, N=595; OR 1.6; 95% CI, 0.74–3.3). Combination therapy with clomiphene plus metformin was more effective than clomiphene alone in achieving both ovulation (11 trials, N=1,278; OR 4.4; 95% CI, 1.4–11) and early pregnancy (10 trials, N=1,218; OR 2.7; 95% CI, 1.5–5.0). In subgroup analyses, early pregnancy was more likely with combination therapy in obese patients (OR 3.7; 95% CI, 1.2–11) but not for nonobese patients (OR 2.7; 0.96–7.6), when compared with clomiphene alone.

A 2012 multicenter RCT involving 320 patients with PCOS examined the efficacy of metformin treatment (1,500 mg in nonobese patients; 2,000 mg in obese patients) for 3 months. If patients were not pregnant at 3 months, then clomiphene was added. Compared with placebo (with clomiphene if no pregnancy in 3 months), metformin (with clomiphene if no pregnancy in 3 months) had higher pregnancy rates (42% vs 29%; P=.014). This effect was present in obese women (body mass index >27 kg/m²) (N=143; 49% vs 31%; P=.04) but not in nonobese women (N=187; 47% vs 35%; P=.09).

The current American College of Obstetricians and Gynecologists Practice Bulletin recommends clomiphene as first-line treatment for ovulation induction and against the use of metformin alone for infertility (no grade provided). The bulletin notes that combination therapy may be more effective, particularly for obese women.

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