

Metformin used alone or combined with clomifene may improve ovulation rates in the polycystic ovary syndrome

Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ*. 2003;327:951-6.

Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2003;(3):CD003053.

QUESTION

In women with the polycystic ovary syndrome (PCOS), what is the effectiveness of insulin-sensitizing drugs?

DATA SOURCES

Studies were identified by searching the Cochrane Menstrual Disorders and Subfertility Group trials register (December 2002), the Cochrane Central Register of Controlled Trials (Cochrane Library, Issue 4, 2002), MEDLINE (1966 to December 2002), and EMBASE/Excerpta Medica (1985 to December 2002); scanning bibliographies of relevant studies; and contacting pharmaceutical companies.

STUDY SELECTION AND ASSESSMENT

Studies were selected if they were randomized controlled trials (RCTs) that compared insulin-sensitizing drugs with placebo, no treatment, or an ovulation-inducing agent in women with PCOS based on biochemical or ultrasonographic evidence. Studies were assessed for allocation concealment, blinding, loss to follow-up, noncompliance, and whether analysis was by intention to treat.

OUTCOMES

Clinical (including live birth rate, clinical pregnancy rate, spontaneous ovulation, men-

strual cyclicality, and adverse pregnancy events) and biochemical outcomes.

MAIN RESULTS

15 RCTs (997 women) were included. 13 RCTs ($n = 543$) used metformin, 1 ($n = 410$) used troglitazone, and 1 ($n = 44$) used d-chiro-inositol. Blinding was present in all but 1 trial. Women had PCOS only in 3 RCTs, PCOS with obesity in 5 RCTs, PCOS with clomifene resistance in 6 RCTs, and PCOS with clomifene sensitivity in 1 RCT. Women's mean age ranged from 21 to 32 years. The duration of the trials ranged from 4 to 44 weeks (median 10 wk). Metformin improved ovulation rate (Table), reduced systolic blood pressure (weighted mean difference [WMD]

-9 mm Hg, 95% CI -15 to -3), and reduced diastolic blood pressure (WMD -6 mm Hg, CI -10 to -2) more than placebo or no treatment. Metformin plus clomifene improved ovulation and clinical pregnancy rates more than clomifene alone (Table).

CONCLUSION

Metformin used alone or combined with clomifene is effective for improving ovulation rates in women with the polycystic ovary syndrome.

Source of funding: Reproductive Medicine Unit, University of Adelaide.

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Metformin vs placebo or no treatment and metformin plus clomifene vs clomifene alone for the polycystic ovary syndrome at median 10 weeks*

Outcomes	Weighted event rates		RBI (95% CI)	NNT (CI)
	Metformin	Placebo or no treatment		
Ovulation rate (fixed-effects model)	46%	24%	96% (47 to 161)	5 (4 to 8)
	Metformin plus clomifene	Clomifene alone		
Ovulation rate (random-effects model)	76%	42%	107% (19 to 260)	4 (2 to 17)
Clinical pregnancy rate (fixed-effects model)†	32%	7%	298% (101 to 690)	5 (3 to 8)

*Abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article.

†Secondary outcome measure in all trials.

COMMENTARY

PCOS is characterized by oligo-ovulation, irregular menses, and symptoms of androgen excess, such as hirsutism and acne. It is a common endocrinopathy affecting 5% to 10% of women of reproductive age. Insulin resistance is felt to play a key role in most women with PCOS, therefore insulin-sensitizing agents have moved to the forefront of management of PCOS. No large-scale, long-term studies of their use in PCOS have been reported thus far. The meta-analysis by Lord and colleagues combines the results of 15 RCTs using insulin-sensitizing agents in the treatment of PCOS. The primary outcome measure in 11 of the 15 RCTs was ovulation. Because data are mainly available for metformin use, the conclusions are essentially restricted to this drug.

Support for improvement in ovulation with metformin alone is based on analysis of 7 RCTs. A relative benefit increase exists for metformin compared with placebo in achieving ovulation. The trials are short, ranging from 4 to 16 weeks, suggesting that improvement occurs early in treatment. Pregnancy rate is not reported as a primary outcome in the reviewed trials, and the trials did not control for other causes of infertility.

The principal method of ovulation induction for women with PCOS for the past 30 years has been clomiphene citrate. Metformin alone has not been shown to be better than clomiphene in a head-to-head trial of ovulation induction. Such a trial is currently under way. From this meta-analysis, one cannot conclude at this time that metformin is the first-line ovulation induction therapy.

Few included RCTs reported biochemical or metabolic outcomes. Hence, few conclusions can be drawn about these outcomes.

This meta-analysis supports a role for metformin in the restoration of ovulation in PCOS. Long-term data on pregnancy rates and changes in metabolic variables are needed. Such factors as lifestyle modification and weight reduction also warrant further study.

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