Review: metformin used alone or combined with clomifene may improve ovulation rates in the polycystic ovary syndrome


GP/FP/Primary care ➤➤➤➤➤ Gynaecology ➤➤➤➤➤ Endocrine ➤➤➤➤➤

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

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

Abstract and commentary also appear in ACP Journal Club.

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 5–10% of women of reproductive age. Insulin resistance is felt to play a key role in most women with PCOS, therefore insulin sensitising 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 et al combines the results of 15 RCTs using insulin sensitising 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 length of the trials is short term, ranging from 4–16 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 underway. 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.

Kathleen M Hoeger, MD
David S Gusick, MD, PhD
University of Rochester School of Medicine and Dentistry
Rochester, New York, USA

Metformin v placebo or no treatment and metformin plus clomifene v clomifene alone for the polycystic ovary syndrome*

<table>
<thead>
<tr>
<th>Outcomes at median 10 weeks</th>
<th>Weighted event rates</th>
<th>RBI (95% CI)</th>
<th>NNT (CI)</th>
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<tbody>
<tr>
<td><strong>Metformin v placebo or no treatment</strong></td>
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<tr>
<td>Ovulation rate (FEM)</td>
<td>46% v 24%</td>
<td>96% (47 to 161)</td>
<td>5 (4 to 8)</td>
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<tr>
<td><strong>Metformin + clomifene v clomifene alone</strong></td>
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<tr>
<td>Ovulation rate (REM)</td>
<td>76% v 42%</td>
<td>107% (19 to 260)</td>
<td>4 (2 to 17)</td>
</tr>
<tr>
<td>Clinical pregnancy rate (FEM)†</td>
<td>32% v 7%</td>
<td>298% (101 to 690)</td>
<td>5 (3 to 8)</td>
</tr>
</tbody>
</table>

*FEM = fixed effects model; REM = random effects model. Other abbreviations defined in glossary; weighted event rates, RBI, NNT, and CI calculated from data in article.
†Secondary outcome measure in all trials.