Use of metformin in polycystic ovary syndrome: a meta-analysis
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CRD summary
This review evaluated the efficacy of metformin, alone or in combination with clomiphene citrate, in women with polycystic ovary syndrome. It concluded that metformin increased the likelihood of ovulation and, in combination with clomiphene, the odds of ovulation and pregnancy, but not live birth. Given the evidence presented, these conclusions are likely to be reliable.

Authors' objectives
To determine the efficacy of metformin, used alone or in combination with clomiphene citrate in women with polycystic ovary syndrome, in terms of ovulation, pregnancy and live birth.

Searching
MEDLINE, EMBASE, SCOPUS and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to February 2007 for relevant publications in English. Search terms were reported. In addition, the Cochrane Database of Systematic Reviews, the US Food and Drug Administration database and relevant review articles and meta-analyses were searched for further relevant evidence.

Study selection
Studies were eligible for inclusion in the review if they were randomised controlled trials (RCTs) that compared metformin alone versus placebo alone, or compared metformin plus clomiphene against placebo plus clomiphene. Trials had to include subjects meeting the Rotterdam revised National Institutes of Health criteria for polycystic ovary syndrome and seeking pregnancy. Eligible trials had to report the impact of treatment on ovulation or early pregnancy.

Some trials included only women known to be clomiphene-resistant, women with a baseline body mass index greater than 30, or both. Among the included trials, metformin was administered at a dose of 1500mg, 1700mg or 2000mg.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
The validity of included trials was assessed according to five criteria: randomisation scheme, blinding process, adequacy of allocation of concealment, statistical power, and loss to follow-up.

It appeared that two reviewers independently assessed the validity of included studies, with disagreements resolved by consensus among the study authors.

Data extraction
Data required to calculate log odds ratios (ORs) and related 95% confidence intervals (CIs) were extracted from the included studies.

It appeared that two reviewers independently extracted the data, with disagreements resolved by consensus among the study authors.

Methods of synthesis
Pooled odds ratios and related 95% confidence intervals were calculated for each outcome using a random-effects model. Trials evaluating metformin alone and those evaluating combined metformin and clomiphene were pooled separately.

Subgroup meta-analyses for clomiphene-resistance, obesity status, duration of follow-up, and trial quality were also
conducted, as were sensitivity analyses.

Statistical heterogeneity was assessed using the $\chi^2$ statistic. Publication bias was assessed using funnel plots and the Begg and Egger tests.

Results of the review
Seventeen RCTs were included in the review (n=1,639 women); sample size ranged from 18 to 626. Trials varied in methodological quality. Four trials did not describe the randomisation procedure or allocation concealment; two described randomisation, but not allocation concealment. Eight trials were double-blinded, two were single-blinded and one was triple-blinded. Five trials reported a study power calculation. Six trials lost more than 10% of participants during follow-up. Follow-up ranged from one to 12 months.

Metformin alone showed a statistically significant increase in ovulation relative to placebo (OR 2.94, 95% CI 1.43 to 6.02; nine RCTs), but did not lead to a statistically significant increase in early pregnancy (six RCTs; p>0.05) or live births (one RCT; p>0.05). No significant heterogeneity was found.

Metformin plus clomiphene showed a statistically significant increase in both ovulation (OR 4.39, 95% CI 1.94 to 9.96; 11 RCTs) and early pregnancy (OR 2.67, 95% CI 1.45 to 4.94; ten RCTs) compared with clomiphene alone; significant heterogeneity was found for both analyses (p<0.001 and p=0.033). The increase in live births associated with combination therapy was not statistically significant (four RCTs; p>0.05).

Subgroup analyses indicated greater effects in terms of ovulation and early pregnancy in trials with short follow-up (less than three months). For metformin alone, effects were greater in women who were not clomiphene resistant. For combination treatment, effects were greater in clomiphene-resistant and obese women.

There was no evidence of publication bias.

Authors’ conclusions
Metformin increased the likelihood of ovulation and, in combination with clomiphene, the odds of ovulation and pregnancy in women with polycystic ovary syndrome, particularly in obese and clomiphene resistant women. However, treatment may not improve the odds of live birth.

CRD commentary
The review question was clearly defined in terms of the participants, interventions, outcomes, comparators and study designs of interest. Efforts were made to identify relevant evidence from a range of sources. However, as the search was limited to English language publications, the potential for language bias could not be entirely discounted. Attempts were made to minimise the potential for bias and error throughout the review.

The quality of included trials was assessed according to predetermined criteria. Trials appeared to be synthesised appropriately. Efforts were made to investigate the heterogeneity and potential for publication bias.

On the basis of the evidence presented, the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the combination of metformin plus clomiphene should be the treatment of choice for clomiphene-resistant women with polycystic ovary syndrome.

Research: The authors stated that future RCTs of metformin (alone or in combination with clomiphene) for polycystic ovary syndrome should: be adequately powered with a sufficiently long follow-up; measure standardised outcomes of ovulation, pregnancy and birth; account for different patient characteristics (e.g. clomiphene resistance); rule out other potential causes of infertility other than polycystic ovary syndrome.
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