Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review concluded that metformin, administered before pregnancy, had no effect on the abortion risk in women with a diagnosis of polycystic ovary syndrome. There was considerable variation between the included trials in their treatment protocols, comparators, cointerventions, and fertility treatments. This and some limitations in the analysis mean that the authors’ conclusions should be interpreted with caution.

Authors' objectives
To determine the effect of pre-gestational metformin on the miscarriage rate in women with polycystic ovary syndrome (PCOS).

Searching
The following databases were searched, without language restriction, up to June 2008: MEDLINE (from 1966), Web of Science, Cochrane Menstrual Disorders and Subfertility Group Trials Register (from December 2007), Cochrane Central Register of Controlled Trials (CENTRAL, from December 2007), and several websites for trial registration. The search terms were reported. Two experts on PCOS were contacted in an attempt to locate unpublished studies. The references of relevant articles and books were checked.

Study selection
Randomised controlled trials (RCTs) of women with a diagnosis of PCOS and who received metformin were eligible for inclusion. The primary outcome was the abortion rate (defined as the involuntary loss of pregnancy before 20 weeks gestation). The diagnosis of PCOS had to be based on: chronic oligoanovulation and clinical or biochemical hyperandrogenism; the presence of two features out of chronic oligoanovulation, clinical or biochemical hyperandrogenism, and ovarian morphology at ultrasonography; or other non-validated criteria. Trials were excluded if the abortion rate was not available.

Trials varied considerably in their treatment protocols, comparators, cointerventions, and fertility treatment. Metformin was mostly used from two weeks to three months before fertility treatment, followed by one-to-six cycles of co-administration. Metformin with or without cointerventions was compared with placebo, no treatment, laparoscopic ovarian drilling, clomiphene citrate, human menopausal gonadotrophin, and rosiglitazone, with or without cointerventions. The cointervention was usually clomiphene citrate. Metformin was not administered during pregnancy in any of the included trials; in most trials, administration continued until a positive pregnancy result was achieved or stopped at human chorionic gonadotrophin injection.

Trials used various fertility treatments, including timed intercourse, intrauterine insemination, highly purified follicle stimulating hormone, intracytoplasmic sperm injection, controlled ovarian stimulation, and in vitro fertilisation. No trial had the abortion rate as the primary end point. The diagnosis of PCOS varied across trials. The participants in half the trials were clomiphene citrate resistant and, in three trials, they were all insulin resistant. The mean age ranged from 24.5 to 32 years, and the mean body mass index ranged from 23.5 to 38.0kg per m$^2$.

Two reviewers independently selected trials for inclusion and disagreements were resolved through discussion or arbitration with a third reviewer.

Assessment of study quality
Trials were assessed according to the Cochrane guidelines. There were criteria for allocation concealment, blinding, intention-to-treat (ITT) analysis, and follow-up. The authors did not state how many reviewers assessed the validity.

Data extraction
The data were extracted for the abortion rate and used to calculate relative risks and 95% confidence intervals. The abortion rate was calculated as the total number of miscarriages per total number of pregnancies, with treatment. Where information was missing attempts were made to contact the authors of the trials.

The number of reviewers who extracted the data was not reported.

Methods of synthesis
A fixed-effect model was used to estimate summary the relative risks and 95% confidence intervals, while heterogeneity was assessed, using the Cochran Q test. A random-effects model was used if there was evidence of unexplained statistical heterogeneity. Subanalyses were performed grouping trials by metformin administered as monotherapy or as a cointervention with fertility drugs. The results were calculated for an ITT analysis and a per-protocol analysis.

Results of the review
Seventeen RCTs were included (n=1,741 participants, range 17 to 626) and the analyses were based on 566 pregnancies, with samples ranging from three to 167 pregnancies. Allocation concealment was adequate in 15 trials and unclear in two trials. No trial was powered to detect differences in miscarriage rate.

No statistically significant effect of metformin was found on the abortion rate for all women, compared with those who received clomiphene citrate, no treatment, or placebo during clomiphene citrate-stimulated cycles for patients who were naive or resistant to clomiphene citrate. No effect was found for metformin with gonadotrophins for controlled ovarian stimulation, nor for in vitro fertilisation. No evidence of significant statistical heterogeneity was found.

Authors' conclusions
There was no significant benefit from pre-gestational metformin on the abortion risk in women with PCOS, and the results of two RCTs that were in progress should help provide more definitive conclusions.

CRD commentary
The inclusion criteria for the review question were clearly defined. Several relevant databases were searched, without language restriction, and attempts were made to locate unpublished data, minimising the likelihood of publication bias. Steps were taken to minimise error and bias in the selection of trials, but it was not clear whether similar steps were taken for data extraction and validity assessment. The quality of the included trials was assessed, using relevant criteria, and the results were reported for each trial, but most of the outcomes of each trial were not reported. No significant statistical heterogeneity was found, but the trials differed in their populations, protocols, and doses used and pooling might have been inappropriate. The numbers of trials and patients included, for most of the analyses, were not reported and this information would have helped in judging whether these analyses were sufficiently powered to detect any differences. Summary scores were reported as odds ratios and not risk ratios as the authors stated.

When events are relatively rare differences between two interventions are small, but the event rates were greater than 20% on the only outcome where these rates were provided. It also seems that the authors were not consistent in their treatment of trials in which no events were found in either group. Given all these considerations, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that there was no clinical evidence of a significant benefit for pre-gestational metformin on the abortion risk in women with PCOS.

Research: The authors did not state any implications for research.

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