A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome

Costello M F, Eden J A

CRD summary
This review assessed the effectiveness of metformin in restoring regular menstrual cycles and ovulation, and in achieving pregnancy in women with polycystic ovary syndrome. The authors concluded that effectiveness was difficult to assess from the available evidence. Although not without some methodological limitations, the authors' conclusions were reasonable and identified where there was insufficient evidence for conclusions to be drawn.

Authors' objectives
To assess the effectiveness of metformin in restoring regular menstrual cycles and ovulation, and in achieving pregnancy in women with polycystic ovary syndrome (PCOS).

Searching
MEDLINE and EMBASE were searched from 1966 to July 2002; the search terms were reported. Reference lists were also checked.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were randomised controlled trials (RCTs), cohort studies, case-control studies and uncontrolled observational studies. Case reports were excluded from the review.

Specific interventions included in the review
The inclusion criteria were metformin alone or combined with other methods of ovulation induction such as clomiphene citrate (CC) or gonadotrophins, or combined with in vitro fertilisation (IVF). Included in the review were studies in which metformin was given alone, with CC, with follicle stimulating hormone (FSH), or with IVF.

Participants included in the review
The inclusion criteria were women with PCOS. The patients included in the review were women with unselected PCOS (i.e. PCOS was not known to be clomiphene-resistant) and women with known clomiphene-resistant PCOS. The majority of the patients included in the review were obese, with an average mean body mass index of 31.3 kg/m² (range: 21.4 to 39.8); only one study contained patients with a mean body mass index of less than 25.

Outcomes assessed in the review
The inclusion criteria were the restoration of regular menstrual cycles, the restoration of ovulation and the achievement of pregnancy. The outcomes included in the review were the restoration of regular menstruation and ovulation, pregnancy rate, time to conception and the number of miscarriages.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study design and external validity (applicability) were assessed using an evidence-based medicine appraisal framework (see Other Publications of Related Interest). The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The data extracted were: study design, study setting, interventions and doses used, control treatment(s), and the numbers of women in each treatment and control group with regular cycles, ovulation and pregnancy.

Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken. The studies were grouped on the basis of the population group (whether or not PCOS patients were known to be clomiphene-resistant), intervention (metformin alone, in combination with CC, with gonadotrophins, or with IVF), outcome reported, and study design. Within these categories the studies were pooled by simply adding the event rates in each study. This was done for RCTs and non RCTs separately.

How were differences between studies investigated?
The tables showed differences in the baseline body mass index, mean fasting insulin level, and doses and duration of treatment.

Results of the review
Thirty studies were included in the review: 12 RCTs, 2 cohort studies and 16 uncontrolled observational studies. The numbers of patients were not provided for all studies, so a total cannot be calculated.

Twelve studies evaluated the effectiveness of metformin alone in restoring regular menstruation in unselected PCOS. Three studies were RCTs, of which 2 reported a significant improvement in menstrual cycle frequency in the metformin group.

Nine studies evaluated the effectiveness of metformin alone in restoring ovulation in unselected PCOS. Four studies were RCTs, of which 2 found that significantly more women ovulated with metformin than with placebo: 34% after 1 month and 82% after 4 months, compared with 4 and 64%, respectively. However, these studies contained totals of only 61 and 94 women respectively. The other 2 studies (n=25 and n=31) showed non significantly higher ovulation in the metformin group. When data from all 4 trials were added together, 56% of the patients ovulated with metformin compared with 35% of those on placebo; the relative risk (RR) was 1.5 (95% confidence interval, CI: 1.2, 2.0, P=0.002).

One study, an RCT, evaluated the effectiveness of metformin alone in restoring ovulation and subsequent pregnancy rate in unselected PCOS. It found that significantly more women ovulated on metformin (37 out of 45, i.e. 82%) than on placebo (30 out of 47, i.e. 64%), while of the women who wished to conceive, 4 (17%) of the 23 became pregnant on metformin compared with 1 (5%) of the 19 on placebo.

Five studies evaluated the effectiveness of metformin combined with CC in restoring ovulation and/or achieving pregnancy in unselected PCOS. The 2 RCTs (n=61 and n=90), which both contained only obese patients, found that significantly more women ovulated with metformin in combination with CC (90 and 80%) than with placebo and CC (8 and 65%). One study also showed a significantly higher pregnancy rate in the metformin and CC group (29%) than the CC and placebo group (8%).

Four studies evaluated the effectiveness of metformin combined with CC in restoring ovulation and/or achieving pregnancy in CC-resistant patients. Three studies were RCTs, of which one (n=20) showed no significant difference between the groups. Two studies (n=56 and n=27) found significantly more women ovulated and became pregnant in the metformin combined with CC group than in the CC and placebo group. When data from the 3 studies were added, more women ovulated on metformin combined with CC than on placebo and CC (RR 4.0, 95% CI: 1.6, 4.1, P<0.001), while more women became pregnant on metformin combined with CC than on CC alone (RR 2.2, 95% CI: 1.5, 3.0, P=0.04).

Two studies evaluated the effect of pretreatment with metformin on FSH treatment in women with CC-resistant PCOS. Both studies were RCTs comparing FSH alone with FSH combined with metformin. One crossover study (n=20) found no difference in ovulation or pregnancy rates between the treatments. One parallel-group RCT (n=32) reported that
metformin combined with FSH produced fewer dominant follicles (2.4 versus 4.5, P<0.01) and a lower treatment cycle cancellation rate (0 versus 32%, P<0.03) because of excessive follicular development.

One study, a retrospective cohort study, evaluated the use of metformin during the IVF treatment of CC-resistant patients. It reported a higher fertilisation rate (64 versus 43%, P<0.05) and a higher clinical pregnancy rate (70 versus 30%, P<0.05) in patients given metformin.

Authors' conclusions
The authors concluded that the effectiveness of metformin in the treatment of PCOS anovulatory infertility in clinical practice was difficult to assess from currently available research.

CRD commentary
The review question and the inclusion criteria were clear. Two relevant electronic databases were searched and the authors did not state that any language restrictions were applied; this may have made language bias less likely. However, no attempt to identify unpublished studies was reported, which may have led to the introduction of publication bias. The authors did not report using any methods to minimise bias and errors in the study selection, data extraction or validity assessment processes. The broad inclusion criteria for study design meant that the included studies differed widely in the evidence strength, but RCTs were clearly identified and discussed separately in the narrative synthesis. However, the authors' method of adding together the results of the studies did not take the statistical properties of each study into account. There was also a considerable amount of clinical and statistical heterogeneity between the studies combined, particularly the uncontrolled studies, which the authors did not explore. The authors' conclusions were reasonable and identified where there was insufficient evidence for conclusions to be drawn.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that well-designed RCTs with an end point of live birth are required to investigate the role of metformin, with or without CC, in restoring fertility in anovulatory women with PCOS.

Bibliographic details

PubMedID
12524053

Other publications of related interest
Guyatt GH, Sacket DL, Cook DJ. Users' guide to the medical literature: II. How to use an article about therapy or prevention. A. Are the results of the study valid? JAMA 1993;270:2598-601.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.