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REVIEW ARTICLE

A systematic review and meta-analysis of metformin among patients with polycystic ovary syndrome undergoing assisted reproductive technology procedures

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ABSTRACT

Background: Metformin is used among patients with polycystic ovary syndrome (PCOS), but findings for its effects on outcomes of assisted reproductive technology (ART) have been conflicting. *Objectives:* To compare ART outcomes among women with PCOS who were and were not given metformin. *Search strategy:* Databases were searched for reports published in English between 2002 and 2013, using combinations of the terms "polycystic ovary syndrome," "PCOS," "insulin-sensitizing," and "metformin." *Selection criteria:* Randomized controlled trials of metformin versus placebo among women with PCOS undergoing ART were included if they assessed rates of pregnancy, live birth, spontaneous abortion, multiple pregnancy, and/or ovarian hyperstimulation syndrome (OHSS). *Data collection and analysis:* Data were extracted from included studies. The Mantel-Haenzel random-effects model was used for meta-analyses. *Main results:* Twelve studies (1516 participants) were included. No significant differences were recorded between metformin and placebo groups for rates of pregnancy (risk ratio [RR] 1.11, 95% CI 0.92–1.33), live birth (RR 1.12, 0.92–1.36), spontaneous abortion (RR 1.00, 0.60–1.67), or multiple pregnancy (RR 0.96, 0.47–1.96). However, OHSS rate was significantly lower among patients who received metformin than among those who received placebo (RR 0.44, 0.26–0.77). *Conclusions:* Metformin does not improve ART outcomes among patients with PCOS, but does significantly reduce their risk of OHSS.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, affecting 5%–10% depending on the population [1–3]. According to the 2003 Rotterdam consensus [4], PCOS should be diagnosed on the basis of the presence of two of three criteria—oligo-ovulation/anovulation, hyperandrogenism, and polycystic ovarian morphology on ultrasonography—after exclusion of other endocrine disorders. PCOS can lead to reproductive health problems (e.g. irregular menstrual cycles, oligo-anovulation, and infertility) and is closely related to metabolic disorders (e.g. obesity, insulin resistance, gestational diabetes mellitus, diabetes, and cardiovascular disease) [5].

Insulin resistance is considered to be the main reason for hyperandrogenism and other clinical characteristics of PCOS, and affects approximately 50%–70% of patients [6]. Insulin sensitizers such as metformin have been shown to improve menstrual abnormalities and ovulation frequency in women with PCOS—effects which are thought to be mediated via increased insulin sensitivity and decreased androgen production [7]. Many prospective trials and RCTs have evaluated metformin treatment in infertile women with PCOS, assessing quality of life [8], cost and safety [9], adverse effects [10], and effectiveness [11–13].

Among women with PCOS who plan to undergo assisted reproductive technology (ART) procedures, metformin is often used as pretreatment before an in vitro fertilization (IVF) cycle or until confirmation of clinical pregnancy [14]. Several studies have evaluated the use of metformin in patients with PCOS undergoing ART, but they have had largely conflicting results. The objective of the present systematic review and meta-analysis was to compare ART outcomes in women with PCOS who were and were not using metformin, using data from randomized controlled trials (RCTs).

2. Materials and methods

As part of a systematic review and meta-analysis, PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched for

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reports published in English between January 1, 2002, and December 31, 2013. Different combinations of the search terms "polycystic ovary syndrome," "PCOS," "insulin-sensitizing," and "metformin" were used.

Studies of metformin versus placebo were included if they met three criteria: (1) the study population included women diagnosed with PCOS (according to the Rotterdam criteria) undergoing IVF or intracytoplasmic sperm injection in non-donor cycles, with any stimulation protocol; (2) the outcomes of clinical pregnancy, live birth, spontaneous abortion, multiple pregnancy, and/or ovarian hyperstimulation syndrome (OHSS) were recorded for all participants; and (3) the investigation was an RCT. The abstracts of all studies identified through the keyword search were screened by two researchers (X.H. and P.W.). Eligibility assessment was performed independently by two reviewers (X.H and F.L.). Any disagreement between reviewers was resolved through discussion.

If a study was deemed eligible on the basis of abstract review, two researchers (X.H. and Y.L.) then carefully read and judged the full texts of the articles independently. The reference lists of selected articles and reviews were manually searched to identify additional potentially relevant studies.

Data for methods (purpose of intervention, methods of recruitment, inclusion/exclusion criteria, and informed consent), participant characteristics (number of participants and age), interventions (time and dose of metformin, and combinations with other drugs), and outcomes (clinical pregnancies, live births, multiple pregnancies, spontaneous abortions, and OHSS) were extracted from included studies by one investigator (X.Z.) and independently verified by another (R.T.). Any disagreement was resolved through discussion. Studies were also evaluated for potential sources of bias, including randomization method, allocation concealment, and blinding.

All results were merged for meta-analysis using Review Manager 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). The number of women who were randomly assigned was taken as the total number of participants in each study. Using the Mantel-Haenszel random-effects model, dichotomous outcomes were summarized by calculating the risk ratio (RR) and 95% confidence intervals (CIs). Heterogeneity between studies was assessed by the χ^2 test and I^2 (<25% deemed low heterogeneity, 25%–50% moderate; and >50% high), with $P < 0.10$ indicating significant heterogeneity.

3. Results

3.1. Identified studies

Overall, 33 articles were fully assessed for eligibility, of which 12 were included in the meta-analysis (Fig. 1, Table 1). Fig. 2 gives the results of the quality assessment of included studies.

3.2. Pregnancy rate

All 12 studies (1516 participants) reported clinical pregnancy as an outcome and were included in the meta-analysis (Fig. 3A). Only one study [20] showed a significantly increased rate of pregnancy among women who received metformin. The pooled analysis using the random-effects model demonstrated no significant difference in pregnancy rate between the metformin and placebo groups (RR 1.11, 95% CI 0.92–1.33; $P = 0.28$). There was moderate heterogeneity between studies ($I^2 = 38\%$).

3.3. Live birth rate

Seven studies reported live birth rates among 1035 patients and were included in the meta-analysis (Fig. 3B). Again, only one study [20] reported a significant increase in the live birth rate among women who received metformin. The meta-analysis showed there was no significant difference in live birth rate between the metformin and placebo groups (RR 1.12, 95% CI 0.92–1.36; $P = 0.26$). Little heterogeneity ($I^2 = 13\%$) was found between studies.

3.4. Rate of spontaneous abortion

There were four studies (499 participants) that reported rates of spontaneous abortion and were included in the meta-analysis (Fig. 4A). The rate of spontaneous abortion did not differ between metformin and placebo groups in any one study or in meta-analysis

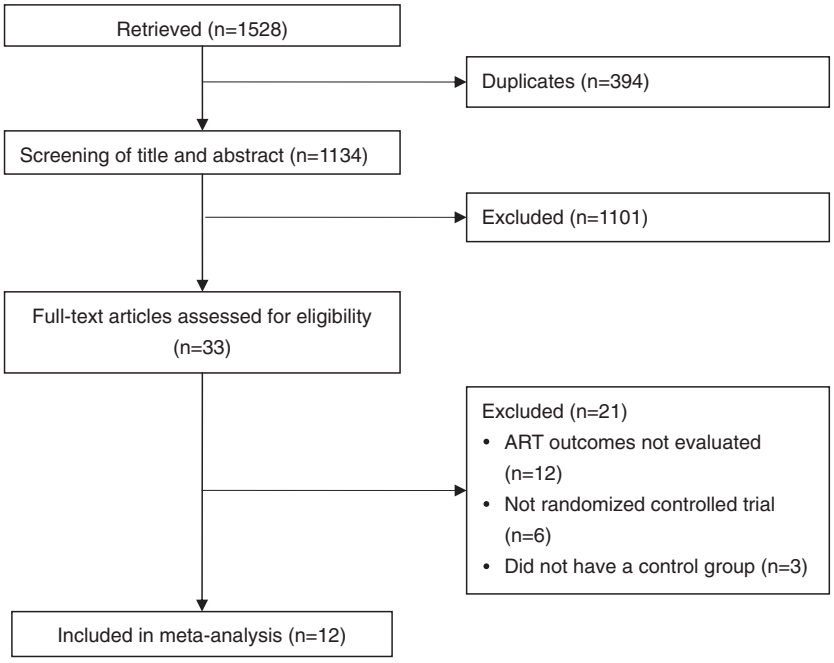

Fig. 1. Flowchart of study selection.