Metformin in polycystic ovary syndrome

Moll, Etelka

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Chapter 3

The role of metformin in polycystic ovary syndrome. A systematic review.

Etelka Moll, Fulco van der Veen, Madelon van Wely

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Abstract

This meta-analysis evaluated the effectiveness of metformin in subfertile women with polycystic ovary syndrome (PCOS). Only randomised trials investigating the effectiveness of metformin and PCOS definition consistent with the Rotterdam consensus criteria were eligible. Primary outcome was live birth rate. A literature search identified 27 trials. In therapy naive women, we found no evidence of a difference in live birth rate when comparing metformin with clomifene citrate (CC) [relative risk (RR) 0.73; 95% confidence interval (CI) 0.51 - 1.1] or comparing metformin plus CC with CC (RR 1.0; 95% CI 0.82 - 1.3). In CC-resistant women, metformin plus CC led to higher live birth rates than CC alone (RR 6.4; 95% CI 1.2 - 35); metformin also led to higher live birth rates than laparoscopic ovarian drilling (LOD) (RR 1.6; 95% CI 1.1 - 2.5). We found no evidence for a positive effect of metformin on live birth when added to LOD (RR 1.3; 95% CI 0.39 - 4.0) or FSH (RR 1.6; 95% CI 0.95 - 2.9), or when co-administered in IVF (RR 1.5; 95% CI 0.92 - 2.5). In IVF, metformin led to fewer cases of ovarian hyperstimulation syndrome (OHSS) (RR: 0.33; 95% CI: 0.13 - 0.80). This meta-analysis demonstrates that CC is still first choice therapy for women with therapy naive PCOS. In CC-resistant women, the combination of CC plus metformin is the preferred treatment option before starting with LOD or FSH. At present, there is no evidence of an improvement in live birth when adding metformin to LOD or FSH. In IVF, metformin leads to a reduced risk of OHSS.
Introduction

The polycystic ovary syndrome (PCOS) affects 5% to 10% of women of reproductive age.\textsuperscript{1} PCOS is characterised by oligo-anovulation, clinical or biochemical hyperandrogenism and / or polycystic ovaries.\textsuperscript{2-4} Insulin resistance accompanied by compensatory hyperinsulinemia constitutes another major biochemical feature of PCOS.

In 1994, more than 70 years after the first description of a patient with insulin resistance and hyperandrogenism, the first study on the insulin sensitizer metformin in women with PCOS was published.\textsuperscript{5} Originally, this trial was meant to study metabolic and endocrinological parameters, but the authors noticed that some (12%) of the women conceived spontaneously.

From that moment on many trials were set up to test insulin sensitizers (mainly metformin) for ovulation induction in women with PCOS. These studies have been summarized in several reviews and meta-analyses.\textsuperscript{6-11} These meta-analyses were based on trials all consisting of a very small number of patients. In the analyses no consistent distinction between therapy naïve and clomifene citrate (CC)-resistant women was made. The reviews separately did not overview the total spectrum of treatment possibilities.

In addition, two large trials were recently published.\textsuperscript{12,13} The total number of patients in each separate trial exceeded the total number of patients in the existing reviews. Both trials found - in contrast to the previously published trials - that metformin does not lead to higher pregnancy rates when combined with CC and the same was true for metformin alone when compared with CC.

In view of this, we felt that updating our knowledge on metformin in subfertility and a critical appraisal of all existing studies might be helpful to guide clinical practice. In this review, we will therefore concentrate on the effect of metformin on live birth rate in women with PCOS for all comparisons studied so far.
Materials and Methods

Search Strategy

We searched the Cochrane Menstrual Disorders & Subfertility Group trials register, the Cochrane Central Register of Controlled Trials (both searched February 2007), MEDLINE (January 1966 to February 2007), the website for registration of controlled trials (controlled-trials.com) and several personal contacts with experts in this field (Balen, Nestler, Palomba). All electronic databases were searched using the following keywords: assisted reproduction, clomifene citrate, gonadotrophins, IVF, IUI, metformin, ovulation induction, PCOS, pregnancy. We handsearched the reference lists of selected trials and of recent reviews concerning this subject. No restrictions were held concerning publication year or language. All retrieved articles were of English language and published from 1996 till February 2007.

Study selection and data extraction

Studies were selected if the target population were women with PCOS. The definition of PCOS had to follow the standards of the ESHRE/ASRM 2003 consensus, or the criteria used in the article had to be, in retrospect, in consensus with the definition. If included patients did not meet the definition of ESHRE/ASRM, the study was not included in this review. Furthermore, the studies had to be of randomised design comparing the effect of metformin with placebo or no treatment, metformin with another ovulation induction agent or method or comparing the effect of metformin as co-treatment in IVF with no co-treatment.

The primary outcome of interest was live birth rate per randomised woman. Secondary outcomes were clinical pregnancy, multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). It appeared that if live birth rate was not given in a manuscript, data on ongoing pregnancy were also not presented. Therefore, clinical pregnancy rate was chosen as a secondary outcome.

The review was undertaken by two reviewers (E.M., M.v.W.). The search strategy was employed to obtain titles and, where possible, abstracts of studies that were potentially relevant to the review. Both reviewers independently assessed whether the studies met the inclusion criteria, with disagreements resolved by discussion and final arbitration by F.V.

For each included trial, information was collected regarding the location of the study, methods of the study (as per quality assessment checklist), the participants
(age range, eligibility criteria), the nature of the interventions and data relating to the outcomes specified above. When possible, missing data were sought from the authors. The trial specific characteristics are expressed in Table 1.

We distinguished three indications: metformin as first-line treatment in therapy naive women; metformin as second-line treatment in CC-resistant women and metformin as co-treatment in women undergoing IVF. We subdivided first-line and second-line treatment into metformin monotherapy or co-treatment in combination with CC, FSH or laparoscopic ovarian drilling (LOD).

**Statistical analysis**

Relative risks (RR) with 95% confidence intervals (95% CI) were calculated for every study. Pooled RR were calculated using fixed effects models.\(^\text{14}\) If there was statistical heterogeneity, we performed a sensitivity analysis by pooling using a ‘random effects’-method.\(^\text{15}\)

Statistical heterogeneity was assessed using forest plots, the \(I^2\) statistic and chi-square test. Clinical heterogeneity was assessed by reviewing differences across trials in characteristics of randomized patients.

Data from cross-over trials were only used from the first phase (i.e. before crossover). Any such trials that did not provide results at this point were excluded from the analysis. Review Manager-software (RevMan 4.2.7, Cochrane Collaboration, Oxford, UK) was used for the statistical analysis. We analysed the data on intention to treat basis.

**Results of search**

Our search selected 443 articles. After reading the titles, 296 articles did not answer our question. From the remaining 147 articles, 94 articles were discarded while they were non-original papers (reviews, letters). The 53 remaining articles were read. Thirty articles did not meet our inclusion criteria for not having a proper control group,\(^\text{5,16-24}\) for not using randomisation,\(^\text{25-27}\) for not providing clear information on live birth or clinical pregnancy rates,\(^\text{28-40}\) for using a cross-over design without clear rates of pregnancy before the cross-over,\(^\text{41-43}\) or because of selection bias.\(^\text{44}\) Furthermore, in one trial women were included that did not intend to get pregnant and had been advised to take contraception (J.Nestler, personal communication).\(^\text{45}\)
By handsearching reference lists, we came across four articles we did not find in the initial search.46-49 In total 27 studies were included in the analysis (Fig. 1). Three studies compared metformin with placebo,46;50;51 two compared metformin with CC,13;52 12 compared metformin plus CC with CC,12;13;41;47;49;53-59 one compared metformin with LOD,60 one compared metformin plus LOD with LOD,61 one compared metformin plus CC with HMG,62 four compared metformin plus FSH with FSH48;63-65 and four compared metformin added in IVF versus IVF without metformin.34;66-68

Results

The quality and the main characteristics of the 27 trials included in this review are presented in Table 1. Most trials were of poor quality. Seventeen of 27 trials used an appropriate method of randomization, with 17 out of 27 having adequate concealment of allocation. A power calculation was only reported in eight trials. Trial size varied from 17 to 626 women.

Eight studies excluded women over the age of 35 years. Most studies did not have restrictions considering BMI. One study included women with BMI <25 kg/m². Two studies included women with BMI <30 and <35 kg/m², respectively. Two studies included women with BMI >29 and 30 kg/m², respectively.

Metformin in CC naïve women

Metformin monotherapy

We retrieved two randomised controlled trials in which metformin was compared with placebo for as first line treatment in 185 therapy naïve infertile women with PCOS (Table 1).46;51 None used HCG for triggering ovulation. Both trials reported clinical pregnancy rate. The pooled RR was 3.3 (95% CI: 0.92-11) (Fig. 2a). Visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity in treatment effect across trials.

Live birth rate was not reported, nor multiple pregnancy rates. One study gave life style modification before starting drug therapy.51 The median weight loss was 2.8 versus 1.5%.

We found two double-blinded randomised controlled trials in which metformin was directly compared with CC as first line treatment in 509 infertile women with
PCOS (Table 1).\textsuperscript{13,52} HCG was not used for triggering ovulation. The pooled clinical pregnancy rate after six months of treatment was significantly lower after metformin (RR: 0.72; 95\% CI: 0.54-0.97) (Fig. 2a). The pooled RR for live birth was 0.73 (95\% CI: 0.51-1.1) (Fig. 2b). However, for both pregnancy outcomes there was significant heterogeneity in treatment effect across the two trials. When the data were pooled using a random effects model the RR was 0.88 (95\% CI: 0.19 – 4.1) and 0.96 (95\% CI: 0.11-8.2) for clinical pregnancy rate and live birth rate respectively. Furthermore, there was no evidence of a difference in multiple pregnancy rate between the two groups (RR: 0.38; 95\% CI: 0.02-7.1).

\textit{Metformin as co-treatment in combination with CC}

Seven randomised controlled trials compared CC plus metformin with CC in 985 infertile women with PCOS (Table 1).\textsuperscript{12,13,47,49,53-55} Two studies used HCG to trigger ovulation.\textsuperscript{47,55} After combining the data, there was a significantly higher clinical pregnancy rate in the metformin plus CC group (RR 1.5; 95\% CI 1.2 - 1.8) (Fig. 2a). However, there was significant heterogeneity in treatment effect across the trials. When the data were pooled using a random effects model the difference in clinical pregnancy was still significant (RR 1.9; 95\% CI: 1.2 – 3.3). The pooled RR for live birth was 1.0 (95\% CI 0.82 - 1.3; three trials with 664 women) (Fig. 2b). For live birth, there was no indication for heterogeneity in treatment effect across trials.

Two studies reported multiple pregnancy rates.\textsuperscript{12,13} After combining these data no significant difference was seen (RR 0.38; 95\% CI 0.09 - 1.5; 193 women).

\textit{Metformin in CC-resistant women}

\textit{Metformin monotherapy}

We retrieved one randomised clinical trial in which metformin was compared with placebo in 18 infertile women with CC-resistant PCOS (Table 1).\textsuperscript{50} In this small number of women there was no evidence of a difference in clinical pregnancy or live birth rate (both RR: 0.50; 95\% CI: 0.05-4.6) (Fig. 3a and b). No data on multiple pregnancy rates were given.
**Metformin as co-treatment in combination with CC**

We retrieved five randomised controlled trials in which CC plus metformin was compared with CC alone in 210 infertile women with CC-resistant PCOS (Table 1).41;56-59 Two trials used HCG to trigger ovulation.56;57

Combining the results showed that metformin plus CC led to a significantly higher clinical pregnancy rate than CC alone (RR: 5.6; 95% CI: 2.3-13) (Fig. 3a). Live birth rate was also in favour of metformin plus CC compared with the CC group (RR: 6.4; 95% CI: 1.2-34; 2 trials with 107 women) (Fig. 3b). For both pregnancy outcomes, visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity in treatment effect across trials.

In the only trial that reported on multiple pregnancy no multiple pregnancies were observed in both groups.59

**Metformin as opposed to LOD**

Only one randomised trial was retrieved in which metformin treatment was compared with LOD (Table 1).60 There was no evidence of a difference in clinical pregnancy rate (RR: 1.3; 95% CI: 0.96-1.7) (Fig 3a). Live birth rate however was higher in the metformin group (RR: 1.6; 95% CI: 1.1-2.5) (Fig 3b). Multiple pregnancies were not observed.

**Metformin as co-treatment in combination with LOD**

One trial randomised 42 PCOS patients between LOD followed by metformin or LOD alone (Table 1).61 There were no significant differences in clinical pregnancy rate (RR: 2.3; 95% CI: 0.82-6.2) or live birth rate (RR: 1.3; 95% CI: 0.39-4.0) (Fig. 3a and 3b).

**Metformin plus CC compared with gonadotrophins**

In one randomised clinical trial, metformin plus CC was compared with gonadotrophins in 60 CC-resistant women (Table 1).62 Both groups were triggered for ovulation with HCG. There was no evidence of a difference in clinical pregnancy rate (RR: 0.71; 95% CI: 0.26-2.0) (Fig. 3a). There were no data on live birth, multiple pregnancy or OHSS.
**Metformin plus FSH compared with FSH alone**

In four randomised controlled trials FSH plus metformin was compared with FSH alone in 154 infertile women with PCOS (Table 1). All studies used HCG to trigger ovulation. The pooled clinical pregnancy rate was significantly higher in the FSH plus metformin group compared with FSH only group (RR: 1.7; 95% CI: 1.1-2.8) (Fig. 3a). A difference in live birth rate could however not be proven (RR: 1.6; 95% CI: 1.0-2.9) (Fig. 3b). For both pregnancy outcomes, visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity in treatment effect across trials. Metformin led to less multiple pregnancies (RR: 0.26; 95% CI: 0.07-0.96). There was no evidence of a difference in OHSS (RR: 0.59; 95% CI: 0.17-2.1).

**Metformin as additional treatment in controlled ovarian hyperstimulation in IVF**

Four trials studied the effect of metformin during ovarian hyperstimulation in IVF/ICSI in 283 women with PCOS (Table 1) (T.Tang, personal communication).

In the first study, reasons for IVF treatment were not specified. In the second study, women received IVF or ICSI because of other fertility problems like tubal pathology, endometriosis or male subfertility. In the third study women with PCOS in whom conventional therapy had not lead to pregnancy, were included. In the fourth study, reasons for IVF were failure of conventional therapy and other fertility problems.

All studies presented data in clinical pregnancy rate. Combining the results did not show a significant difference between the women treated with metformin or placebo (RR: 1.2; 95% CI: 0.85-1.6) (Fig. 4). Visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity in treatment effect across trials. Live birth rate was reported in two studies. There was no evidence of a significant difference between the two groups (RR: 1.5; 95% CI: 0.92-2.5) (Fig. 4). Pooling the data of the two trials that reported multiple pregnancy gave no evidence of a significant difference between the two groups on multiple pregnancy rate (RR: 0.93; 95% CI: 0.42-2.1). OHSS was reported in all studies. When combining the results, there was a significant reduced risk in favour of metformin (RR: 0.33; 95% CI: 0.13-0.80).
Discussion

In this review, we evaluated whether metformin leads to a more effective fertility treatment for women with PCOS. From the placebo controlled trials performed in infertile women with therapy naïve PCOS it is clear that metformin can induce ovulation and can lead to pregnancies. The important clinical question however is not whether metformin "works", but whether it is better than CC in terms of live birth in CC naïve women or whether it has additional benefit in terms of live birth when used as co-treatment in therapy naïve or CC-resistant women.

At present, there is no evidence of a difference between metformin and CC in therapy naïve women in favour of metformin. The two trials that studied this comparison had conflicting results. In the study by Palomba et al, the live birth rate was three times higher in the metformin group. In contrast, in the study by Legro et al, with quadruple the number of patients, the live birth rate was three times lower in the metformin group. Of interest is that in the Palomba study, live birth rate in the CC group was unusually low due to a high miscarriage rate. Legro included patients previously treated with CC or metformin. We presumed these patients not to be CC-resistant. Through personal communication we were informed that it is not clear how many of these patients were CC-resistant. (R. Legro, personal communication). Still, this particular mixture of patients can explain the low live birth rate in this study.

Meta-analysis of the studies that compared co-treatment of metformin with CC versus CC alone did not show any benefit of metformin for live birth rate. These data, taken together, make it highly unlikely that metformin – as monotherapy or as co-treatment in combination with CC - is beneficial over CC in CC naïve women.

The clinical pregnancy rate in the comparison metformin plus CC versus CC alone was significantly higher in the metformin group. However, there was significant heterogeneity between studies as the small studies all favoured metformin plus CC above CC alone while this difference was not found in the larger studies. This difference between the larger and smaller studies may be a result of publication bias or low study quality bias. The sensitivity analysis using pooling with a random effects method was not helpful here as a random effects meta-analysis will award relatively more weight to smaller studies.

In CC-resistant women, two studies showed a clear benefit of adding metformin to CC over CC alone in terms of live birth. One should interpret these
results with some caution as one study was not blinded and the total number of patients in these two studies was only 107.

Metformin appears to be superior to LOD considering live birth rate in CC-resistant women, but these data are also based on a small number of women and from one monocenter study. This being so, metformin is quite a different treatment strategy than LOD and avoids the considerable risks of laparoscopic surgery, especially in obese patients.

No differences in live birth were detected when metformin was added to LOD compared with LOD alone and when metformin was added to FSH compared with FSH alone, but again few studies, including few patients, have been carried out so far.

Up till now, there is no evidence for better results on live birth rates when metformin is added during ovarian hyperstimulation in IVF. This is based on two studies with a limited number of patients and with probably totally different populations of women, as in one study a mix of women after failed ovulation induction and with other indications was included, while in the other studies only women with other fertility problems were included. Metformin may however, reduce the risk of OHSS.

In general, duration of metformin therapy differed substantially over the studies and we can only speculate which effects this will have on outcome parameters.

In summary, this meta-analysis demonstrates that CC is still first choice therapy for women with therapy naïve PCOS. In CC-resistant women, the combination of CC plus metformin is the preferred treatment option before starting with LOD or FSH. At present, there is no evidence of an improvement in live birth rates when adding metformin to LOD or FSH.
References


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**Notes:**
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- OHSS: Ovarian Hyperstimulation Syndrome
- IVF: In Vitro Fertilization
- ICSI: Intracytoplasmic Sperm Injection
- CC: Clomiphene Citrate
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<td></td>
<td></td>
</tr>
<tr>
<td>Raja 2005</td>
<td>CC-naive</td>
<td>Metformin 500mg 3/day + CC 50mg 6 cycles</td>
<td>CC 50mg 6 cycles</td>
<td>Randomisation not clear; Not blinded.</td>
<td></td>
</tr>
<tr>
<td>(n=50 versus 50)</td>
<td>PCO ultrasound + 2 or more of: oligomenorrhoea, hyperandrogenism, LH-FSH-ratio &gt; 2, hirsutism, elevated LH; Age: 27 versus 27 BMI: not available</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Eligibility Criteria</td>
<td>Randomisation</td>
<td>Intervention</td>
</tr>
<tr>
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</tr>
<tr>
<td>Sahin</td>
<td>2004</td>
<td>CC-naive; 3 or more of oligomenorrhoea, PCO ultrasound, hyperandrogenism, LH-FSH-ratio &gt;2, hirsutism; Age: 27 versus 25 BMI: 30 versus 26</td>
<td>Metformin 850mg 2/day + CC 100mg 3 months</td>
<td>CC 100mg 3 months</td>
<td>Ovulation Pregnancy</td>
</tr>
<tr>
<td>Singh</td>
<td>2001</td>
<td>CC-naive; Oligomenorrhoea + PCO ultrasound + LH-FSH-ratio &gt; 2; Age: 26 versus 28 BMI: not available</td>
<td>Metformin 500mg 2/day + CC 50mg 4 months</td>
<td>CC 50mg 4 months</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Sturrock</td>
<td>2002</td>
<td>CC-resistant; Oligomenorrhoea; Age: 29 versus 31 BMI: 34 versus 35</td>
<td>Metformin 500mg 3/day + CC 50-150mg 3 months + 3 cycles</td>
<td>Placebo + CC 50-150mg 3 months + 3 cycles</td>
<td>Ovulation Pregnancy</td>
</tr>
<tr>
<td>Tang</td>
<td>2006</td>
<td>CC-naive; Oligomenorrhoea + PCO ultrasound + BMI &gt;30; Age: 30 versus 30 BMI: 38 versus 39</td>
<td>Metformin 850mg 2/day 6 months</td>
<td>Placebo 6 months</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Definition</td>
<td>Treatment</td>
<td>Randomisation</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------------</td>
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<td>------------------------------</td>
</tr>
<tr>
<td><strong>Tang 2006b</strong></td>
<td>(n=51 versus 47); 4 patients entered twice</td>
<td>ESHRE 2003; Age: 31 versus 31 BMI: 28 versus 27</td>
<td>Metformin 850mg 2/day + IVF/ICSI treatment 28 days</td>
<td>Placebo + IVF/ICSI treatment 28 days</td>
<td>Pregnancy Live birth OHSS</td>
</tr>
<tr>
<td><strong>Tasdemir 2004</strong></td>
<td>(n=16 versus 16)</td>
<td>CC - resistant; Oligomenorroea + PCO ultrasound + hyperandrogenism; Age: 32 versus 31 BMI: 29 versus 29</td>
<td>Metformin 850mg 2/day + FSH 8 weeks + 1 cycle (FSH was started after 8 weeks treatment)</td>
<td>FSH 8 weeks + 1 cycle (FSH was started after 8 weeks treatment)</td>
<td>Pregnancy Ovarian response</td>
</tr>
<tr>
<td><strong>van Santbrink 2005</strong></td>
<td>(n=11 versus 7)</td>
<td>CC-resistant or CC-failure; Oligomenorroea + insulin resistance; Age: 28 versus 28 BMI: 38 versus 34</td>
<td>Metformin 850mg 2/day + FSH step-up 35 days and 1 cycle (FSH was added if no ovulation after 35 days)</td>
<td>Placebo 850mg bid + FSH step-up 35 days and 1 cycle (FSH was added if no ovulation after 35 days)</td>
<td>Ovarian response</td>
</tr>
<tr>
<td><strong>Vandermolen 2001</strong></td>
<td>(n=12 versus 15)</td>
<td>CC-resistant; Oligomenorroea + hyperandrogenism; Age: 29 versus 30 BMI: 38 versus 38</td>
<td>Metformin 500mg 3/day + CC 50-150mg 6 weeks and 6 cycles (CC was added if no ovulation after 6 weeks)</td>
<td>Placebo + CC 50-150mg 6 weeks and 6 cycles (CC was added if no ovulation after 6 weeks)</td>
<td>Ovulation Pregnancy</td>
</tr>
<tr>
<td>Yaralı 2002 (n=16 versus 16)</td>
<td>CC-resistant; Oligomenorrhea + PCO ultrasound + testosterone &gt; 2.4 nmol/l; Age: 30 versus 28 BMI: 29 versus 30</td>
<td>Metformin 850mg 2/day + FSH step-up 6 weeks and 1 cycle (FSH was added if no ovulation after 6 weeks)</td>
<td>Placebo 850mg bid + FSH step-up 6 weeks and 1 cycle (FSH was added if no ovulation after 6 weeks)</td>
<td>Ovarian response</td>
<td>Sealed envelopes; Double blinded.</td>
</tr>
</tbody>
</table>
**Figure 1. Trial flow**

Potentially relevant trials; 
\(n=443\)

Trials retrieved for evaluation;  
\(n=147\)

Potentially appropriate trials;  
\(n=53\)

Articles excluded not meeting inclusion criteria by title;  
\(n=296\)

Articles excluded not meeting inclusion criteria by abstract;  
\(n=94\)

Trials withdrawn not meeting inclusion criteria;  
\(n=30\)
- 10 no control group
- 3 no randomisation
- 13 no pregnancy rates
- 3 cross-over design
- 1 selection bias

Trials extra found in reference lists;  
\(n=4\)

Trials included in meta-analysis;  
\(n=27\)
Figure 2. Forest plots for clomifene citrate naïve women

(A) Clinical pregnancy rate in clomifene citrate naïve women
(B) Live birth rate in clomifene citrate naïve women

<table>
<thead>
<tr>
<th>Treatments and studies</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin versus CC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polled</td>
<td>34/50</td>
<td>33/50</td>
<td>3.89 [1.51, 5.53]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>331</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 95 (Treatment), 92 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mfol</td>
<td>36/111</td>
<td>42/114</td>
<td>0.91 [0.24, 3.51]</td>
<td></td>
</tr>
<tr>
<td>Lego</td>
<td>54/209</td>
<td>47/209</td>
<td>0.88 [0.61, 1.26]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>331</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours no metformin  | Treatment metformin
Figure 3. Forest plots for clomifene citrate resistant women

(A) Clinical pregnancy rate in clomifene citrate resistant women
**(B)** Live birth rate in clomifene citrate resistant women

<table>
<thead>
<tr>
<th>Treatments and studies</th>
<th>Treatment rate (n=2)</th>
<th>Control rate (n=2)</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin versus placebo</td>
<td>3/8</td>
<td>3/8</td>
<td>0.50 (0.27, 0.93)</td>
<td>0.50 (0.27, 0.93)</td>
</tr>
<tr>
<td>Metformin + CC versus CC</td>
<td>4/12</td>
<td>1/15</td>
<td>5.00 (0.49, 49.96)</td>
<td>9.00 (0.80, 111.86)</td>
</tr>
<tr>
<td>Totsal (95% CI)</td>
<td>52</td>
<td>55</td>
<td>6.44 (1.19, 34.90)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: CH^2 = 0.11, df = 1 (P = 0.74), I^2 = 0%</td>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin versus LOD</td>
<td>32/84</td>
<td>26/85</td>
<td>1.43 (1.08, 2.44)</td>
<td>1.63 (1.08, 2.44)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>55</td>
<td>1.43 (1.08, 2.44)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totsal events: 32 (Treatment), 20 (Control)</td>
<td>0.01</td>
<td>0.1</td>
<td>0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>Test for heterogeneity: CH^2 = 0.05, df = 3 (P = 0.82), I^2 = 0%</td>
<td>Test for overall effect: Z = 1.77 (P = 0.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 4.** Forest plots for clinical pregnancy rate and live birth rate in women treated with IVF.

<table>
<thead>
<tr>
<th>Outcomes and studies</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy per woman</td>
<td>12/25</td>
<td>20/81</td>
<td>3.79 (0.84, 18.82)</td>
<td>2.78 (0.46, 16.37)</td>
</tr>
<tr>
<td></td>
<td>20/81</td>
<td>2.78 (0.46, 16.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32/106</td>
<td>2.78 (0.46, 16.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>65 (Treatment): 43 (Control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity:</td>
<td>Ch ² = 8.33, df = 3 (P = 0.08), I² = 54.8%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>z = 0.05 (P = 0.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Live birth per woman</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17/51</td>
<td>23</td>
<td>1.06 (0.54, 2.09)</td>
<td>1.57 (0.92, 2.64)</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25/51</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity:</td>
<td>Ch ² = 0.02; df = 1 (P = 0.88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>z = 0.10 (P = 0.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>