The role of metformin in polycystic ovary syndrome: a systematic review

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This meta-analysis evaluated the effectiveness of metformin in subfertile women with polycystic ovary syndrome (PCOS). Only randomized 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 naïve women, we found no evidence of a difference in live birth rate when comparing metformin with clomifene citrate (CC) [relative risks (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 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 when adding metformin to LOD or FSH. In IVF, metformin leads to a reduced risk of OHSS.

Keywords: infertility; metformin; PCOS; pregnancy; review

Introduction

The polycystic ovary syndrome (PCOS) affects 5–10% of women of reproductive age (Asuncion et al., 2000). PCOS is characterized by oligo-anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries (Franks, 1995; Knochenhauer et al., 1998; Fauser, 2004). 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 (Achard and Thiers, 1921; Velazquez et al., 1994). 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 (De Leo et al., 2003; Lord et al., 2003a,b; Cheang and Nestler, 2004; Norman, 2004; Costello, 2005). 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 (Moll et al., 2006; Legro et al., 2007). 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 and Subfertility Group trials register, the Cochrane Central Register of Controlled Trials (both searched February 2007), MEDLINE (from 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 and 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 to 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 (Fauser, 2004). 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 randomized 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 randomized 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 naïve 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 (Mantel and Haenszel, 1959). If there was statistical heterogeneity, we performed a sensitivity analysis by pooling using a ‘random effects’-method (DerSimonian and Laird, 1986).

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 (Velazquez et al., 1994; Parsanezhad et al., 2001; Heard et al., 2002; Vribikova et al., 2002; Aruna et al., 2004; Kriplani and Agarwal, 2004; Weerakiet et al., 2004; Kumari et al., 2005; Qublan and Malkawi, 2005; Zafar, 2005), for not using randomization (Stadtmauer et al., 2001,2002; Zhao et al., 2003), for not providing clear information on live birth or clinical pregnancy rates (Nestler et al., 1998; Glueck et al., 1999; Moghetti et al., 2000; Loverro et al., 2002; Chou et al., 2003; Fedorcsak et al., 2003; Malkawi et al., 2003; Ramzy et al., 2003; Carmina and Lobo, 2004; Hoeger et al., 2004; Doldi et al., 2006; Eisenhardt et al., 2006; Turner et al., 2006), for using a cross-over design without clear rates of pregnancy before the cross-over (De Leo et al., 1999; Batukan and Baysal, 2001; Sturrock et al., 2002) or because of selection bias (Jakubowicz et al., 2001). 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) (Nestler and Jakubowicz, 1996).

By handsearching reference lists, we came across four articles we did not find in the initial search (El-Biely and Habba, 2001; Singh et al., 2001; Fleming et al., 2002; van Santbrink et al., 2005). In total, 27 studies were included in the analysis (Fig. 1).

Three studies compared metformin with placebo (Ng et al., 2001; Fleming et al., 2002; Tang et al., 2006a), two compared metformin with CC (Palomba et al., 2005a,b; Legro et al., 2007), 12 compared metformin plus CC with CC (El-Biely and Habba, 2001; Vandermolen et al., 2001; Singh et al., 2001; Kocak et al., 2002; Malkawi and Qublan, 2002; Sturrock et al., 2002; Sahin et al., 2004; Hwu et al., 2005; Raja et al., 2005; Moll et al., 2006; Khorram et al., 2006; Legro et al., 2007), one compared metformin with LOD (Palomba et al., 2004), one compared metformin plus LOD with LOD (Kocak and Ustun, 2006), one compared metformin plus CC with HMG (George et al., 2003), four compared metformin plus FSH with FSH (Yarali et al., 2002; Tasdemir et al., 2004; Palomba et al., 2005a,b; van Santbrink et al., 2005) and four compared metformin added in IVF versus IVF without metformin (Fedorcsak et al., 2003; Kjotrod et al., 2004; Onalan et al., 2005; Tang et al., 2006b).

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.
<table>
<thead>
<tr>
<th>Trial (n = number of randomised patients)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Main outcomes</th>
<th>Quality features</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Biely 2001 (n = 45 versus 45)</td>
<td>CC-naive; oligomenorrhoea + PCO ultrasound; Age: 26 versus 26; BMI: 29 versus 27</td>
<td>Metformin 500 mg; 3/day + CC 50–150 mg; 6 months</td>
<td>Placebo + CC 50–150 mg; 6 months</td>
<td>Ovulation; pregnancy; OHSS</td>
<td>Randomization with computer-generated blocks; single blinded</td>
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<tr>
<td>Fedorcsak et al. (2003) (n = 9 versus 8)</td>
<td>PCO ultrasound + 2 out of hyperandrogenism, hirsutism; Insulin resistance. Age and BMI: not available</td>
<td>Metformin 500 mg; 3/day + IVF/ICSI 5 weeks</td>
<td>IVF/ICSI; 5 weeks</td>
<td>Pregnancy</td>
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<tr>
<td>Fleming et al. (2002) (n = 45 versus 47)</td>
<td>CC-naive; oligomenorrhoea + PCO ultrasound; Age: 29 versus 29; BMI: 34 versus 35</td>
<td>Metformin 850 mg; 2/day 16 weeks</td>
<td>Placebo; 16 weeks</td>
<td>Ovulation</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>George et al. (2003) (n = 30 versus 30)</td>
<td>CC-resistant; oligomenorrhoea + hyperandrogenism + 1 out of PCO ultrasound, LH-FSH ratio &gt; 2; Age: 25 versus 26; BMI: 26 versus 26</td>
<td>Metformin 500 mg; 3/day + CC 150–200 mg; 6 months + 3 cycles (CC was started after 6 months treatment)</td>
<td>hMG, step-up; 3 cycles</td>
<td>Ovulation; pregnancy</td>
<td>Randomization with computer-generated blocks; not blinded</td>
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<tr>
<td>Hwu et al. (2005) (n = 40 versus 40)</td>
<td>CC-resistant; oligomenorrhoea + PCO ultrasound + hyperandrogenism; Age: 29 versus 28; BMI: 25 versus 24</td>
<td>Metformin 500 mg; 3/day + CC 150 mg; 1 cycle</td>
<td>CC 150 mg; 1 cycle</td>
<td>Ovulation; pregnancy</td>
<td>Randomization not clear; not blinded</td>
</tr>
<tr>
<td>Khorram et al. (2006) (n = 16 versus 15)</td>
<td>CC-naive; oligomenorrhoea + PCO ultrasound + hyperandrogenism + BMI&gt;29; Age: 28 versus 28; BMI: 35 versus 39</td>
<td>Metformin 500 mg; 3/day + CC 100 mg; 2 weeks</td>
<td>CC 100 mg; 2 weeks</td>
<td>Ovulation</td>
<td>Card out of box with treatment; not blinded</td>
</tr>
<tr>
<td>Kjotrod et al. (2004) (n = 37 versus 36)</td>
<td>Mixed fertility problems; oligomenorrhoea + PCO ultrasound + testosterone &gt; 2 nmol/l + one of LH-FSH ratio &gt; 2, hirsutism, SHBG &lt; 30 nmol/l, baseline insulin &gt; 1 nmol/l; Age: 29 versus 30; BMI: stratified &lt; or ≥ 28</td>
<td>Metformin 1000 mg; 2/day + IVF/ICSI treatment 16 weeks</td>
<td>Placebo + IVF/ICSI; 16 weeks</td>
<td>Pregnancy; live birth; OHSS</td>
<td>Randomization with pharmacy-generated blocks; double blinded</td>
</tr>
<tr>
<td>Kocak and Ustan (2006) (n = 21 versus 21)</td>
<td>CC-failure; 3 or more of: oligomenorrhoea, PCO ultrasound, hyperandrogenism, anovulation, infertility, hirsutism, obesity; Age: 27 versus 28; BMI: 27 versus 32</td>
<td>LOD + Metformin 850 mg; 2/day 6 months</td>
<td>LOD; 6 months</td>
<td>Ovulation; pregnancy</td>
<td>Randomization not clear; not blinded</td>
</tr>
<tr>
<td>Kocak et al. (2002) (n = 28 versus 28)</td>
<td>CC-resistant; oligomenorrhoea + 1 or more of PCO ultrasound, hyperandrogenism; Age: 26 versus 27; BMI: 32 versus 31</td>
<td>Metformin 850 mg; 2/day + CC 100 mg; 2 cycles (CC was added if no ovulation after 1 cycle)</td>
<td>Placebo 850 mg bid + CC 100 mg; 2 cycles (CC was added if no ovulation after 1 cycle)</td>
<td>Ovulation; pregnancy</td>
<td>Sealed envelopes; double blinded</td>
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<tr>
<td>Legro et al. (2007) (n = 208 versus 209 versus 209)</td>
<td>CC-naive/~50% used CC or metformin or combination prior to study; oligomenorrhoea + elevated testosterone; Age: 28 versus 28; BMI: 36 versus 36</td>
<td>Metformin 1000 mg; 2/day + placebo; 30 weeks</td>
<td>Placebo + CC 50–150 mg; 30 weeks. Third group: Metformin 1000 mg bid + CC 50–150 mg</td>
<td>Live birth</td>
<td>Interactive voice system; stratified based on study site and previous exposure to either of the study drugs; double blinded</td>
</tr>
<tr>
<td>Malkawi and Qublan (2002) (n = 16 versus 12)</td>
<td>CC-resistant or failure; PCO ultrasound + 3 or more of oligomenorrhoea, hyperandrogenism, LH-FSH ratio &gt; 2, elevated LH, Ferriman–Gallwey score &gt; 7; Age: 29 versus 29; BMI: 28 versus 28</td>
<td>Metformin 850 mg; 2/day + CC 50–200 mg; 6 cycles</td>
<td>Placebo + CC 50–200 mg; 6 cycles</td>
<td>Ovulation; pregnancy</td>
<td>Centralized randomization process; double blinded</td>
</tr>
<tr>
<td>Moll (2006) (n = 111 versus 114)</td>
<td>CC-naive; definition conform ESHRE 2003; Age: 28 versus 28; BMI: 29 versus 28</td>
<td>Metformin 500 mg; 4/day + CC 50–150 mg; 6 cycles</td>
<td>Placebo + CC 50–150 mg; 6 cycles</td>
<td>Ovulation; pregnancy</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Ng et al. (2001) (n = 9 versus 9)</td>
<td>CC-resistant; PCO ultrasound; Age: 31 versus 32; BMI: 24 versus 24</td>
<td>Metformin 500 mg; 3/day + CC 100 mg; 3 months and 1 cycle (CC was added if no ovulation after 3 months)</td>
<td>Placebo 500 mg; 3/day + CC 100 mg; 3 months and 1 cycle (CC was added if no ovulation after 3 months)</td>
<td>Ovulation</td>
<td>Randomization with computer-generated list in envelopes; double blinded</td>
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Table 1: Continued

<table>
<thead>
<tr>
<th>Trial (n = number of randomised patients)</th>
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<th>Comparison</th>
<th>Main outcomes</th>
<th>Quality features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onalan et al. (2005) (n = 53 versus 55)</td>
<td>Last fertility treatment; oligomenorrhea + hyperandrogenism; Age: 29 versus 30; BMI: 25 versus 24</td>
<td>Metformin 850 mg; 2–3/ day (depending on BMI &lt; or ≥ 28) + IVF/ICSI treatment 12 weeks</td>
<td>Placebo + IVF/ICSI treatment; 12 weeks</td>
<td>Pregnancy; abortion; OHSS</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Palomba et al. (2004) (n = 54 versus 55)</td>
<td>CC-resistant; oligomenorrhea + elevated testosterone; Age: 27 versus 28; BMI: 28 versus 28</td>
<td>Diagnostic laparoscopy + Metformin 850 mg; 2/ day 6 months Metformin 850 mg; 2/ day + placebo; 6 months</td>
<td>LOD + placebo; 6 months</td>
<td>Pregnancy; OHSS</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Palomba et al. (2005a) (n = 50 versus 50)</td>
<td>CC-naïve; oligomenorrhea + elevated testosterone; Age: 26 versus 26; BMI: 27 versus 27</td>
<td>Metformin 850 mg; 2/ day + FSH step up; 3 months + 3 cycles (FSH was started after 8 weeks treatment)</td>
<td>Placebo + CC 150 mg; 6 months</td>
<td>Pregnancy; OHSS</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Palomba et al. (2005b) (n = 35 versus 35)</td>
<td>CC-resistant; oligomenorrhea + elevated testosterone; Age: 26 versus 27; BMI: 27 versus 26</td>
<td>Metformin 500 mg; 3/ day + CC 50 mg; 6 cycles</td>
<td>Placebo + FSH step up; 3 months + 3 cycles (FSH was started after 8 weeks treatment)</td>
<td>Pregnancy; OHSS</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Raja et al. (2005) (n = 50 versus 50)</td>
<td>CC-naïve; PCO ultrasound + 2 or more of: oligomenorrhea, hyperandrogenism, LH-FSH ratio &gt; 2, hirsutism, elevated LH; Age: 27 versus 27; BMI: not available</td>
<td>Metformin 850 mg; 2/ day + CC 100 mg; 3 months</td>
<td>CC 50 mg; 6 cycles</td>
<td>Pregnancy; OHSS</td>
<td>Randomization not clear; not blinded</td>
</tr>
<tr>
<td>Sahin et al. (2004) (n = 11 versus 10)</td>
<td>CC-naïve; 3 or more of oligomenorrhea, PCO ultrasound, hyperandrogenism, LH-FSH ratio &gt; 2, hirsutism; Age: 27 versus 25; BMI: 30 versus 26</td>
<td>Metformin 850 mg; 2/ day + CC 50 mg; 4 months</td>
<td>CC 50 mg; 4 months</td>
<td>Pregnancy</td>
<td>Randomization not clear; presumed not blinded. Only abstract available</td>
</tr>
<tr>
<td>Singh et al. (2001) (n = 53 versus 47)</td>
<td>CC-naïve; oligomenorrhea + PCO ultrasound + LH-FSH ratio &gt; 2; Age: 26 versus 28; BMI: not available</td>
<td>Metformin 500 mg; 3/ day + CC 50–150 mg; 3 months + 3 cycles</td>
<td>Placebo + CC 50–150 mg; 3 months + 3 cycles</td>
<td>Pregnancy; OHSS</td>
<td>Randomization performed by pharmacy; cross-over (only data before cross-over are used); double blinded</td>
</tr>
<tr>
<td>Sturrock et al. (2002) (n = 54 versus 55)</td>
<td>CC-resistant; oligomenorrhea; Age: 29 versus 31; BMI: 34 versus 35</td>
<td>Metformin 500 mg; 2/ day + IVF/ICSI treatment 28 days</td>
<td>Placebo + IVF/ICSI treatment; 28 days</td>
<td>Pregnancy; live birth; OHSS</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Tang et al. (2006a) (n = 56 versus 66)</td>
<td>CC-naïve; oligomenorrhea + PCO ultrasound + BMI &gt; 30; Age: 30 versus 30; BMI: 38 versus 39</td>
<td>Metformin 850 mg; 2/ day 6 months</td>
<td>Placebo; 6 months</td>
<td>Pregnancy</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Tang et al. (2006b) (n = 51 versus 47); 4 patients entered twice</td>
<td>Definition conform ESHRE 2003; Age: 31 versus 31; BMI: 28 versus 27</td>
<td>Metformin 850 mg; 2/ day + IVF/ICSI treatment 28 days</td>
<td>Placebo + IVF/ICSI treatment; 28 days</td>
<td>Pregnancy</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Tasdemir et al. (2004) (n = 16 versus 16)</td>
<td>CC-resistant; oligomenorrhea + PCO ultrasound + hyperandrogenism; Age: 32 versus 31; BMI: 29 versus 29</td>
<td>Metformin 850 mg; 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>
<td>Randomization not clear; not blinded</td>
</tr>
<tr>
<td>van Santbrink et al. (2005) (n = 11 versus 7)</td>
<td>CC-resistant or CC-failure; oligomenorrhea + insulin resistance; Age: 28 versus 28; BMI: 38 versus 34</td>
<td>Metformin 850 mg; 2/ day + FSH step-up; 35 days and 1 cycle (FSH was added if no ovulation after 35 days)</td>
<td>Placebo 850 mg; bid + FSH step-up; 35 days and 1 cycle (FSH was added if no ovulation after 35 days)</td>
<td>Ovarian response</td>
<td>Sealed envelopes; double blinded</td>
</tr>
<tr>
<td>Vandermolen et al. (2001) (n = 12 versus 15)</td>
<td>CC-resistant; oligomenorrhea + hyperandrogenism; Age: 29 versus 30; BMI: 38 versus 38</td>
<td>Metformin 500 mg; 3/ day + CC 50–150 mg; 6 weeks and 6 cycles (CC was added if no ovulation after 6 weeks)</td>
<td>Placebo + CC 50–150 mg; 6 weeks and 6 cycles (CC was added if no ovulation after 6 weeks)</td>
<td>Ovarian response</td>
<td>Randomization with computer-generated blocks; double blinded</td>
</tr>
<tr>
<td>Yarali et al. (2002) (n = 16 versus 16)</td>
<td>CC-resistant; oligomenorrhea + PCO ultrasound + testosterone ≥ 2.4 nmol/l; Age: 30 versus 28; BMI: 29 versus 30</td>
<td>Metformin 850 mg; 2/ day + FSH step-up; 6 weeks and 1 cycle (FSH was added if no ovulation after 6 weeks)</td>
<td>Placebo 850 mg; 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>
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</table>
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/m$^2$. Two studies included women with BMI $<30$ and $<35$ kg/m$^2$, respectively. Two studies included women with BMI $>29$ and 30 kg/m$^2$, respectively.

**Metformin in CC naïve women**

**Metformin monotherapy**

We retrieved two randomized controlled trials in which metformin was compared with placebo for as first-line treatment in 185 therapy naïve infertile women with PCOS (Table 1) (Fleming et al., 2002; Tang et al., 2006a). 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 $I^2$ 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 (Tang et al., 2006a). The median weight loss was 2.8 versus 1.5%.

We found two double-blinded randomized controlled trials in which metformin was directly compared with CC as first-line treatment in 509 infertile women with PCOS (Table 1) (Palomba et al., 2005a,b; Legro et al., 2007). 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 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 (Moll et al., 2006; Legro et al., 2007). After combining these data no significant difference was seen (RR 0.38; 95% CI 0.09–1.5; 193 women).

**Metformin in CC-resistant women**

**Metformin monotherapy**

We retrieved one randomized clinical trial in which metformin was compared with placebo in 18 infertile women with CC-resistant PCOS (Table 1) (Ng et al., 2001). In this small number of women there was no evidence of a difference in multiple pregnancy rate between the two groups (RR 0.38; 95% CI 0.02–7.1).

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

Seven randomized controlled trials compared CC plus metformin with CC in 985 infertile women with PCOS (Table 1) (El-Biely and Habba, 2001; Singh et al., 2001; Sahin et al., 2004; Raja et al., 2005; Khorram et al., 2006; Moll et al., 2006; Legro et al., 2007). Two studies used HCG to trigger ovulation (El-Biely and Habba, 2001; Sahin et al., 2004). 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.

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**Metformin in CC-naïve women**

**Metformin monotherapy**

We retrieved two randomized controlled trials in which metformin was compared with placebo for as first-line treatment in 185 therapy naïve infertile women with PCOS (Table 1) (Fleming et al., 2002; Tang et al., 2006a). 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 $I^2$ 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 (Tang et al., 2006a). The median weight loss was 2.8 versus 1.5%.

We found two double-blinded randomized controlled trials in which metformin was directly compared with CC as first-line treatment in 509 infertile women with PCOS (Table 1) (Palomba et al., 2005a,b; Legro et al., 2007). 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 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 (Moll et al., 2006; Legro et al., 2007). After combining these data no significant difference was seen (RR 0.38; 95% CI 0.09–1.5; 193 women).

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

We retrieved five randomized controlled trials in which CC plus metformin was compared with CC alone in 210 infertile women with CC-resistant PCOS (Table 1) (Vandermolen et al., 2001;...
...and Hwu et al., 2005). Two trials used HCG to trigger ovulation (Kocak et al., 2002; Hwu et al., 2005).

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 (Vandermolen et al., 2001).

**Metformin as opposed to LOD**

Only one randomized trial was retrieved in which metformin treatment was compared with LOD (Table 1) (Palomba et al., 2004). There was no evidence of a difference in clinical pregnancy rate...
### Role of metformin in PCOS

#### A. Clinical pregnancy rate in clomifene citrate resistant women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>RR (fixed) 95% CI</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin versus placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 1</td>
<td>N = 1</td>
<td>0.50 (0.05, 4.58)</td>
<td>0.50 (0.05, 4.58)</td>
</tr>
<tr>
<td>Total events: 2 (Treatment), 2 (Control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.81 (P = 0.54)</td>
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</tr>
<tr>
<td>Metformin versus lopinopirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 6</td>
<td>N = 6</td>
<td>7.25 (0.94, 56.12)</td>
<td>7.25 (0.94, 56.12)</td>
</tr>
<tr>
<td>Total events: 5 (Treatment), 9 (Control)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.17 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metformin versus LOD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 3</td>
<td>N = 3</td>
<td>1.25 (0.80, 2.04)</td>
<td>1.25 (0.80, 2.04)</td>
</tr>
<tr>
<td>Total events: 6 (Treatment), 9 (Control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.85 (P = 0.0002)</td>
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</tbody>
</table>

#### B. Live birth rate in clomifene citrate resistant women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>RR (fixed) 95% CI</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin versus placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 1</td>
<td>N = 1</td>
<td>0.50 (0.05, 4.58)</td>
<td>0.50 (0.05, 4.58)</td>
</tr>
<tr>
<td>Total events: 1 (Treatment), 1 (Control)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.81 (P = 0.54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin versus CC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 4</td>
<td>N = 4</td>
<td>5.00 (0.64, 39.66)</td>
<td>5.00 (0.64, 39.66)</td>
</tr>
<tr>
<td>Total events: 4 (Treatment), 4 (Control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.82 (P = 0.07)</td>
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<td></td>
</tr>
<tr>
<td>Metformin versus LOD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 2</td>
<td>N = 2</td>
<td>0.40 (0.57, 2.14)</td>
<td>0.40 (0.57, 2.14)</td>
</tr>
<tr>
<td>Total events: 4 (Treatment), 4 (Control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.70 (P = 0.04)</td>
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</tbody>
</table>

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**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

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(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 randomized 42 PCOS patients between LOD followed by metformin or LOD alone (Table 1) (Kocak and Ustun, 2006). 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 b).

**Metformin plus CC compared with gonadotrophins**

In one randomized clinical trial, metformin plus CC was compared with gonadotrophins in 60 CC-resistant women (Table 1) (George et al., 2003). 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) (Yarali et al., 2002; Tasdemir et al., 2004; Palomba et al., 2005a,b; van Santbrink et al., 2005). 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) (Fedorcsak et al., 2003; Kjotrod et al., 2004; Onalan et al., 2005; Tang et al., 2006b). 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 (Harborne et al., 2003; Kashyap et al., 2004; Norman, 2004; Saleh and Khalil, 2004; Checa et al., 2005; Costello et al., 2006). From the placebo controlled trials performed in infertile women with
therapy naı"ve 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 naı"ve women or whether it has additional benefit in terms of live birth when used as co-treatment in therapy naı"ve or CC-resistant women.

At present, there is no evidence of a difference between metformin and CC in therapy naı"ve women in favour of metformin. The two trials that studied this comparison had conflicting results. In the study by Palomba et al. (2005a,b), the live birth rate was three times higher in the metformin group. In contrast, in the study by Legro et al. (2007) 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 naı"ve women.

The clinical pregnancy rate in the comparison metformin plus CC versus CC in therapy naı"ve women 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 (Poole and Greenland, 1999; Kjaergard et al., 2001). 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 until 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 naı"ve 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.

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