A systematic review and meta-analysis of randomized controlled trials on metformin co-administration during gonadotrophin ovulation induction or IVF in women with polycystic ovary syndrome

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BACKGROUND: A systematic review of randomized controlled trials (RCTs) comparing whether metformin co-administration with gonadotrophins for ovulation induction (OI) with timed intercourse or IVF improves outcome in women with polycystic ovary syndrome (PCOS). METHODS: The quality of reporting of meta-analyses (QUOROM) guidelines were followed. A systematic computerized literature search of three bibliographic databases was performed. RESULTS: Eight RCTs were included in the overall review. Meta-analysis demonstrated that the co-administration of metformin to gonadotrophin OI does not significantly improve ovulation (odds ratio (OR) = 3.27; 95% confidence interval (95% CI) = 0.31–34.72) or pregnancy (OR = 3.46; 95% CI = 0.98–12.2) rates. Metformin co-administration to IVF treatment does not improve pregnancy (OR = 1.29; 95% CI = 0.84–1.98) or live birth (OR = 2.02, 95% CI = 0.98–4.14) rates but reduces the risk of ovarian hyperstimulation syndrome (OHSS) (OR = 0.21; 95% CI = 0.11–0.41, \( P < 0.00001 \)). CONCLUSIONS: Current data on the use of metformin in the gonadotrophin OI or IVF treatment settings are inconclusive because of the review’s failure to exclude an important clinical treatment effect. Further RCTs are necessary to definitively clarify whether metformin co-administration during gonadotrophin OI or IVF will improve the efficacy of these treatments in PCOS women.

Key words: FSH/gonadotrophins/IVF/metformin/ovulation induction/polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is characterized by chronic anovulation and hyperandrogenism and affects approximately 5–10% of women of reproductive age (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999). PCOS is probably the most prevalent endocrinopathy in women and by far the most common cause of anovulatory infertility (Homburg, 1996).

The primary aetiology of PCOS is unknown (Balen, 2004). However, insulin resistance with compensatory hyperinsulinaemia is a prominent feature of the syndrome and appears to have a pathophysiologic role in the hyperandrogenism of the disorder for both lean and obese women with PCOS (Dunaif et al., 1989). Hyperinsulinaemia results in increased ovarian androgen biosynthesis in vivo and in vitro (Adashi et al., 1985; Barbieri et al., 1986) and decreased sex hormone-binding globulin (SHBG) synthesis from the liver (Nestler et al., 1991), leading to increased bioavailability of free androgens.

Women with PCOS who are anovulatory and wishing to become pregnant have traditionally been treated with the anti-estrogen clomiphene citrate as first-line medical therapy to induce ovulation. Ovulation induction (OI) with gonadotrophin therapy usually follows for those women who fail to either ovulate or conceive with a course of clomiphene citrate treatment (Balen, 1998). IVF is an effective therapy for PCOS patients who are refractory to OI or who have co-existing infertility factors (Buyalos and Lee, 1996).

The association of insulin resistance contributing to anovulation has led to the novel and promising therapy of administering insulin-sensitizing drugs to women with PCOS to restore ovulation and enhance pregnancy. Of the insulin-sensitizing drugs, metformin has been the one studied most widely and has the most reassuring safety profile (Nestler et al., 2002). Metformin enhances insulin sensitivity in both the liver, where it inhibits hepatic glucose production, and the peripheral tissue, where it increases glucose uptake and utilization into muscle tissue. By increasing insulin sensitivity, metformin reduces insulin resistance, insulin secretion and hyperinsulinaemia (Dunn and Peters, 1995).
Patients with PCOS undergoing gonadotrophin OI or IVF usually show an increased response to gonadotrophins and consequently produce large numbers of follicles and oocytes with high serum estradiol (E2) levels, resulting in an increased risk of ovarian hyperstimulation syndrome (OHSS) (Aboulghar and Mansour, 2003; Anonymous, 2003; Yarali and Zeyneloglu, 2004). PCOS women with insulin resistance undergoing gonadotrophin OI have a longer duration of treatment, use a higher total FSH dose, have an elevated cancellation rate and a lower conception rate (Dale et al., 1998). On the other hand, insulin resistance in PCOS women undergoing IVF has been not been shown to be independently related to IVF outcome (Fedorcsak et al., 2001).

There is physiologic rationale for believing that suppression of insulin levels, with insulin-sensitizing agents such as metformin, in women with PCOS undergoing gonadotrophin OI or IVF might ameliorate the adverse effects on ovarian stimulation and consequently improve treatment outcomes such as ovulation and pregnancy rates (Dunaif et al., 1989). In addition, metformin may also act directly on ovarian thecal cells to decrease androgen production (Attia et al., 2001).

Three recent systematic reviews have demonstrated that metformin co-administration with clomiphene citrate OI improves both ovulation and pregnancy rates in both unselected and clomiphene citrate-resistant PCOS women (Costello and Eden, 2003; Lord et al., 2003, 2004; Kashyp et al., 2004). Our previous systematic review analysed both observational studies and randomized controlled trials (RCTs) and located only two published studies (both RCTs) on the use of metformin in FSH OI, and no meta-analysis was performed. In addition, only a single observational study was identified assessing the effect of co-administering metformin during IVF treatment of PCOS patients (Costello and Eden, 2003). The systematic reviews and meta-analyses of RCTs by Lord et al. (2003, 2004) and Kashyp et al. (2004) did not evaluate the effect of metformin co-administration with either FSH OI or IVF.

The objective of this review was to investigate the effectiveness of metformin used in combination with gonadotrophins for OI or IVF in restoring ovulation and achieving pregnancy and live birth in women with PCOS.

Materials and methods

The electronic search strategy involved conducting a literature search for all pertinent published RCTs on the use of metformin in combination with gonadotrophins for OI with timed intercourse or IVF for restoring ovulation and achieving pregnancy and live birth in women with PCOS using the Cochrane central register of controlled trials (Cochrane Library, 3rd Quarter, 2005) and the bibliographic databases MEDLINE (January 1966 to August 2005) and EMBASE (January 1980 to August 2005). References of selected articles identified were hand-searched for additional relevant citations. Experts and specialists in the field were also contacted for additional relevant studies. There was no restriction on the language of publication (Moher et al., 2000; Juni et al., 2002). Only RCTs were considered as these studies generally provide the least biased estimates of treatment effect and are therefore more suitable for meta-analysis (Hughes, 1996).


Inclusion criteria for selecting RCTs were based on patient population (PCOS), treatment intervention versus comparison (metformin and gonadotrophin OI with timed intercourse versus gonadotrophin OI with timed intercourse and no treatment or placebo, metformin and IVF versus IVF and no treatment or placebo) and primary (restoration of ovulation, pregnancy and live birth) and secondary (ovarian response and OHSS) outcomes of interest. There were no restrictions on the language of publication. Only parallel-group designed trials or pre-crossover data from crossover trials were included because crossover trials may exaggerate estimates of effectiveness when compared to parallel-group designed trials (Khan et al., 1996).

The methodological standards of all studies were assessed according to standards most likely to provide valid results (Guyatt et al., 1993). Down-weighting of studies of doubtful quality for the purpose of meta-analysis was not performed because of such weighting being too arbitrary, even though quality criteria have been published (Chalmers et al., 1981; Thompson and Pocock, 1991). In addition, the incorporation of such weighting by quality scores lacks statistical or empirical justification (Detsky et al., 1992; Juni et al., 2001). The analysis of individual components of trial quality overcomes many of the shortcomings of composite scores (Juni et al., 2001). Institutional review board approval was not sought for this systematic review because only previously published data were used.

Statistical analysis

Statistical analysis was performed using RevMan 4.2 software provided by the Cochrane Collaboration. For dichotomous data, results for each study were expressed as odds ratios (OR) with 95% confidence intervals (95% CIs) and combined for meta-analysis to calculate a pooled estimate of treatment effect for each outcome across studies. For continuous data, the mean post-treatment/intervention values and standard deviation for each group were measured, and weighted mean differences (WMD) with 95% CI were calculated.

The combined results of each study for meta-analysis and statistical homogeneity between trials were assessed using the fixed-effects model where Cochran Q-test (chi-squared test) $P \geq 0.05$ represents statistical homogeneity. The random-effects model of meta-analysis was used in the presence of unexplained statistical heterogeneity. $P$ values $<0.05$ or 95% CI not containing 1.00 (OR) or 0 (WMD) were considered statistically significant.

Results

Trial flow

Eight RCTs that met the inclusion criteria were identified and thus consulted in the review (De Leo et al., 1999; Yarali et al., 2002; Fedorcsak et al., 2003; Visnova et al., 2003; Kjettrud et al., 2004; Tasdemir et al., 2004; Onalan et al., 2005; Tang et al., 2005) (Figure 1). All the eight RCTs were included in the review.

Study characteristics and validity assessment

Tables I and II summarize the characteristics of the included RCTs evaluating the effectiveness of metformin co-administration with gonadotrophin OI and IVF, respectively, in women with PCOS. Only one of the eight RCTs completely fulfilled the
Pregnancy. Figure 3 demonstrates the forest (or CI) plot of RCTs reporting on pregnancy rate as an outcome measure. No improvement in pregnancy rates was seen in any of the individual trials or meta-analysis. However, the meta-analysis demonstrated a trend towards an improvement in pregnancy rates with metformin co-administration (28 versus 10%; OR = 3.46, \( P = 0.05, 95\% \ CI = 0.98–12.2 \)).

Live birth. There were no trials identified comparing metformin combined with gonadotrophin OI versus gonadotrophin OI and placebo or no treatment reporting live birth as an outcome measure (Table I).

Secondary outcomes

Length of ovarian stimulation. Figure 4 demonstrates the forest plot of RCTs reporting on the length of ovarian stimulation as an outcome measure. The meta-analysis of the two RCTs shows that metformin significantly reduces the length of ovarian stimulation at gonadotrophin OI (WMD = –41.14 days, \( P = 0.0002, 95\% \ CI = –6.36 \) to –1.93).

Total FSH dose. The co-administration of metformin with gonadotrophin OI significantly decreases the total dose of FSH used during the treatment cycle (WMD = –425.05 IU, \( P < 0.00001, 95\% \ CI = –507.08 \) to –343.03) (Figure 5).

Serum E2 level on the day of HCG trigger. Metformin significantly reduces the serum E2 level on the day of HCG trigger (WMD = –1.24 nmol/l, \( P < 0.00001, 95\% \ CI = –1.5 \) to –0.98) (Figure 6).

OHSS. There were no RCTs identified comparing metformin combined with gonadotrophin OI versus gonadotrophin OI and placebo or no treatment reporting on the outcome measure of OHSS.

**Meta-analysis results**

**Metformin and gonadotrophin OI versus gonadotrophin OI and placebo or no treatment**

**Primary outcomes**

**Ovulation.** A single RCT was identified assessing the effect on ovulation of metformin co-administration with gonadotrophin OI in PCOS (Table I). This trial by Yarali et al. (2002) demonstrated that metformin did not improve the ovulation rate in clomiphene citrate-resistant PCOS women undergoing gonadotrophin OI (Figure 2).

**Secondary outcomes**

**Length of ovarian stimulation.** The addition of metformin to IVF treatment has no effect on the length of ovarian stimulation (WMD = –0.09 days, \( P = 0.66, 95\% \ CI = –0.49 \) to –0.31) (Figure 9).
### Table I. Characteristics of published RCTs on the effect of metformin combined with gonadotrophin OI versus gonadotrophin alone OI in women with PCOS

<table>
<thead>
<tr>
<th>Reference and location</th>
<th>RCT type</th>
<th>Method of randomization (allocation concealment)</th>
<th>Outcomes reported</th>
<th>Infertility factor testing</th>
<th>Prior clomiphene citrate exposure</th>
<th>Prior Gn OI</th>
<th>n</th>
<th>Age (years)</th>
<th>Duration of infertility (years)</th>
<th>BMI</th>
<th>FI</th>
<th>Intervention</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Leo et al. (1999), Italy</td>
<td>RCT</td>
<td>Random numbers table (NA)</td>
<td>Pregnancy</td>
<td>Exclusion of male factor</td>
<td>Resistant</td>
<td>NA</td>
<td>20</td>
<td>28.8</td>
<td>5.4</td>
<td>27.3</td>
<td>NA</td>
<td>M 500 mg three times daily + Gn OI for one cycle (M terminated on day of HCG trigger)</td>
<td>Gn OI for one cycle</td>
</tr>
<tr>
<td>Yarali et al. (2002), Turkey</td>
<td>DBPC</td>
<td>Computer-generated numbers (NA)</td>
<td>Ovulation</td>
<td>Exclusion of male and tubal uterine factors</td>
<td>Resistant</td>
<td>No</td>
<td>32</td>
<td>29.1</td>
<td>5.0</td>
<td>29.1</td>
<td>11</td>
<td>M 850 mg twice daily + Gn OI for one cycle (M terminated on day of HCG trigger)</td>
<td>P twice daily + Gn OI for one cycle</td>
</tr>
<tr>
<td>Tasdemir et al. (2004), Turkey</td>
<td>RCT</td>
<td>NA</td>
<td>Pregnancy</td>
<td>Exclusion of male and tubal uterine factors</td>
<td>Resistant</td>
<td>NA</td>
<td>32</td>
<td>31.2</td>
<td>3.5</td>
<td>28.7</td>
<td>14.5</td>
<td>M 850 mg twice daily + Gn OI for one cycle (M terminated on day of pregnancy test)</td>
<td>Gn OI for one cycle</td>
</tr>
</tbody>
</table>

BMI, mean body mass index (kg/m²); DB, double blind; FI, mean fasting insulin (mU/l); Gn, gonadotrophin; M, metformin; NA, not available; OI, ovulation induction; P, placebo; PC, placebo controlled; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial.

*aDiagnosis of PCOS meets The Rotterdam Consensus Group 2003 criteria (Fauser et al., 2004).*
<table>
<thead>
<tr>
<th>Reference and location</th>
<th>RCT type</th>
<th>Method of randomization (allocation concealment)</th>
<th>Outcomes reported</th>
<th>Other infertility factor present</th>
<th>Prior IVF or ICSI treatment</th>
<th>n</th>
<th>Age (years)</th>
<th>Duration of infertility (years)</th>
<th>BMI</th>
<th>FI</th>
<th>Intervention</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fedorcsak et al. (2003), Norway</td>
<td>RCT</td>
<td>Random numbers table (yes)</td>
<td>Pregnancy Ovarian response OHSS</td>
<td>NA</td>
<td>NA</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.0</td>
<td>NA</td>
<td>31.5</td>
<td>26.5</td>
<td>M 500 mg three times daily starting 3 weeks before down-regulation with GnRHa began and continued throughout ovarian stimulation for one cycle of IVF or ICSI. M stopped on day of HCG trigger</td>
<td>Down-regulation with GnRHa followed by ovarian stimulation for one cycle of IVF or ICSI. All women were insulin resistant. This trial was a crossover trial and only pre-crossover data were considered. Gn = rFSH. Embryo transfer day 3. Intention-to-treat analysis</td>
</tr>
<tr>
<td>Visnova et al. (2003), Czech Republic</td>
<td>RCT</td>
<td>NA</td>
<td>Pregnancy Ovarian response OHSS</td>
<td>Yes (n = NA)</td>
<td>137</td>
<td>28.7</td>
<td>NA</td>
<td>23.5</td>
<td>NA</td>
<td>M 500 mg twice daily starting with FSH injections during long down-regulation protocol with GnRHa and continued throughout ovarian stimulation for one cycle of IVF. M stopped at diagnosis of pregnancy</td>
<td>Down-regulation with GnRHa followed by ovarian stimulation for one cycle of IVF</td>
<td>Gn = rFSH or highly purified uFSH. IVF or ICSI NA. Day of embryo transfer NA. Per protocol analysis</td>
</tr>
<tr>
<td>Kjotrod et al. (2004), Norway</td>
<td>DBPC</td>
<td>NA</td>
<td>Pregnancy Live birth Ovarian response OHSS</td>
<td>Tubal (n = 12), endometriosis (n = 3), male factor (n = 22)</td>
<td>NA</td>
<td>73&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.6</td>
<td>4.1</td>
<td>29.2</td>
<td>NA</td>
<td>M 1g twice daily for 16 weeks before down-regulation with GnRHa and continued throughout ovarian stimulation for one cycle of IVF or ICSI. M stopped on day of HCG trigger</td>
<td>Down-regulation with GnRHa and continued throughout ovarian stimulation for one cycle of IVF or ICSI. P stopped on day of HCG trigger</td>
</tr>
</tbody>
</table>
### Table II. Continued

<table>
<thead>
<tr>
<th>Reference and location</th>
<th>RCT type</th>
<th>Method of randomization (allocation concealment)</th>
<th>Outcomes reported</th>
<th>Other infertility factor present</th>
<th>Prior IVF or ICSI treatment</th>
<th>n</th>
<th>Age (years)</th>
<th>Duration of infertility (years)</th>
<th>BMI</th>
<th>FI</th>
<th>Intervention</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang <em>et al.</em> (2005), United Kingdom</td>
<td>DBPC</td>
<td>Random numbers table (yes)</td>
<td>Pregnancy Live birth Ovarian response OHSS</td>
<td>Tubal (n = 11), endometriosis (n = 5), male (n = 50)</td>
<td>Yes (n = 58)</td>
<td>101</td>
<td>31.2</td>
<td>4.25</td>
<td>27.3</td>
<td>7.1</td>
<td>M 850 mg twice daily starting at down-regulation with GnRHa and continued throughout ovarian stimulation for one cycle of IVF or ICSI. M stopped on day of egg collection</td>
<td>Published in abstract format only. Gn = rFSH. Embryo transfer day 2. Intention-to-treat analysis. Additional information to that contained in the abstract acquired through personal communication</td>
</tr>
<tr>
<td>Onalan <em>et al.</em> (2005), Turkey</td>
<td>DBPC</td>
<td>Computer generated (yes)</td>
<td>Pregnancy Ovarian response OHSS</td>
<td>No</td>
<td>No</td>
<td>110</td>
<td>29.5 (all &lt;40)</td>
<td>7.9</td>
<td>24.8</td>
<td>15.2</td>
<td>M 850 mg twice daily (BMI &lt; 28 kg/m²) or three times daily (BMI ≥ 28 kg/m²) for 8 weeks before down-regulation with GnRHa and continued throughout ovarian stimulation for one cycle of ICSI. M stopped on day of pregnancy test</td>
<td>P twice daily (BMI &lt; 28 kg/m²) or three times daily (BMI ≥ 28 kg/m²) for 8 weeks before down-regulation with GnRHa and continued throughout ovarian stimulation for one cycle of ICSI. M stopped on day of pregnancy test</td>
</tr>
</tbody>
</table>

BMI, mean body mass index (kg/m²); DB, double blind; FI, mean fasting insulin (mU/l); Gn, gonadotrophin; M, metformin; NA, not available; OHSS, ovarian hyperstimulation syndrome; P, placebo; PC, placebo controlled; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; rFSH, recombinant FSH; uFSH, urinary FSH.

*Diagnosis of PCOS meets The Rotterdam Consensus Group 2003 criteria (Fauser *et al.*, 2004).
**Review:** Metformin and Gonadotrophins in PCOS

**Comparison:** 01 Metformin versus placebo or no treatment (Gonadotropin OI)

**Outcome:** 01 Ovulation rate

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Metformin</th>
<th>Control</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yarali 2002</td>
<td>9/10</td>
<td>11/15</td>
<td></td>
<td>100.00</td>
<td>3.27 [0.31, 34.72]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10</td>
<td>15</td>
<td></td>
<td>100.00</td>
<td>3.27 [0.31, 34.72]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

**Figure 2.** Comparison of metformin versus placebo or no treatment in gonadotrophin ovulation induction (OI) with outcome of ovulation rate.

**Review:** Metformin and Gonadotrophins in PCOS

**Comparison:** 01 Metformin versus placebo or no treatment (Gonadotropin OI)

**Outcome:** 02 Pregnancy rate

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Metformin</th>
<th>Control</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Lao 1999</td>
<td>3/10</td>
<td>1/10</td>
<td></td>
<td>25.36</td>
<td>3.86 [0.33, 45.57]</td>
</tr>
<tr>
<td>Yarali 2002</td>
<td>3/10</td>
<td>1/15</td>
<td></td>
<td>20.29</td>
<td>6.09 [0.52, 68.72]</td>
</tr>
<tr>
<td>Tasdemir 2004</td>
<td>4/16</td>
<td>2/16</td>
<td></td>
<td>54.35</td>
<td>2.33 [0.36, 15.05]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>36</td>
<td>41</td>
<td></td>
<td>100.00</td>
<td>3.46 [0.98, 12.20]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 3.67, df = 1, P = 0.05
Test for overall effect: Z = 1.93 (P = 0.05)

**Figure 3.** Comparison of metformin versus placebo or no treatment in gonadotrophin ovulation induction (OI) with outcome of pregnancy rate.

**Review:** Metformin and Gonadotrophins in PCOS

**Comparison:** 01 Metformin versus placebo or no treatment (Gonadotropin OI)

**Outcome:** 10 Length of ovarian stimulation (days)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Metformin Mean (SE)</th>
<th>Control Mean (SE)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yarali 2002</td>
<td>17.10(3.30)</td>
<td>15.50(3.40)</td>
<td>1.60 [0.38, 2.82]</td>
<td>91.19</td>
<td>-2.60 [-9.90, 4.70]</td>
</tr>
<tr>
<td>Tasdemir 2004</td>
<td>11.20(3.30)</td>
<td>15.50(3.40)</td>
<td>1.30 [0.08, 2.54]</td>
<td>91.41</td>
<td>-3.90 [-13.52, 6.72]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>26</td>
<td>31</td>
<td></td>
<td>100.00</td>
<td>-4.14 [-13.36, 5.08]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 3.67 (P = 0.0002)

**Figure 4.** Comparison of metformin versus placebo or no treatment in gonadotrophin ovulation induction (OI) with outcome of length of ovarian stimulation.

**Review:** Metformin and Gonadotrophins in PCOS

**Comparison:** 01 Metformin versus placebo or no treatment (Gonadotropin OI)

**Outcome:** 11 Total FSH dose (IU)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Metformin Mean (SE)</th>
<th>Control Mean (SE)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yarali 2002</td>
<td>1607.40(87.10)</td>
<td>2062.50(139.10)</td>
<td>-454.70 [44.04, 940.94]</td>
<td>99.16</td>
<td>-424.80 [-907.37, -242.93]</td>
</tr>
<tr>
<td>Tasdemir 2004</td>
<td>1500.30(75.10)</td>
<td>1478.10(150.40)</td>
<td>-100.00 [-420.06, 220.06]</td>
<td>100.00</td>
<td>-100.00 [-420.06, 220.06]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 10.16 (P < 0.00001)

**Figure 5.** Comparison of metformin versus placebo or no treatment in gonadotrophin ovulation induction (OI) with outcome of total FSH dose used.

**Total FSH dose.** The co-administration of metformin with gonadotrophin OI significantly decreases the total dose of FSH used during the treatment cycle (WMD = -290.42 IU, P = 0.0004, 95% CI = -450.34 to -130.51) (Figure 10).

**Serum E2 level on the day of HCG trigger.** Metformin did not reduce the serum E2 level on the day of HCG trigger (WMD = -3.53 nmol/l, P = 0.23, 95% CI = -9.24 to 2.18) (Figure 11).

**Number of oocytes collected at IVF.** Metformin has no effect on the number of oocytes collected at IVF (WMD = 0.44, P = 0.54, 95% CI = -0.98 to 1.86) (Figure 12).

Statistical heterogeneity (variability in the treatment effects being evaluated in the different trials) was present (P < 0.00001, χ² = 29.12, I² = 93.1%).
Figure 6. Comparison of metformin versus placebo or no treatment in gonadotrophin ovulation induction (OI) with outcome of maximum serum estradiol level during stimulation.

Figure 7. Comparison of metformin versus placebo or no treatment in IVF with outcome of pregnancy rate.

Figure 8. Comparison of metformin versus placebo or no treatment in IVF with outcome of live birth rate.

Figure 9. Comparison of metformin versus placebo or no treatment in IVF with outcome of length of ovarian stimulation.

Discussion
This is the first systematic review and meta-analysis of the use of metformin co-administration in PCOS patients undergoing gonadotrophin OI or IVF. This systematic review demonstrates that the co-administration of metformin to gonadotrophin OI

OHSS. Figure 13 demonstrates the forest plot of RCTs reporting the development of OHSS as an outcome measure. The meta-analysis of the four RCTs shows that metformin significantly reduces the risk of OHSS at IVF (5.6 versus 21.0%; OR = 0.21, P < 0.00001, 95% CI = 0.11–0.41).

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and IVF does not improve ovulation, pregnancy or live birth rates in PCOS women. However, the number of subjects in both the individual trials and combined meta-analysis was small, as evidenced by the wide confidence limits, thus limiting the power of the meta-analysis to exclude a treatment benefit.

Metformin has a consistent effect on ovarian response during gonadotrophin OI, with the length of ovarian stimulation, total dose of FSH used and serum E2 level on the day of HCG triggering all reduced with the use of metformin. Metformin has a variable effect on ovarian response during IVF treatment.
Metformin reduced the total FSH dose used but had no effect on the length of ovarian stimulation, serum E2 level on the day of HCG trigger or number of oocytes collected. The risk of OHSS in PCOS women undergoing IVF was reduced with metformin.

A recent international consensus workshop group recommended that all clinicians and investigators now use the internationally agreed definition of PCOS to ensure uniformity in routine clinical management and research studies (Fauser et al., 2004). We therefore believed it important to note whether the definition of PCOS in each of the individual RCTs of this systematic review met the new Rotterdam Consensus Group 2003 criteria (Tables I and II). Subjects in only one of the eight RCTs in this review did not meet the new consensus criteria (Visnova et al., 2003).

**Metformin co-administration with gonadotrophin OI**

The primary outcome measure in all the three studies assessing the effect of metformin in gonadotrophin OI was ovarian response rather than ovulation or pregnancy rate (Table I; Figures 2–6). Each of the trials was small (n < 50) and thus underpowered to assess pregnancy rates. All the trials included PCOS patients who met the Rotterdam consensus criteria and who were resistant to clomiphene citrate. The patients as a group tended to be young and overweight in the individual studies. Two of the three RCTs excluded both tubal uterine and male factor causes of infertility (Yarali et al., 2002; Tasdemir et al., 2004).

The trials used different gonadotrophin OI protocols, and no mention was made of coital timing in any of the three trials. The length of pretreatment with metformin ranged between 1 and 2 months, and metformin was terminated either on the day of HCG trigger or on the day of pregnancy test. The study by Yarali et al. (2002) measured biochemical pregnancies only (positive serum pregnancy test 13–15 days after HCG trigger injection), whilst the other two papers (De Leo et al., 1999; Tasdemir et al., 2004) did not define the diagnosis of pregnancy. No patients in any of the three RCTs had to discontinue their metformin as a result of side effects (De Leo et al., 1999; Yarali et al., 2002; Tasdemir et al., 2004).

Only one of the three trials assessed endocrine and/or metabolic parameters and found that there was no change in insulin sensitivity indices following a 6-week pretreatment period with metformin or placebo (Yarali et al., 2002). The only endocrine change noted during this same period was a decline in serum-free testosterone concentration with metformin.

Metformin appears to have a favourable effect on ovarian response parameters at gonadotrophin OI in terms of reducing the length of ovarian stimulation by approximately 4 days, total dose of FSH used by around 425 IU and serum E2 on the day of HCG trigger by about 1.24 nmol/l (1240 pmol/l or 338 pg/ml) (Figures 4–6). These findings translate into a saving of both time and pharmacological expense for the patient being treated with metformin during gonadotrophin OI, even for the patient who undergoes up to 8 weeks of pretreatment with metformin (MIMS Australia Online Prescribing Section, 2005).

The meta-analysis demonstrated no improvement in pregnancy rates with metformin use in gonadotrophin OI (Figure 3). However, all the three small (n < 50) individual trials and the meta-analysis showed a trend towards an improvement in cycle pregnancy rates with metformin co-administration. A very likely reason for this lack of statistically significant benefit with metformin use is a lack of study power (the probability of finding an effect when it does exist), resulting in type 2 or beta error, commonly seen in small trials, where no significant difference in treatment effect can be detected, while in fact a real difference exists. The combined data, comparing only approximately 40 cycles in each group, demonstrated a non-significant 3.46 OR improvement in pregnancy with metformin co-administration. The power of this meta-analysis (Figure 3) to detect a significant difference (P value <0.05) between the two treatments, given the observed differences, is 73%. In other words, the meta-analysis has a 73% chance of detecting (or 27% likelihood of missing) a true difference between the intervention and control groups; compared to an acceptable level of 80% (Kirby et al., 2002).

Further evidence of the lack of study power in the meta-analysis is seen in the very wide CIs in the individual trials and the meta-analysis, although the latter’s confidence limits are considerably narrower as a result of the increased patient numbers. The upper limit of the combined data’s 95% CI is 12.20. If the OR at this upper boundary were true, then this would be clinically important (i.e. metformin may increase the odds of pregnancy in gonadotrophin OI by 12-fold), and thus the meta-analysis has failed to exclude an important treatment effect of metformin co-administration.

It was not possible to perform a meta-analysis of the rate of OHSS development as it was not reported in two of the trials (Yarali et al., 2002; Tasdemir et al., 2004). The third (crossover) trial by De Leo et al. (1999) did not report OHSS events before treatment crossover but did report no difference in the number of cycles with ‘hyperstimulation after HCG’ with (1/8 = 12.5%) or without (5/19 = 26.3%) metformin co-treatment in the women who completed both pre- and post-crossover treatment arms.

**Metformin co-administration with IVF**

None of the five trials assessing the effect of metformin in IVF treatment assessed pregnancy rate as the main outcome measure (Fedorcak et al., 2003; Visnova et al., 2003; Kjøttrød et al., 2004; Onalan et al., 2005; Tang et al., 2005). The primary endpoints were either not reported (Visnova et al., 2003; Onalan et al., 2005) or based on ovarian response parameters (Fedorcak et al., 2003; Kjøttrød et al., 2004; Tang et al., 2005). Only two of the trials performed a priori sample size calculations to assess their primary outcome measures (Kjøttrød et al., 2004; Tang et al., 2005).

The patients in one of the trials did not meet the Rotterdam consensus criteria (Fauser et al., 2004) as other causes for hyperandrogenism which mimic PCOS (such as congenital adrenal hyperplasia, Cushing’s syndrome or androgen-secreting tumours) were not excluded (Visnova et al., 2003). The patients in the five trials were young and were overweight or
obese in three of the five trials (Table II). Previous exposure to clomiphene citrate including whether the patients were clomiphene citrate resistant was not stated in any of the five RCTs.

All five trials used the long down-regulation protocol using a GnRH agonist (Fedorcsak et al., 2003; Visnova et al., 2003; Kjøtrød et al., 2004; Onalan et al., 2005; Tang et al., 2005). Four of the trials assessed clinical pregnancies (intraterine pregnancy on ultrasound) (Fedorcsak et al., 2003; Kjøtrød et al., 2004; Onalan et al., 2005; Tang et al., 2005), whilst pregnancy was not defined in the other trial (Visnova et al., 2003). No women had to stop their metformin treatment as a result of side effects in the two trials which reported on such adverse effects (Fedorcsak et al., 2003; Kjøtrød et al., 2004). Only one of the trials (Tang et al., 2005) compared the changes in endocrine or metabolic variables over the course of the study between the treatment and control groups (personal communication).

Metformin reduced the total FSH dose used by about 290 IU but had no effect on the length of ovarian stimulation, serum E2 level on the day of HCG trigger or number of oocytes collected (Figures 9–12). Again, this finding translates into a saving of pharmacological expense for the patient being treated with metformin during IVF, even for the patient who undergoes up to 16 weeks of pretreatment with metformin before down-regulation (MIMS Australia Online Prescribing Section, 2005).

Caution is needed in interpreting the meta-analysis result on the serum E2 level on the day of HCG trigger as statistical heterogeneity was present (P < 0.00001, $\chi^2 = 29.12, I^2 = 93.1\%$) (Figure 11). The results of Visnova et al. (2003) were considerably different to the other two trials (Kjøtrød et al., 2004; Onalan et al., 2005). Statistically significant heterogeneity implies a low probability that the observed differences in results from study to study are due to random error (chance) alone, indicating that differences in clinical parameters (patients, exposures or outcomes) or study methodology (design or conduct) are responsible for the varying treatment effect rather than the interventions being compared (Oxman et al., 1994).

Statistical heterogeneity could possibly be explained by differences in the study design/quality, patient population or interventions between the three trials (Visnova et al., 2003; Kjøtrød et al., 2004; Onalan et al., 2005) (Table II). However, these possible causes of the heterogeneity cannot be explored using subgroup sensitivity analyses because of too few studies to perform this adequately. Therefore, as the statistical heterogeneity is unexplained, the random-effects model of meta-analysis was used.

The co-administration of metformin does not improve the pregnancy or live birth rate at IVF (Figures 7 and 8). However, the meta-analysis showed a trend towards an improvement in pregnancy and live birth rates with metformin co-administration. Only one of five RCTs and one of two RCTs demonstrated an improvement in pregnancy rate and live birth rate, respectively, with metformin (Tang et al., 2005). This trial by Tang et al. did not seem to differ from the other four trials in terms of patient selection or intervention (Table II).

The most likely reason for the meta-analysis showing no significant benefit for metformin co-administration in terms of pregnancy or live birth rates at IVF is type 2 or beta error as the power of the meta-analysis in Figures 7 and 8 is only 20 and 56%, respectively, given the sample sizes of each study group, observed differences seen between the groups and $\alpha = 0.05$ (5% significance level). Therefore, the meta-analyses in Figures 7 and 8 are inconclusive, and this is further evidenced by the upper limit of the CIs which is 1.98 for pregnancy rate and 4.14 for live birth rates. If the OR at this upper boundary were true (i.e. metformin co-treatment in IVF approximately doubling the odds of pregnancy and quadrupling the odds of live birth), then the meta-analyses have failed to exclude an important clinical treatment effect.

Metformin appears to reduce the risk of developing OHSS at IVF (Figure 13). This finding is interesting, particularly when the meta-analysis also shows that metformin does not affect the serum E2 levels on the day of HCG or the number of oocytes collected (Figures 11 and 12). All five RCTs evaluated the rate of OHSS but did not define the condition or its severity, with the exception of Tang et al. (2005) who defined OHSS as severe requiring hospitalization (personal communication). No cases of OHSS were seen in the trial by Fedorcsak et al. (2003). None of the authors offered an explanation as to why metformin may reduce the risk of OHSS.

The underlying reason for a reduction in the incidence of OHSS with metformin is not known definitively. Improvement in insulin sensitivity with consequent lowering of insulin levels may be one possible explanation. Hyperinsulinaemia is a risk factor for OHSS as women with PCOS who are hyperinsulinaemic have a higher level of E2 and incidence of ovarian hyperstimulation in response to ovarian stimulation with FSH compared to those with normoinsulinaemia (Fulghesu et al., 1997). Insulin increases vascular endothelial growth factor (VEGF) expression in vascular smooth muscle cells (Doronzo et al., 2004), and VEGF has emerged as one of the factors most likely involved in the pathophysiology of OHSS (Anonymous, 2003). Therefore, it may be postulated that metformin reduces the risk of OHSS by decreasing serum insulin levels, leading to a consequent reduction in the production of VEGF.

**Limitations**

There are a number of limitations to this review. The value of any meta-analysis is totally dependent on the quality and lack of bias in its component primary studies. A significant concern with any meta-analysis is that meta-analytic methods may be used inappropriately to combine biased and disparate studies, leading to misleading systematic reviews. The careful assessment of study validity and heterogeneity is essential in minimizing this risk (Hughes, 1996). Therefore, it is important to restrict inclusion to RCTs, ideally with adequate randomization, objective or blinded outcome assessment, complete follow-up information and intention-to-treat analysis (Guyatt et al., 1993). Unfortunately, very few of the RCTs included in this review satisfied all these criteria (Tables I and II).

Five of the eight RCTs clearly described the method used for random allocation (De Leo et al., 1999; Yarali et al., 2002; Fedorcsak et al., 2003; Onalan et al., 2005; Tang et al., 2005), and only three of the trials reported on allocation concealment (Fedorcsak et al., 2003; Onalan et al., 2005; Tang et al., 2005) (Tables I and II). Trials with insecure treatment allocation
concealment report effect sizes that are 30–40% larger than studies with secure randomization (Schulz et al., 1995; Moher et al., 1998). Allocation concealment aims to avoid selection bias by ensuring that both study groups are equal at the start of the trial (Juni et al., 2001).

Only four of the eight RCTs in this meta-analysis were blinded to ensure that both the study groups are treated and assessed equally (Yarali et al., 2002; Kjøttred et al., 2004; Onalan et al., 2005; Tang et al., 2005). Blinding of patients and care providers prevents performance bias (i.e. where additional treatment interventions are provided preferentially to one group), whilst the blinding of those assessing outcomes (i.e. patients, care providers, others etc.) prevents detection bias (Juni et al., 2001). Lack of double blinding has been shown to exaggerate treatment effects by 17% (Schulz et al., 1995).

Analysis should be ideally performed according to the intention-to-treat principle (i.e. ensuring that the patient groups are equivalent at the end of the trial as they were at the beginning) to avoid attrition bias by excluding patients who either deviated from the protocol or were lost to follow-up; as such patients excluded after treatment allocation or randomization are unlikely to be representative of patients remaining in the study (Juni et al., 2001). However, studies addressing attrition bias have demonstrated that trials with inadequate reporting on patient exclusions did not affect treatment estimates (Schulz et al., 1995; Juni et al., 2001).

Four of the eight trials in this review specifically stated whether the participating couples had undergone prior infertility treatment cycles beforehand (Yarali et al., 2002; Visnova et al., 2003; Onalan et al., 2005; Tang et al., 2005). A subfertile population that has already undergone infertility treatment is likely to have lower fecundity as couples with the highest fecundity might have conceived already. If differences between treatments are more likely to show in a more fertile population that has already undergone infertility treatment cycles beforehand (Yarali et al., 2003; Onalan et al., 2005; Tang et al., 2005). A subfertile population that has already undergone infertility treatment is likely to have lower fecundity as couples with the highest fecundity might have conceived already. If differences between treatments are more likely to show in a more fertile population, this may lead to underestimation of treatment differences in a trial (Cohlen et al., 2003).

Despite the absence of statistically significant heterogeneity between the RCTs combined for the meta-analyses of pregnancy and ovarian response parameters (apart from Figure 11 discussed above), clinical heterogeneity or diversity existed because of inherent variability in patient selection (i.e. different definitions of clomiphene citrate resistance in the gonadotrophin OI trials, other causes of infertility in the IVF trials, prior treatment cycles in gonadotrophin OI or IVF, age, duration of infertility, BMI and insulin resistance), interventions including co-interventions (i.e. different gonadotrophin OI protocols, different FSH injection types and doses for OI or IVF ovarian stimulation, different metformin dosages, different pretreatment periods with metformin, different times for stopping the metformin, different cycle monitoring and HCG triggering criteria, probable different coital timing in gonadotrophin OI trials, different luteal phase support for the IVF studies) and outcomes (i.e. methods of measuring serum E2, definition of OHSS and pregnancy) between the individual trials. Such differences observed between the trials are to be expected because of the variability in the nature of clinical practice where such studies should be conducted.

Although the inclusion of unpublished studies is controversial (Cook et al., 1993), reliance upon published studies alone may distort the results of a meta-analysis because positive studies (statistically significant) are more likely to be published than negative ones (non-significant), with the attendant risk for the review to overestimate treatment efficacy (Dickersin et al., 1987). However, only one of the individual trials in this meta-analysis was a positive study for the primary outcome measures of ovulation, pregnancy or live birth (Tang et al., 2005), thus limiting any potential for publication bias.

A treatment can be evaluated according to several criteria. Efficacy is usually the most important outcome parameter, but the number and severity of side effects, the cost associated with treatment and the treatment effects on quality of life are also important to assess. This review focused on efficacy, particularly in terms of pregnancy rate. No assessment of treatment cost or its effect on quality of life was performed in this review as none of the trials assessed these outcome measures.

Conclusions

This systematic review and meta-analysis, based on limited available level 1 evidence, demonstrates that metformin co-treatment does not significantly improve ovulation, pregnancy or live birth rates in women with PCOS undergoing gonadotrophin OI or IVF. However, the review is inconclusive in terms of not being able to exclude an important clinical treatment effect because of the small number of trials and small sample sizes of the individual trials limiting the power of the meta-analysis. It is too soon to draw conclusions from the literature. Further large, well-designed and executed RCTs are necessary to definitively answer the important clinical question of whether metformin use in PCOS women improves pregnancy and live birth rates in gonadotrophin OI or IVF.

Metformin has a consistent effect on ovarian response during gonadotrophin OI, with the length of ovarian stimulation, total dose of FSH used and maximal E2 level all reduced with the use of metformin. Metformin reduces the total FSH dose used in IVF but has no effect on the length of ovarian stimulation, serum E2 level on the day of HCG trigger or number of oocytes collected. The risk of OHSS in PCOS women undergoing IVF was reduced with metformin.

Acknowledgement

The authors thank the Cochrane Collaboration for providing the RevMan 4.2 software used for statistical analysis and construction of forest (or CI) plots. A full review on metformin and Assisted Reproductive Technology is currently in progress by the Cochrane Menstrual Disorders and Subfertility Group and will be available on the Cochrane Library upon completion.

The authors also wish to thank Dr T. Tang and Dr G. Onalan for supplying additional information on their trials and Dr Eva Durna at the Royal Hospital for Women in Sydney, Australia for translating the Czech publication (Visnova et al., 2003) into English.

References
