Metformin versus clomiphene citrate for infertility in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis

Marie L. Misso1,2, Michael F. Costello3,4,5, Marie Garrubba6, Jennifer Wong7, Roger Hart8,9, Luk Rombauts10, Angela M. Melder6, Robert J. Norman11,12, and Helena J. Teede1,2,7,*

1Women’s Public Health Research, School of Public Health and Preventive Medicine, Monash University, Level 1, 41-43 Kanooka Grove, Clayton, Melbourne 3168, Australia 2Jean Hailes for Women’s Health, Melbourne 3168, Australia 3Department of Reproductive Medicine, Royal Hospital for Women, Sydney, Australia 4OBstetrics and Gynaecology, University of New South Wales, Sydney, Australia 5Department of Reproductive Medicine, Royal Hospital for Women, Sydney, Australia 6Centre for Clinical Effectiveness, Southern Health, Melbourne 3168, Australia 7Department of Diabetes and Endocrinology, Southern Health, Melbourne 3168, Australia 8School of Women’s and Infant’s Health, University of Western Australia, Perth 6008, Australia 9Fertility Specialists of Western Australia, Perth 6010, Australia 10Department of Obstetrics and Gynaecology, Monash University, Melbourne 3168, Australia 11The Robinson Institute, University of Adelaide, Adelaide, Australia 12Fertility SA, Adelaide, Australia

Correspondence address. E-mail: helena.teede@monash.edu

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BACKGROUND: Recent studies suggest that metformin may be more effective in women with polycystic ovary syndrome (PCOS) who are non-obese. The objective here is to determine and compare the effectiveness of metformin and clomiphene citrate for improving fertility outcomes in women with PCOS and a BMI <32 kg/m² (BMI 32 kg/m² was used to allow for international differences in BMI values which determine access to infertility therapy through the public health system).

METHODS: Databases were searched for English language articles until July 2011. Inclusion criteria: women of any age, ethnicity and weight with PCOS diagnosed by all current criteria, who are infertile; at least 1000 mg of any type of metformin at any frequency, including slow release and standard release, compared with any type, dose and frequency of clomiphene citrate. Outcomes: rates of ovulation, live birth, pregnancy, multiple pregnancies, miscarriage, adverse events, quality of life and cost effectiveness. Data were extracted and risk of bias assessed. A random effects model was used for meta-analyses of data, using risk ratios (relative risk).

RESULTS: The search returned 4981 articles, 580 articles addressed metformin or clomiphene citrate and four randomized controlled trials (RCTs) comparing metformin with clomiphene citrate were included. Upon meta-analysis of the four RCTs, we were unable to detect a statistically significant difference between the two interventions for any outcome in women with PCOS and a BMI <32 kg/m², owing to significant heterogeneity across the RCTs.

CONCLUSIONS: Owing to conflicting findings and heterogeneity across the included RCTs, there is insufficient evidence to establish a difference between metformin and clomiphene citrate in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates in women with PCOS and a BMI <32 kg/m². However, a lack of superiority of one treatment is not evidence for equivalence,
and further methodologically rigorous trials are required to determine whether there is a difference in effectiveness between metformin and placebo (or no treatment) or between metformin and clomiphene citrate for ovulation induction in women with PCOS who are non-obese. Until then, caution should be exercised when prescribing metformin as first line pharmacological therapy in this group of women.

Key words: clomiphene citrate / metformin / polycystic ovary syndrome / infertility / systematic review

Introduction

Polycystic ovary syndrome (PCOS) is a complex condition with psychological, metabolic and reproductive manifestations that impacts on health across the lifespan (Teede et al., 2010). PCOS is one of the most common conditions in reproductive-aged women, with a prevalence of 12–21% depending on the criteria used and the population studied (March et al., 2010). Insulin resistance underpins the aetiology of PCOS in the majority of those affected (Dunaif et al., 1989; DeUgarte et al., 2005; Teede et al., 2005, 2007). Hyperinsulinaemia results in increased ovarian androgen biosynthesis and decreased hepatic sex hormone-binding globulin synthesis, leading to increased bioavailability of free androgens. Androgens augmented by hyperinsulinaemia contribute to elevated primary and pre-antral follicles and impaired dominant follicle selection (Pellatt et al., 2010) with subsequent anovulation (Costello and Eden, 2003), resulting in infertility.

The majority of women with PCOS are overweight adversely affecting ovarian function both directly and via exacerbation of PCOS (Rachon and Teede, 2010). Being overweight per se has a negative influence on the oocyte, embryonic development and implantation and underlying mechanisms are likely to be complex and include insulin resistance (Norman and Clark, 1998; Teede et al., 2010). Lifestyle therapy is recommended first line for improving fertility in overweight women with PCOS (PCOS Australian Alliance, 2011; Teede et al., 2011). Pharmacological therapy is recommended second line, with the two most commonly used pharmacological agents being clomiphene citrate and metformin (PCOS Australian Alliance, 2011; Teede et al., 2011). Clinically, the comparative efficacy of metformin and clomiphene citrate is important to address.

As an insulin-sensitizer, metformin has traditionally been used for many decades as an oral antihyperglycaemic agent in type 2 diabetes (Elizur and Tuland, 2008) and early studies examining the reproductive effects of metformin in PCOS have shown promising results, but there are limitations to existing data with marked heterogeneity in some clinical outcomes (Costello and Eden, 2003). Acting as an anti-estrogen (Shelly et al., 2008), clomiphene citrate is approved for use in women with anovulation and has been used as a first line ovulation induction agent for over 40 years (Pritts, 2010). There is high-quality evidence that clomiphene citrate is better than placebo for ovulation and pregnancy rates, thus providing confidence for recommending use of clomiphene citrate as first line therapy (Brown et al., 2009; PCOS Australian Alliance, 2011; Teede et al., 2011; Misso et al., 2012a, b). Yet, there is much debate about the comparative effectiveness and role of metformin and of clomiphene citrate for infertility therapy in women with PCOS (Palomba et al., 2005; Moll et al., 2007; Creanga et al., 2008; Tang et al., 2010; Misso et al., 2012a, b). With uncertainty around efficacy, the use of these two agents is variable with endocrinologists more likely to use metformin and gynaecologists more likely to use clomiphene citrate (Cussens et al., 2005).

Insulin resistance underpins the PCOS aetiology in the majority of cases, contributing to anovulation and other reproductive and metabolic PCOS features (Teede et al., 2007). Potentially, metformin may be relatively more effective in non-obese women with milder degrees of insulin resistance, mediated by different intrinsic mechanisms (Dunaif, 1997; Corbould et al., 2005). In this setting, women respond to metformin by reducing insulin and androgen production, leading to improved fertility (Kumari et al., 2005; Romualdi et al., 2010). Theoretically, in obese women, metformin is unable to overcome the more severe insulin resistance and fails to consistently improve fertility outcomes.

A high-quality Cochrane systematic review has reported on randomized controlled trials (RCTs) comparing metformin with clomiphene citrate in women with PCOS (Tang et al., 2010). This review subgrouped and analysed the RCTs depending on whether the women had a BMI $\geq 30$ kg/m$^2$ and found that the statistical heterogeneity disappeared. Clomiphene citrate had a significantly higher pregnancy and live birth rate in women with a BMI $>30$ kg/m$^2$ (two RCTs) whereas the result was reversed in women with a BMI $<30$ kg/m$^2$ (one RCT). Since the Tang et al. (2010) review, two subsequent RCTs and a narrative review with meta-analysis have been published showing no difference in pregnancy and live birth rates between metformin and clomiphene citrate in women with PCOS with a BMI between 25–30 kg/m$^2$ (Karimzadeh and Javedani, 2010) and BMI $\leq 32$ kg/m$^2$ (Johnson et al., 2010; Johnson, 2011). Therefore, the randomized evidence comparing metformin with clomiphene citrate appears to be conflicting in women with a BMI $<32$ kg/m$^2$.

In this setting, and given that this is a clinically important area to address, our objective was to conduct a methodologically rigorous systematic review and meta-analysis of RCTs comparing metformin to clomiphene citrate in the subgroup of women with PCOS and a BMI $<32$ kg/m$^2$.

Methods

This systematic review is an update of an evidence review, prepared to inform clinical practice recommendations in the National Health and Medical Research Council (NHMRC) approved ‘Evidence-based guideline for the assessment and management of PCOS’ (PCOS Australian Alliance, 2011; Teede et al., 2011). The systematic search was updated in July 2011. The guideline, including detailed information about the rigorous methodology used for development of the guideline, composition of the multidisciplinary guideline development committees, and for obtaining NHMRC approval, can be found at www.managingpcos.org.au/pcos-evidence-based-guidelines. The clinical question posed in this systematic review is: in women with PCOS and a BMI $<32$ kg/m$^2$, what is the effectiveness of metformin compared with clomiphene citrate for improving fertility outcomes?
### Selection criteria

The PICO (Population, Intervention, Comparison, Outcome) framework in Table I established a priori was used to include and exclude studies for this systematic evidence review. In order to be inclusive of different definitions of international study populations according to BMI thresholds for access to infertility therapy through the public health system (Johnson, 2011), we defined non-obese as BMI < 32 kg/m². As outlined in Table I, the primary outcomes were live birth rate, adverse events; and the secondary outcomes were pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, quality of life, cost effectiveness.

### Systematic search for evidence

A broad-ranging systematic search (Misso et al., 2012a, b) for terms related to PCOS was developed and combined with terms relevant to infertility. The search strategy was limited to English language articles and there were no limits on the year of publication. The literature was searched from as early as 1950 until July 2011 for RCTs and systematic reviews of RCTs. The following electronic databases were employed to identify relevant literature: Australasian Medical Index (from 1968), CINAHL (from 1982), EMBASE (from 1980), Medline (from 1948), PsycINFO (from 1967) and All EBM reviews containing: ACP Journal Club (from 1991), The Cochrane Library (from 2005), including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Database of Methodology Reviews, The Cochrane Methodology Register, Health Technology Assessment Database and NHS Economic Evaluation Database. Bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analyses were also searched for identification of additional studies.

### Inclusion of studies

To determine the literature to be assessed further, a reviewer (M.L.M.) scanned the titles, abstract sections and keywords of every record retrieved by the search strategy using the selection criteria described in Table I. Full articles were retrieved for further assessment if the information given suggested that the study met the inclusion criteria. Studies were selected and appraised by a reviewer (M.L.M.) in consultation with colleagues (M.F.C., A.M.M.), using the selection criteria established a priori. Where there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification.

### Quality appraisal of the evidence

Methodological quality, in terms of risk of bias, of the included studies was assessed by a reviewer (M.G.) using criteria developed a priori (Centre for Clinical Effectiveness, 2010). Individual quality items were investigated using a descriptive component approach that included items such as conflict of interest of authors, prespecified selection criteria, methods of randomization and allocation of patients to study groups, blinding of patients, carers, investigators or outcome assessors, methods of outcome assessment and reporting, and statistical issues such as powering and methods of data analysis. Any disagreement or uncertainty was resolved by discussion (with M.L.M., M.F.C., A.M.M.) to reach a consensus. Using this approach, each study was allocated a risk of bias rating (Centre for Clinical Effectiveness, 2010; Misso et al., 2012a, b).

### Data extraction

Data, according to the selection criteria described in Table I, were extracted from included studies by a reviewer (M.G.) using a specifically developed data extraction form (Centre for Clinical Effectiveness, 2010). Information was collected on general details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses to follow-up, subgroups), results (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants, intention-to-treat analysis) and validity of results.
Data synthesis

Meta-analyses were performed with the included RCTs (M.L.M.). Owing to clinical heterogeneity from differences in dose and timing of treatment, a random effects model was used for meta-analyses of the data. Risk ratios (relative risk) were used to present the effect estimate for all meta-analyses with the exception of ovulation rate per cycle. The ovulation rate per cycle data required a separate analysis using an inverse variance method (used for count data, i.e. events rather than patients) because of the possibility that cycles may be counted more than once. A rate ratio is used to present the effect estimate for the ovulation rate per cycle meta-analysis. High heterogeneity $I^2 > 50\%$ was explored through sensitivity analysis using risk of bias. Where it was not appropriate to conduct meta-analyses, study data are presented narratively.

Results

The search (conducted in July 2011) returned 4981 articles of which 580 addressed metformin or clomiphene citrate. The articles were reviewed by title and abstract. Thirty-two full text articles were retrieved for further review and four studies met the selection criteria for this systematic review. A list of the excluded studies can be found in Supplementary data, Table S1.

Characteristics and quality of included RCTs

Four RCTs comparing metformin with clomiphene citrate for up to six treatment cycles in a head to head manner were included in this systematic review. The characteristics of included RCTs can be found in Table II. One high-quality RCT with a low risk of bias included women with PCOS, of which 6–20% had undergone previous fertility treatment with clomiphene citrate or metformin for <5 months before commencing the study (Johnson et al., 2010). Another high-quality RCT with a low risk of bias included women with PCOS who were therapy naive (Palomba et al., 2005). Two medium quality RCTs with a moderate risk of bias included women with PCOS but previous exposure to clomiphene citrate and/or metformin was not reported (Karimzadeh and Javedani, 2010) or who may have undergone previous fertility treatment with clomiphene citrate or metformin (Legro et al., 2007). Setting and follow-up was often not reported or was unclear. Study locations were New Zealand, Italy, USA and Iran. Where reported, treatment duration was 6 months and studies were similar in terms of age and BMI and are generalizable to the target population for this systematic review. See Supplementary data, Table SII for further information on the four RCTs included in the present study.

Metformin versus clomiphene citrate in women with PCOS and BMI < 32 kg/m²

The individual RCTs reported conflicting results (Table III) with no difference in ovulation rate per cycle but higher pregnancy rate per cycle with metformin (Palomba et al., 2005), higher ovulation, pregnancy and live birth rate per patient with clomiphene citrate (Legro et al., 2007; Fig. 1) and no difference in ovulation rate (Johnson et al., 2010), pregnancy rate (Johnson et al., 2010; Karimzadeh and Javedani, 2010) or live birth rate (Johnson et al., 2010) per patient between the two treatments. Palomba et al. (2005), in a high-quality RCT but with a small sample size, reported that metformin was statistically better than clomiphene citrate for pregnancy rate per cycle [Metformin = 31/205 (15.1%), clomiphene citrate = 16/221 (7.2%) $P = 0.009$]. Three of the four RCTs reported the outcome measure of miscarriage rate per patient but did not perform a statistical test of comparison between metformin and clomiphene citrate treatments (Palomba et al., 2005; Legro et al., 2007; Johnson et al., 2010). Again, three of the four RCTs reported the outcome measure of multiple pregnancy rate per patient (Legro et al., 2007; Johnson et al., 2010; Karimzadeh and Javedani, 2010) with only one RCT performing a statistical test of comparison and showing no difference between the two treatments (Karimzadeh and Javedani, 2010). Only one RCT reported on adverse events but did not perform a statistical test of comparison between the two treatments (Johnson et al., 2010). None of the included RCTs reported cost effectiveness data.

Upon meta-analysis of the four RCTs, we were unable to detect a statistically significant difference between metformin and clomiphene citrate for any outcome in this group of women with PCOS, and there was a high level of heterogeneity across the RCTs (Figs I and 2). A single RCT (Johnson et al., 2010) addressed ovulation rate per patient therefore meta-analysis was not performed for this outcome and the authors found no significant difference between the interventions (Table III). Based on two RCTs, ovulation rate per cycle resulted in a rate ratio 0.79 [95% confidence interval (CI) 0.54, 1.17], $I^2 = 78\%$, $P = 0.24$ (Palomba et al., 2005; Legro et al., 2007). Meta-analysis of four RCTs for pregnancy rate per patient resulted in a relative risk of 0.98 [95% CI 0.49, 1.96], $I^2= 80\%$, $P = 0.96$ (Fig. 1a; Palomba et al., 2005; Legro et al., 2007; Johnson et al., 2010; Karimzadeh and Javedani, 2010). Meta-analysis of three RCTs for live birth rate per patient resulted in a relative risk of 0.84 (95% CI 0.22, 3.26), $I^2= 90\%$, $P = 0.8$ (Palomba et al., 2005; Legro et al., 2007; Johnson et al., 2010). A single RCT (Palomba et al., 2005) addressed live birth rate per pregnancy therefore meta-analysis was not performed for this outcome and the authors found no significant difference between the interventions (Table III). Miscarriage rate per pregnancy, based on two RCTs, resulted in a relative risk of 0.90 (95% CI 0.54, 1.50), $I^2 = 91\%$, $P = 0.94$ (Palomba et al., 2005; Legro et al., 2007; Fig. 2a). Multiple pregnancy rate per patient, based on three RCTs, resulted in a relative risk of 2.69 (95% CI 0.50, 14.45), $I^2 = 0\%$, $P = 0.25$ (Legro et al., 2007; Johnson et al., 2010; Karimzadeh and Javedani, 2010; Fig. 2b). The high level of heterogeneity found for all outcomes except multiple pregnancy rate per patient was explored using sensitivity analysis for risk of bias, however upon removal of the RCTs with medium risk of bias, there was no difference in the direction of effect or the heterogeneity. Meta-analysis for the outcome of adverse events could not be performed as only one RCT reported this outcome and found the incidence of adverse events to be 49% with metformin and 44% with clomiphene citrate ($P$-value not reported; Johnson et al., 2010).

Discussion

This systematic review and meta-analysis of RCTs found that there was insufficient evidence to establish a difference between metformin and clomiphene citrate in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates in women with PCOS who are non-obese with a BMI < 32 kg/m². However, the ovulation, pregnancy and live birth rate results are based on highly statistically
<table>
<thead>
<tr>
<th>RCT</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Relevant outcomes</th>
<th>Risk of bias</th>
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<tbody>
<tr>
<td>Johnson et al. (2010)</td>
<td>71 women with oligo- or anovulatory infertility owing to PCOS. Six to 20% of patients had past treatment with metformin or clomiphene citrate. M = 35, CC = 36 Mean age: M = 28.9 ± 4.4 years, CC = 28.2 ± 4.0 years Mean BMI: M = 26.5 ± 3.5 kg/m², CC = 26.2 ± 3.4 kg/m² All women had BMI ≤ 32 kg/m²</td>
<td>Metformin 500 mg three times daily in a gradual increasing dose over 2 weeks in the form of standard release tablets with identical placebo tablets (to maintain blinding). Each patient received up to two 3-month treatment packages. Treatment duration: 6 months</td>
<td>CC 50 mg tablets the initial dose and 150 mg the highest dose used with identical placebo tablets (to maintain blinding). Each patient received up to two 3-month treatment packages. Treatment duration: 6 months</td>
<td>Ovulation rate, clinical pregnancy, live birth, spontaneous abortion, ectopic pregnancy and multiple pregnancy rates, adverse events</td>
<td>Low</td>
</tr>
<tr>
<td>Karimzadeh and Javedani (2010)</td>
<td>180 infertile women with PCOS. Sensitivity to clomiphene citrate has not been reported. M = 90, CC = 90 Mean age: M = 27.33 ± 2.34 years, CC = 27.47 ± 2.38 years Mean BMI: M = 27.17 ± 1.73 kg/m², CC = 27.2 ± 2.93 kg/m² All women had BMI 25–30 kg/m²</td>
<td>Initial dose of 500 mg metformin, which was increased in a stepwise manner during the first 3 weeks to accommodate the side effects until the patients were taking a total of 1500 mg/day (for 3–6 months)</td>
<td>100 mg CC on Days 3–7. Transvaginal sonography and follicular tracking were done. If there was evidence of ovulation but the patient did not get pregnant, the same dosage was continued for a maximum of three to six cycles</td>
<td>Pregnancy and multiple pregnancy rates and improvement in menstrual cycle</td>
<td>Moderate</td>
</tr>
<tr>
<td>Legro et al. (2007)</td>
<td>114 infertile women with PCOS. 55% exposed to past infertility treatment (of total cohort = 417). In women with BMI &lt; 30 kg/m², past infertility treatment was not reported. M = 57, CC = 57 Mean age: M = 28.1 ± 4.0 years, CC = 27.9 ± 4.0 years Mean BMI: M = 25.3 ± 3.2 kg/m², CC = 25.2 ± 3.2 kg/m² All women had BMI ≤ 30 kg/m² (in women stratified by BMI analysis)</td>
<td>500-mg metformin tablets or matching placebo, increased the dose of the study drug until maximum dose of four tablets (two tablets twice a day) for up to six cycles or 30 weeks</td>
<td>50-mg clomiphene tablets or matching placebo per day for 5 days, beginning on Day 3 of menses; this dose was maintained if adequate ovulation was documented. In subjects who had no response or a poor response, the dose was increased by one tablet a day on a treatment cycle basis either after 5 weeks of anovulation or after a menses until the maximum dose of three tablets per day was reached</td>
<td>Pregnancy, ovulation, abortion and live birth rates, adverse events</td>
<td>Moderate</td>
</tr>
<tr>
<td>Palomba et al. (2005)</td>
<td>92 non-obese primary infertile anovulatory women with PCOS. Therapy naïve. M = 45, CC = 47 Mean age: M = 26.4 ± 2.9 years, CC = 25.9 ± 2.7 years Mean BMI: M = 27.0 ± 2.9 kg/m², CC = 26.7 ± 2.8 kg/m² All women had BMI ≤ 30 kg/m²</td>
<td>850 mg metformin cloridrate (Metforal, Laboratori Guidotti, Pisa, Italy) twice daily plus placebo tablets (three tablets daily for 5 days starting from the third day of a progesterone-induced withdrawal bleeding; 10 mg natural progesterone i.m.)</td>
<td>Placebo tablets (two tablets daily) plus 150 mg (three tablets) CC (Serophene, Serono, Rome, Italy) for 5 d starting from the third day of a progesterone-induced withdrawal bleeding.</td>
<td>Pregnancy, ovulation, abortion and live birth rates, adverse events</td>
<td>Low</td>
</tr>
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</table>

M, metformin; CC, clomiphene citrate.
Table III: Findings of the four RCTs included in the meta-analysis.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Low ROB.</td>
<td>6–20% of metformin versus clomiphene citrate groups had past treatment with clomiphene citrate or metformin</td>
<td>Moderate ROB. Previous exposure to clomiphene citrate and/or metformin not reported</td>
<td>Low ROB. Therapy naive</td>
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<tr>
<td>Live birth rate per patient</td>
<td>M = 10/35 (29%)</td>
<td>Outcome not reported</td>
<td>M = 5/57 (8.8%)</td>
<td>M = 26/50 (52%)</td>
</tr>
<tr>
<td></td>
<td>CC = 13/36 (36%)</td>
<td></td>
<td>CC = 21/57 (36.8%)</td>
<td>CC = 9/50 (18%)</td>
</tr>
<tr>
<td>Live birth rate per pregnancy</td>
<td>M = 23/35 (+2 suggestive, ovulation not confirmed) (66%)</td>
<td>Menstrual cycle improvement rate</td>
<td>M = 100/261 (38.3%)</td>
<td>M = 129/205 (62.9%)</td>
</tr>
<tr>
<td></td>
<td>CC = 23/36 (+0) (64%)</td>
<td></td>
<td>CC = 135/222 (60.8%)</td>
<td>CC = 148/221 (67%)</td>
</tr>
<tr>
<td>Ovulation rate per patient</td>
<td>M = 14/35 (40%)</td>
<td></td>
<td>M = 7/57 (12.3%)</td>
<td>M = 31/50 (62%)</td>
</tr>
<tr>
<td></td>
<td>CC = 14/36 (39%)</td>
<td></td>
<td>CC = 21/57 (36.8%)</td>
<td>CC = 16/50 (32%)</td>
</tr>
<tr>
<td>Ovulation rate per cycle</td>
<td>M = 1/35 (3%)</td>
<td></td>
<td>M = 3/50 (6%)</td>
<td>M = 31/205 (15.1%)</td>
</tr>
<tr>
<td></td>
<td>CC = 1/36 (3%)</td>
<td></td>
<td>CC = 2/57 (3.6%)</td>
<td>CC = 16/221 (7.2%)</td>
</tr>
<tr>
<td>Pregnancy rate per patient</td>
<td>M = 0/90 (0%)</td>
<td></td>
<td>M = 0/7 (0%)</td>
<td>M = 0/50 (0%),</td>
</tr>
<tr>
<td></td>
<td>CC = 2/90 (2.2%)</td>
<td></td>
<td>CC = 0/36 (0%)</td>
<td>CC = 2/57 (3.6%)</td>
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<tr>
<td>Pregnancy rate per cycle</td>
<td>M = 7/12 (58.3%)</td>
<td></td>
<td>M = 3/31 (9.7%)</td>
<td>CC = 6/16 (37.5%)</td>
</tr>
<tr>
<td>Multiple pregnancy rate per patient</td>
<td>M = 7/12 (58.3%)</td>
<td></td>
<td>M = 3/31 (9.7%)</td>
<td>CC = 6/16 (37.5%)</td>
</tr>
<tr>
<td>Miscarriage rate per patient</td>
<td>M = 1/35 (3%)</td>
<td></td>
<td>M = 7/57 (12.3%)</td>
<td>M = 3/50 (6%)</td>
</tr>
<tr>
<td></td>
<td>CC = 1/36 (3%)</td>
<td></td>
<td>CC = 3/57 (5.3%)</td>
<td>CC = 6/50 (12%)</td>
</tr>
<tr>
<td>Miscarriage rate per pregnancy</td>
<td>M = 0/90 (0%)</td>
<td></td>
<td>M = 0/7 (0%)</td>
<td>M = 0/50 (0%),</td>
</tr>
<tr>
<td></td>
<td>CC = 2/90 (2.2%)</td>
<td></td>
<td>CC = 0/36 (0%)</td>
<td>CC = 2/57 (3.6%)</td>
</tr>
<tr>
<td>Adverse events per patient</td>
<td>M = 17/35 (49%)</td>
<td></td>
<td>M = 13/31 (9.7%)</td>
<td>Data not reported but noted to be not statistically significant between groups</td>
</tr>
<tr>
<td></td>
<td>CC = 16/36 (44%)</td>
<td></td>
<td>CC = 11/16 (68.8%)</td>
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</table>

ROB, risk of bias.

Figure 1: Metformin versus clomiphene citrate: pregnancy and live birth. (a) Pregnancy rate per patient. (b) Live birth rate per patient.
heterogeneous data and therefore should be interpreted with caution. In addition, the pregnancy, live birth and multiple pregnancy rates have wide CIs indicating insufficient power and therefore we are unable to exclude an important difference in favour of either metformin or clomiphene citrate for these outcomes. Furthermore, given that none of the included studies were specifically designed to test equivalence, caution must be applied and it cannot yet be assumed that metformin is equally effective as clomiphene citrate. This is in the context of our previous reports that after first line lifestyle intervention, clomiphene citrate should be overall first line pharmacological therapy for infertility in women with PCOS and anovulatory infertility, with no other infertility factors (PCOS Australian Alliance, 2011; Teede et al., 2011; Misso et al., 2012a, b).

Clinically, the comparative efficacy of metformin and clomiphene citrate is important. Clinical consensus suggests that metformin is low cost, addresses the underlying physiological abnormalities in PCOS, improves metabolic features of PCOS, can be prescribed in primary care, carries only minor side effects and does not require monitoring or induce multiple pregnancies. Potentially it offers a simple therapy for improving fertility in non-obese women with PCOS (Teede et al., 2011). Clomiphene citrate, a selective estrogen receptor modulator, has been used as a first-line medical ovulation induction agent since 1967 (Pritts, 2010), is clearly an effective, low cost, well-established therapy for infertility in PCOS but needs specialist administration, monitoring and carries an increased risk of multiple pregnancy (Legro et al., 2007; Teede et al., 2011).

A Cochrane systematic review and meta-analysis of RCTs comparing the insulin-sensitizing drug metformin with placebo or no treatment in PCOS women showed that metformin improves ovulation rate and clinical pregnancy rate but not live birth rate (Tang et al., 2010). Another Cochrane systematic review and meta-analysis comparing clomiphene citrate with placebo demonstrated that clomiphene citrate improves ovulation rate and pregnancy rate (Brown et al., 2009). It is important to note that the patients in the RCTs included in the Brown et al. (2009) review were diagnosed according to World Health Organization criteria as type 2 patients and thus do not account for the more recent increases in obesity which are known to exacerbate the features of the current diagnostic criteria of PCOS by an increase in insulin resistance leading to disordered ovulation and hyperandrogenaemia (Pellatt et al., 2010) with subsequent anovulation (Costello and Eden, 2003). However, the role of metformin in women with PCOS and a BMI < 30 kg/m² may be different. The systematic review by Tang et al. (2010) comparing metformin with placebo performed a subgroup meta-analysis on RCTs with women with PCOS with a BMI < 30 kg/m² and found a higher ovulation rate and clinical pregnancy rate with metformin. However, as per the current meta-analysis, heterogeneity was moderate to high, raising caution about the reliability of these findings. There was either no difference or insufficient evidence for comparisons of miscarriage rate, multiple pregnancy rate and adverse events; however, mild gastrointestinal adverse events were significantly higher with metformin than placebo in an analysis of five RCTs (Tang et al., 2010). Hence, it does not support the contention at present that metformin is superior to clomiphene in this lower BMI subgroup.

Given the availability of recent RCTs that were not included in previous subgroup analyses (described above), we undertook a systematic review and meta-analyses of four RCTs and were unable to detect a difference between metformin and clomiphene citrate for rates of ovulation, pregnancy, live birth and miscarriage in women with PCOS and a BMI < 32 kg/m². Furthermore, the results for all of the outcomes were conflicting across the four included RCTs. This significant heterogeneity is demonstrated in the forest plots (Figs 1 and 2). In terms of limitations of individual RCTs, Legro et al. (2007) conclude that clomiphene citrate is superior to metformin for live births in infertile women.
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with PCOS, and acknowledge that multiple births is a complication but they fail to provide values of precision (P-value or CIs) for their results and had a >20% drop out in each treatment group. We are unable to draw firm conclusions from the results of this study with moderate risk of bias demonstrating trends favouring clomiphene citrate (Table III). The RCT by Karimzadeh and Javadian (2010) also had a moderate risk of bias and like the other two studies (Palomba et al., 2005; Johnson et al., 2010), did not detect any differences between the comparisons addressed. The findings of studies with a moderate or high risk of bias should be interpreted with caution, as the direction of bias reflects the reliability of the findings. A high-quality RCT with low risk of bias by Johnson et al. (2010) reported no difference between metformin and placebo, or metformin and clomiphene citrate, for rates of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy in women with PCOS and a BMI < 32 kg/m². None of the included RCTs reported cost effectiveness data and there was insufficient information provided in all four included RCTs to perform a power calculation for this meta-analysis. Future trials addressing the costs associated with each intervention, including costs associated with adverse effects, such as monitoring, specialist intervention, multiple pregnancies and ovarian hyperstimulation syndrome (OHSS), are required. There are believed to be certain clinical features of patients, such as obesity, that may predict a reduction in clomiphene citrate efficacy and thus it is important that the limitation of inconsistent reporting of previous infertility treatment be addressed in future trials.

The results of the current meta-analyses are consistent with a recent meta-analysis in this lower BMI group (Johnson, 2011), which included three RCTs (Palomba et al., 2005; Legro et al., 2007; Johnson et al., 2010) and excluded the RCT by Karimzadeh and Javadian (2010) as it did not report on live birth data. Meta-analysis of the three RCTs showed no difference in clinical pregnancy rate or live birth rate between metformin and clomiphene citrate; and similar to our results, that high statistical heterogeneity was present and results should therefore be interpreted with caution. Importantly, a difference between the two treatments could not be excluded because of the wide CIs, and the authors went on to conclude that metformin and clomiphene are both suitable options for first-line treatment. However, whilst no differences were detected, this is distinct from the concept of equivalence. No studies were designed to test equivalence of metformin and clomiphene citrate, therefore some caution should be exercised when concluding that these interventions are equally effective. Whilst there are some theoretical advantages in the use of metformin in non-obese women with PCOS, it is important to be mindful that strong evidence (high-quality systematic review with low risk of bias) exists demonstrating that clomiphene citrate is better than placebo for ovulation rate and pregnancy rate (Brown et al., 2009). There is, in contrast, a lack of strong evidence about the effectiveness of metformin compared with placebo or no treatment. There is also a need for greater research including equivalence studies comparing metformin and clomiphene citrate in therapy-naïve women with PCOS.

It should not be assumed that metformin is equally effective as clomiphene citrate in non-obese women with PCOS, pending further research. In the context of evidence-based guideline recommendations, given the overall established efficacy of clomiphene citrate (PCOS Australian Alliance, 2011; Teede et al., 2011; Misso et al., 2012a, b) and the lack of clear evidence around metformin, metformin should not be used as first line pharmacological therapy. Metformin may be used as second line pharmacological therapy, either alone or combined with clomiphene citrate, in women with PCOS who are clomiphene citrate-resistant and infertile with no other infertility factors (PCOS Australian Alliance, 2011; Teede et al., 2011; Misso et al., 2012a, b). In addition, it is important to inform patients about the potential side effects of both medications before commencing treatment. If clomiphene citrate is prescribed, potential side effects include multiple pregnancy and OHSS and the patient will need monitoring to ensure mono-follicular ovulation. With metformin, the response may take up to 3 months to be determined and there may be gastrointestinal side effects (PCOS Australian Alliance, 2011; Teede et al., 2011; Misso et al., 2012a, b).

In conclusion, this review demonstrates that there is insufficient evidence to establish a difference in ovulation, pregnancy or live birth rates between metformin and clomiphene citrate in non-obese women with PCOS. Based on the available research to date, there is insufficient evidence to either support or refute that there is no difference between these two interventions in women with PCOS and BMI < 32 kg/m². Clomiphene citrate has been widely accepted as a first line ovulation induction agent for over 40 years with little difference in adverse effects between clomiphene citrate and placebo in high-quality evidence, whereas high-quality evidence to date demonstrates a statistically significant increase in gastrointestinal adverse effects with metformin and has been unable to prove that metformin is equivalent or superior to this current well-established first line medical treatment of clomiphene citrate in PCOS. Whilst it is low cost and can be prescribed in primary care, metformin needs to be proved as equivalent or superior to clomiphene citrate before one can consider it as a first line treatment agent in women with PCOS. Further methodologically rigorous trials, including in PCOS subgroups, for example according to BMI and previous therapy, are required to determine whether there is a difference in effectiveness between metformin and placebo (or no treatment), or metformin and clomiphene citrate, for ovulation induction in anovulatory and infertile women with PCOS who are non-obese, with particular consideration for safety and adverse effects, such as the mild gastrointestinal effects of metformin and the multiple pregnancy risk and need for monitoring with clomiphene citrate.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

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M.L.M. contributed substantially to the design of the study; acquisition, analysis and interpretation of data; prepared, drafted and revised the article critically for important intellectual content and approved the final draft for publication. M.G. contributed substantially to the acquisition and analysis of data; and revised the article critically for important intellectual content and approved the final draft for publication. J.W., R.H., L.R., R.N. contributed to the conception of the study; interpretation of data; and revised the article critically for important intellectual content and approved the final draft for publication. A.M.M. contributed to the design of the study; interpretation of data; and revised the article critically for important intellectual content and approved the final draft for publication. M.F.C. contributed substantially to the conception of this specific study; interpretation of data; and revised the article critically for important intellectual content and approved the final draft for publication. H.J.T. conceptualized and directed the overall PCOS project, acquired the funding, contributed to conception of this manuscript or development of the guideline and have not influenced the scope or conclusions herein.

Roger Hart declares the following:
(i) Medical Director of Fertility Specialists of WA.
(ii) Medical Director of Fertility Specialists South.
(iii) Member of the Fertility Advisory Board Schering Plough.
(iv) Member of the Fertility Advisory Board Merck Serono.
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(iv) Member of the MSD Advisory Board.

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PCOS Australian Alliance. Evidence Based Guidelines for Assessment and Management of Polycystic Ovary Syndrome. Melbourne: Jean Hailes Foundation for Women’s Health on behalf of the PCOS Australian Alliance, 2011.


