Aromatase inhibitors for PCOS: a systematic review and meta-analysis

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BACKGROUND: The effectiveness of aromatase inhibitors (AIs) in the treatment of anovulatory polycystic ovary syndrome (PCOS) remains unclear. The objective was to determine whether AIs are effective in improving fertility outcomes in women with PCOS.

METHODS: Databases were searched until July 2011. Inclusion criteria were women with PCOS, who are infertile, receiving any type, dose and frequency of AI compared with placebo, no other treatment or other infertility treatment. Outcomes were rates of: ovulation, pregnancy, live birth, multiple pregnancies, miscarriage and adverse events, as well as quality of life and cost effectiveness. Data were extracted and risk of bias was assessed. A random-effects model was used for the meta-analyses, using odds ratios (ORs) and rate ratios (RRs).

RESULTS: The search returned 4981 articles, 78 articles addressed AIs and 13 randomized controlled trials (RCTs) met the inclusion criteria. No RCTs compared AIs versus placebo or no treatment, in therapy naïve women with PCOS. Meta-analyses of six RCTs comparing letrozole with clomiphene citrate (CC) demonstrated that letrozole improved the ovulation rate per patient [OR 2.90 (95% confidence interval (CI) 1.72, 4.88), I² = 0%, P < 0.0001]; however, there was no statistical difference for the ovulation rate per cycle or the pregnancy, live birth, multiple pregnancy or miscarriage rates. Letrozole also did not improve pregnancy or live birth rates compared with placebo or with CC plus metoformin in women with CC-resistant PCOS. Results of comparisons of letrozole and anastrozole in women with CC-resistant PCOS were conflicting in terms of ovulation and pregnancy rates.

CONCLUSIONS: In the absence of supportive high-quality evidence, AIs should not be recommended as the first-line pharmacological therapy for infertility in women with PCOS, and further research is needed.

Key words: aromatase inhibitor / polycystic ovary syndrome / ovulation induction / infertility / systematic review
Introduction

Infertility has been estimated to affect up to 27.4% of women aged 15–44 (11% in the 15–29 age group) and 7.3 million (12%) women accessed infertility services in the USA in 2002 (Chandra et al., 2005). Chambers et al. (2009) reported that in 2003 Australia had the highest levels of assisted reproductive technologies (ARTs) at 1574 cycles per million population, followed by Scandinavia (1465 cycles), USA (373 cycles) and Canada (311 cycles). Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility (~90%), and indeed is one of the most common endocrine conditions in reproductive-aged women, with a prevalence of 12–21% (Azziz et al., 2006; Diamanti-Kandarakis et al., 2006; March et al., 2010).

PCOS is a chronic condition with manifestations that begin most commonly in adolescence with menstrual irregularity and hyperandrogenism, with a transition over time into problems including infertility and metabolic complications. Pharmacological ovulation induction can be used to induce ovulation, but it is generally second line after intensive lifestyle therapy in overweight or obese women with PCOS. The Australian Longitudinal Study on Women’s Health found that women with PCOS were more proactive than others about seeking advice and treatment for infertility (Herbert et al., 2009), and a recent Swedish study found that the use of ART was more common in women with PCOS (Roos et al., 2011) than those without. However, for women with PCOS, there is a lack of clarity about the effectiveness and safety of ovulation induction agents and other costly infertility treatments such as surgical options or IVF.

Clomiphene citrate (CC), an oral ovulation induction agent in use for over 40 years, is generally considered to be the first-line pharmacological therapy to improve fertility outcomes in anovulatory women with PCOS (Pritts, 2010; Teede et al., 2011). If ovulation cannot be achieved with CC, then the patient is said to have CC resistance. If pregnancy cannot be achieved after six ovulatory cycles with CC, then the patient is described as having CC failure.

Aromatase inhibitors (AIs), originally used for the treatment of breast cancer in post-menopausal women, were first proposed as ovulation-inducing drugs in anovulatory women with an inadequate response to CC in 2001 (Mitwally and Casper, 2001). The most commonly used AIs in ovulation induction are letrozole and anastrozole, with letrozole being the most widely used (Elizur and Tuland, 2008).

The enzyme aromatase is a member of the cytochrome P450 hemoprotein containing enzyme complex super family and catalyses the conversion of androgens to estrogens, specifically the conversion of testosterone and androstenedione to estradiol (E2) and estrone, respectively in the ovary. Therefore, AIs inhibit estrogen biosynthesis, releasing the hypothalamic/pituitary axis from the estrogens negative feedback and increasing the secretion of FSH by the pituitary. As a result, the ovary receives increased FSH stimulation, allowing for greater follicular growth and development. In addition, androgens that are normally converted to estrogens accumulate in the ovary and these androgens increase follicular sensitivity to FSH (Holzer et al., 2006).

The main incentives for the development of AIs as ovulation induction agents were to avoid some of the adverse effects of CC, including the peripheral anti-estrogenic effects on the endometrium and cervical mucus (Healey et al., 2003) and the increased risk of multiple pregnancy (Casper, 2003). AIs, unlike CC, do not affect estrogen receptors centrally or the thin endometrial lining (Holzer et al., 2006). The increasing E2 levels secreted by the multiple developing ovarian follicles first appear on Day 7 and result in a normalized negative feedback on FSH secretion later in the follicular phase (Casper, 2003). Follicles that are smaller than the dominant follicle undergo atresia, resulting, in most cases, in single follicle ovulation (Casper, 2003).

The AI, letrozole, is typically administered on Days 3–7 of the menstrual cycle at doses of 2.5–7.5 mg/day in 2.5 mg increments (Pritts, 2010). Adverse effects include gastrointestinal disturbances, asthenia, hot flushes, headache and back pain (Holzer et al., 2006). Initially, there was concern that the use of letrozole for infertility treatment may be associated with teratogenic effects (Biljan et al., 2005), but later publications did not find an association with fetal anomalies (Tulandi et al., 2006; Forman et al., 2007). Given that AIs have recently been used in the treatment of infertile women with PCOS, it is important to evaluate their effectiveness in improving fertility outcomes in this group of women.

Methods

This systematic evidence review is an update (systematic search has been updated) of an initial review prepared to inform clinical practice recommendations in the National Health and Medical Research Council (NHMRC) approved Evidence-based guideline for the assessment and diagnosis of PCOS (PCOS Australian Alliance, 2011; Teede et al., 2011). The guideline, including detailed information about the rigorous methodology used for development of the guideline, composition of the multidisciplinary guideline development committees and NHMRC approval processes, 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, are AIs (compared with placebo, no intervention or other infertility treatment) effective for improving fertility outcomes?

Selection criteria

The population, intervention, comparison and outcome framework in Table I established a priori was used to include and exclude studies for this systematic evidence review.

Systematic search for evidence

A broad-ranging systematic search (found in Supplementary data, Table S1: Systematic search terms) 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 year of publication. The literature was searched from as early as 1950 until July 2011 for randomized controlled trials (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. and 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.L.M.) 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.F.C., A.M.M.) to reach a consensus. Using this approach, each study was allocated a risk of bias rating (found in Supplementary data, Table SII: Risk of bias ratings). Findings from the body of evidence and their applicability to the clinical question were discussed in light of risk of bias.

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

Data synthesis
Meta-analyses were performed using ‘Review Manager 5’ with the six RCTs that compared letrozole with CC (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. Odds ratios (ORs) 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) due to the possibility that cycles for each patient may be counted more than once. A rate ratio (RR) is used to present the effect estimate for ovulation rate per cycle meta-analysis. High heterogeneity $\chi^2 > 50\%$ 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 returned 4981 articles, of which 78 articles addressed AIs. The articles were reviewed by title and abstract. There were 23 full-text articles retrieved for further review, and 13 RCTs met the inclusion and exclusion criteria. A table of excluded studies with reasons for exclusion of full-text articles can be found in Supplementary data, Table SIII: Table of excluded studies.

Characteristics and quality of included RCTs
Brief characteristics of included RCTs can be found in Table II and full characteristics of included studies can be found in Supplementary data, Table SIV.
<table>
<thead>
<tr>
<th>RCT</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole versus placebo</td>
<td>Kamath et al. (2010) 36 women with CCR PCOS. 18 per group</td>
<td>2.5 mg/day of L for 5 days from Day 2–6 of menses</td>
<td>Placebo</td>
<td>OR, PR, LBR, MR</td>
<td>Low</td>
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<tr>
<td>Long-term letrozole versus short-term letrozole</td>
<td>Badawy et al. (2009a,b) 218 (444 cycles) women with CCR PCOS. Short: 110 (225 cycles) Long: 108 (219 cycles)</td>
<td>Short: 5 mg/day of L for 5 days from Day 1 of menses</td>
<td>Long: 2.5 mg/day of L for 10 days from Day 1 of menses</td>
<td>PR, MR</td>
<td>Low</td>
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<tr>
<td>Letrozole versus anastrozole</td>
<td>Al-Omari et al. (2004) 40 women with CCR PCOS. L: 22, A: 18</td>
<td>2.5 mg/day of L for 5 days from Day 3 of menses</td>
<td>1 mg/day of A for 5 days from Day 3 of menses</td>
<td>OR, PR, MR, OR</td>
<td>Low</td>
</tr>
<tr>
<td>Letrozole versus CC</td>
<td>Badawy et al. (2008) 220 (574 cycles) women with CCR PCOS. L: 111 (295 cycles), A: 109 (279 cycles)</td>
<td>2.5 mg/day of L for 5 days from Day 3 of menses</td>
<td>1 mg/day of A for 5 days from Day 3 of menses</td>
<td>OR, PR, MR, OR</td>
<td>Low</td>
</tr>
<tr>
<td>Letrozole versus CC plus metformin</td>
<td>Begum et al. (2009) 64 women with CCR PCOS. 32 in each group</td>
<td>7.5 mg/day of L daily for 5 days from Day 3 of menses</td>
<td>150 mg/day of CC for 5 days from Day 3 of menses</td>
<td>OR, PR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Letrozole versus laparoscopic ovarian drilling</td>
<td>Dehbashi et al. (2009) 100 therapy naive women with PCOS. 50 in each group</td>
<td>5 mg/day of L for one cycle from 3 to 7 days of menses</td>
<td>100 mg/day of CC for one cycle from 3 to 7 days of menses</td>
<td>OR, PR, LBR, MPR, MR, LBR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Letrozole versus laparoscopic ovarian drilling</td>
<td>Zeinalzadeh et al. (2010) 107 women with PCOS CCR not reported. L: 50, CC: 57</td>
<td>5 mg/day of L for 5 days within Days 3–7 of menses</td>
<td>100 mg/day of CC for 5 days within Days 3–7 of menses</td>
<td>OR, PR, MPR</td>
<td>High</td>
</tr>
<tr>
<td>Letrozole versus CC plus metformin</td>
<td>Abu Hashim et al. (2010a,b) 250 (582 cycles) women with CCR PCOS. L: 123 (285 cycles), CC + M: 127 (297 cycles)</td>
<td>2.5 mg/day of L for 5 days from Day 3 of menses</td>
<td>500 mg/day × 3 of M for 6–8 weeks, then 150 mg/day of CC for 5 days from Day 3 of menses</td>
<td>OR, PR, MR</td>
<td>Moderate</td>
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<tr>
<td>Letrozole versus laparoscopic ovarian drilling</td>
<td>Abdellah (2011) 140 women with CCR PCOS. L: 70 (346 cycles), LOD: 70 patients (373 cycles)</td>
<td>5 mg/day of L for 5 days from Day 3 of menses</td>
<td>Triple-puncture LOD</td>
<td>OR, PR, MR</td>
<td>Low</td>
</tr>
<tr>
<td>Letrozole versus laparoscopic ovarian drilling</td>
<td>Abu Hashim et al. (2010a,b) 260 women with CCR PCOS. L: 128 (512 cycles), LOD: 132 (525 cycles)</td>
<td>2.5 mg/day of L for 5 days from Day 3 of menses</td>
<td>Three-puncture LOD</td>
<td>OR, PR, MR, LBR</td>
<td>Low</td>
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</table>

Full characteristics of included RCTs, including detailed intervention, comparison and population characteristics such as mean age and BMI, can be found in Supplementary information IV.

A, anastrozole; BMI, body mass index; CC, clomiphene citrate; CCR, clomiphene-citrate resistant; L, letrozole; LBR, live birth rate; LOD, laparoscopic ovarian drilling; M, metformin; MPR, multiple pregnancy rate; MR, miscarriage rate; OR, ovulation rate; P, placebo; PCOS, polycystic ovary syndrome; PR, pregnancy rate.

One high-quality RCT with a low risk of bias compared letrozole with placebo in women with PCOS who were CC-resistant (Kamath et al., 2010).

Two RCTs, one with a high risk of bias (Al-Omari et al., 2004) and the other with a low risk of bias (Badawy et al., 2008) compared letrozole with anastrozole in women with PCOS who were CC-resistant.

One high-quality RCT with low risk of bias compared short-term therapy of letrozole with long-term therapy of letrozole (Badawy et al., 2009a,b).

Six RCTs compared letrozole with CC and were deemed sufficiently homogenous to conduct meta-analyses. Two of these had a high risk of bias (Atay et al., 2006; Zeinalzadeh et al., 2010), two had a moderate risk of bias (Begum et al., 2009; Dehbashi et al., 2009) and two had a low risk of bias (Bayar et al., 2006; Badawy et al., 2009a,b). These six RCTs included women with PCOS who were therapy naive (Bayar et al., 2006; Dehbashi et al., 2009), CC-resistant (Begum et al., 2009) or the type of PCOS (therapy naive or CC-resistant) was not reported (Atay et al., 2006; Badawy et al., 2009a,b; Zeinalzadeh et al., 2010).
One medium-quality RCT with moderate risk of bias compared letrozole with CC plus metformin in women with PCOS who were CC-resistant (Abu Hashim et al., 2010a,b). Two high-quality RCTs with low risk of bias compared letrozole with laparoscopic ovarian drilling (LOD) in women with PCOS who were CC-resistant (Abu Hashim et al., 2010a;b; Abdellah, 2011). Study setting and follow up were often not reported.

Treatment duration of AIs in all of the RCTs was 5 days except in the RCT comparing a short (5 days) versus long (10 days) course of letrozole (Badawy et al., 2009a,b). Where reported, age and BMI were similar across the study populations. All of the RCTs used validated measures where appropriate or described in detail how outcome data were collected. Detailed appraisal and data tables can be found in Supplementary data, Table SV: Evidence tables.

**Letrozole versus placebo**

There is evidence from one high-quality RCT with low risk of bias, in women with PCOS who were CC-resistant, that letrozole was better than placebo for ovulation rate per patient (L: 6 of 18, 33.33% versus P: none of 18, 0%, P = 0.006) but there was no statistical difference between letrozole and placebo for pregnancy rate per patient (L: 1 of 18, 5.55% versus P: none of 18, 0%, P = 0.324) or live birth rate per patient (L: 1 of 18, 5.55% versus P: none of 18, 0%, P = 0.324) (Kamath et al., 2010).

**Duration of letrozole therapy**

Evidence from one high-quality RCT with low risk of bias suggests that long-term therapy (10 days at 2.5 mg/day) of letrozole may be better than short-term therapy (5 days at 5 mg/day) for pregnancy rate per cycle in CC-resistant women with PCOS (short: 28 pregnancies/225 cycles, 12.4% versus long: 38 pregnancies/219 cycles, 17.4%, P = 0.03) (Badawy et al., 2009a,b). The same RCT found no statistical difference between long-term and short-term therapy for ovulation rate per patient (short: 68 of 110, 61.8% versus long: 71 of 108, 65.7%, P = 0.11) or miscarriage rate per pregnancy (short: 5 miscarriages/28 pregnancies, 17.9% versus long: 7 miscarriages/38 pregnancies, 18.4%, P = 0.64) in CC-resistant women with PCOS (Badawy et al., 2009a,b).

**Letrozole versus anastrozole**

One high-quality RCT with low risk of bias found that there is no statistical difference between letrozole and anastrozole for ovulation rate per cycle [L: 183 cycles/295 cycles, 62% versus A: 177 cycles/279 cycles, 63.4%, P and confidence interval (CI) not reported but the authors state that this was not significant], pregnancy rate per cycle (L: 36 pregnancies/295 cycles, 12.2% versus A: 42 pregnancies/279 cycles, 15.1%, P = 0.31) or miscarriage rate per pregnancy (L: 4 miscarriages/36 pregnancies, 11.1% versus A: 4 miscarriages/42 pregnancies, 9.5%, P = 0.92) in CC-resistant women with PCOS (Badawy et al., 2008). A low-quality RCT with a high risk of bias addressed the same comparison and outcomes and found that letrozole is better than anastrozole for ovulation rate per cycle (L: 84.4%, A: 60%, P < 0.05) and pregnancy rate per patient (L: 27%, A: 16.6%, P < 0.05); however, only percentages were presented and it is possible that the effect may be overestimated in a study with a high risk of bias. Therefore, the results should be interpreted with caution (Al-Omari et al., 2004).

**Letrozole versus CC**

When three RCTs (Atay et al., 2006; Begum et al., 2009; Dehbashi et al., 2009), including women with PCOS who were therapy naïve or CC-resistant or women with PCOS without clarification as to whether they were therapy naïve or CC-resistant, were combined in a meta-analysis, letrozole was better than CC for ovulation rate per patient [Fig. 1a: OR 2.90 (95% CI 1.72, 4.88), I² = 0%, P < 0.0001]. There was no statistical difference between letrozole and CC for ovulation rate per cycle when two RCTs (Bayar et al., 2006; Badawy et al., 2009a,b) were combined in a meta-analysis [Fig. 1b: RR 0.94 (95% CI 0.82, 1.07), I² = 0%, P = 0.37]. This meta-analysis included a mixed population of women with PCOS who were either therapy naïve (Bayar et al., 2006) or women with PCOS without clarification as to whether they were therapy naïve or CC-resistant (Badawy et al., 2009a,b). There was no statistical difference between letrozole and CC for pregnancy rate per patient (Fig. 2) (Atay et al., 2006; Bayar et al., 2006; Badawy et al., 2009a,b; Begum et al., 2009; Dehbashi et al., 2009; Zeinalzadeh et al., 2010) [OR 1.53 (95% CI 0.91, 2.58), I² = 50%, P = 0.11], miscarriage rate per pregnancy (Bayar et al., 2006; Begum et al., 2009; Dehbashi et al., 2009; Badawy et al., 2009a,b) [OR 0.66 (95% CI 0.22, 1.95), I² = 0%, P = 0.45], live birth rate per pregnancy (Bayar et al., 2006; Dehbashi et al., 2009) [OR 0.48 (95% CI 0.07, 3.55), I² = 0%, P = 0.48] or multiple pregnancy rate per patient (Atay et al., 2006; Badawy et al., 2009a,b; Dehbashi et al., 2009; Zeinalzadeh et al., 2010) [OR 2.53 (95% CI 0.53, 12.16), I² = 0%, P = 0.25] in women with PCOS who were therapy naïve (Bayar et al., 2006; Dehbashi et al., 2009), CC-resistant (Begum et al., 2009), or type of PCOS was not reported (Atay et al., 2006; Badawy et al., 2009a,b; Zeinalzadeh et al., 2010). High heterogeneity in the pregnancy rate per patient meta-analysis was explored using sensitivity analysis for risk of bias, however upon removal of the two RCTs with high risk of bias (Atay et al., 2006; Zeinalzadeh et al., 2010), there was no difference in the effect estimate for this outcome. The results of individual RCTs comparing letrozole and CC are presented in Table III.

**Letrozole versus CC plus metformin**

Evidence from one medium-quality RCT with moderate risk of bias demonstrated that there is no statistical difference between letrozole and CC plus metformin for ovulation rate per cycle (L: 185 cycles/285 cycles, 64.9% versus CC + M: 207 cycles/297 cycles, 69.6%, P = 0.82), pregnancy rate per cycle (L: 42 pregnancies/285 cycles, 14.7% versus CC + M: 43 pregnancies/297 cycles, 14.4%, P = 0.53), miscarriage rate per pregnancy (L: 4 miscarriages/42 pregnancies, 10.2% versus CC + M: 4 miscarriages/43 pregnancies, 9.5%, P = 0.43) or multiple pregnancy rate per pregnancy (three twin pregnancies in the CC + M group and none in the letrozole group, statistical significance not reported) in 250 CC-resistant women with PCOS (Abu Hashim et al., 2010a,b).

**Letrozole versus LOD**

Evidence from one high-quality RCT with low risk of bias in 147 CC-resistant women with PCOS suggest that six cycles of letrozole is
better than LOD at 6 months follow-up for ovulation rate per cycle (L: 204 cycles/346 cycles, 59% versus LOD: 177 cycles/373 cycles, 47.5%, P < 0.001); however, there is no statistical difference between letrozole and LOD for pregnancy rate per patient (L: 25 pregnancies/70 patients, 35.7% versus LOD: 20 pregnancies/70 patients, 28.6%, P = 0.24), live birth rate per patient (L: 23 births/70 patients, 32.9% versus LOD: 16 births/70 patients, 22.9%, P = 0.129) or miscarriage rate per pregnancy (L: 2 miscarriages/25 pregnancies, 8% versus LOD: 4 miscarriages/20 pregnancies, 20%, P = 0.231) (Abdellah, 2011). Another high-quality RCT with low risk of bias compared the same interventions over the same follow-up time periods and found that there are no statistical differences for ovulation rate per cycle (L: 335 of 512, 65.4% versus LOD: 364 of 525, 69.3%, actual P-value not given but was reported as not significant), pregnancy rate per cycle (L: 80 of 512, 15.6% versus LOD: 92 of 525, 17.5%, actual P-value not given but was reported as not significant), pregnancy rate per patient (L: 36 of 128, 28.1% versus LOD: 37 of 132, 28.0%, actual P-value not given but was reported as not significant), live birth rate per pregnancy (L: 32 of 36, 89.0% versus LOD: 33 of 37, 89.2%, actual P-value not given but was reported as not significant), biochemical miscarriage rate per patient (L: 44 of 80, 55.0% versus LOD: 55 of 92, 59.8%, actual P-value not given but was reported as not significant) or clinical miscarriage rate per pregnancy (L: 4 of 36, 11.1% versus LOD: 4 of 37, 10.8%, actual P-value not given but was reported as not significant) between letrozole and LOD (Abu Hashim et al., 2010a,b).

Discussion

This systematic review did not identify any RCTs evaluating the efficacy of AIs as first-line therapy (i.e. AIs versus placebo or no treatment) in women with PCOS who are therapy naive. However, there are a number of RCTs addressing the effectiveness of AIs as second-line therapy specifically in women with PCOS and CC-resistance.

As per evidence-based guidelines in PCOS, first-line therapy for infertility in women with PCOS should always start with a focus on support, education, addressing psychological factors and strongly emphasizing healthy lifestyle interventions, with targeted pharmacological therapy as second-line option (Fig. 3) (PCOS Australian Alliance, 2011; Teede et al., 2011).

In second-line therapy, letrozole is superior to placebo in terms of ovulation rate, but not pregnancy or live birth rate per patient, in women with CC-resistant PCOS, based on a single high-quality RCT powered for difference in ovulation rate (Kamath et al., 2010). A medium-quality RCT comparing letrozole with CC in women with CC-resistant PCOS, showed a higher ovulation rate per patient with letrozole but no difference in pregnancy rate per patient between the two treatments (Begum et al., 2009). Both RCTs had low numbers of participants. Therefore, there is insufficient evidence to support the use of AIs specifically in women with CC-resistant PCOS to improve pregnancy and live birth.

Meta-analyses in the systematic review addressing second-line use of AIs demonstrated that for infertile, anovulatory women with
Figure 2. Letrozole versus clomiphene citrate: rate of pregnancy, miscarriage and live birth. (a) Pregnancy rate per patient. (b) Miscarriage rate per pregnancy. (c) Live birth rate per pregnancy. (d) Multiple pregnancy rate per pregnancy. CC, clomiphene citrate; HRB, high risk of bias; LRB, low risk of bias; MRB, moderate risk of bias.
<table>
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<tr>
<th>RCT</th>
<th>Ovulation rate</th>
<th>Pregnancy rate</th>
<th>Live birth rate</th>
<th>Multiple pregnancy rate</th>
<th>Miscarriage rate</th>
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<tr>
<td><strong>Atay et al. (2006)</strong></td>
<td>Per patient L: 42 patients/51 patients (82.4%) CC: 35 patients/55 patients (63.6%), P = 0.016</td>
<td>Per patient L: 11 patients/51 patients (21.6%) CC: 5 patients/55 patients (9.1%), P = 0.037</td>
<td>Per patient L: 0 multiple pregnancies/11 pregnancies (0%) CC: one multiple pregnancy/five pregnancies (20%), P not reported</td>
<td>Per patient L: 4 miscarriages/218 patients (12.1%) CC: 4 miscarriages/220 patients (9.7%), P = 0.43</td>
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<td><strong>Badawy et al. (2009a,b)</strong></td>
<td>Per cycle L: 365 cycles/540 cycles (67.5%) CC: 371 cycles/523 cycles (70.9%), P not reported but the authors state that this was not significant</td>
<td>Per cycle L: 82 pregnancies/540 cycles (13.1%) CC: 94 pregnancies/523 cycles (17.9%), P = 0.72</td>
<td>Per pregnancy L: 0 multiple pregnancies/82 pregnancies (0%) CC: 3 multiple pregnancies/94 pregnancies (3.2%), P not reported</td>
<td>Per pregnancy L: 1 miscarriage/99 cycles (1%) CC: 0 miscarriages/95 cycles (0%), P not reported</td>
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<td><strong>Bayar et al. (2006)</strong></td>
<td>Per cycle L: 65 cycles/99 cycles (65.7%) CC: 71 cycles/95 cycles (74.7%), P = 0.17</td>
<td>Per cycle L: 9 pregnancies/99 cycles (9.1%) CC: 7 pregnancies/95 cycles (7.4%), P = 0.66</td>
<td>Per cycle L: 8 live births/99 cycles (8.1%) CC: 7 live births/95 cycles (7.4%), P = 0.92</td>
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<td><strong>Begum et al. (2009)</strong></td>
<td>Per patient L: 20 patients/32 patients (62.5%) CC: 12 patients/32 patients (37.5%), P &lt; 0.05</td>
<td>Per patient L: 13 patients/32 patients (40.62%) CC: 6 patients/32 patients (18.75%), P &gt; 0.05</td>
<td>L: 10 patients/13 pregnancies (77%) CC: 6 patients/7 pregnancies (86%), P and CI not reported</td>
<td>No multiple pregnancy or other side effects were noted in either of the groups</td>
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<td><strong>Dehbashi et al. (2009)</strong></td>
<td>Per patient L: 30 patients/50 patients (60%) CC: 16 patients/50 patients (32%), P = 0.009</td>
<td>Per patient L: 13 patients/50 patients (26%) CC: 7 patients/50 patients (14%), P = 0.21</td>
<td>Per pregnancy L: 10 patients/13 pregnancies (77%) CC: 6 patients/7 pregnancies (86%), P and CI not reported</td>
<td>Per pregnancy L: 3 patients/13 pregnancies (23%) CC: 1 patients/7 pregnancies (14.3%), P = 1</td>
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<td><strong>Zeinalzadeh et al. (2010)</strong></td>
<td>Per patient L: 86% (number of patients not reported) CC: 75.5% (number of patients not reported), P = 0.07</td>
<td>Per patient L: 10 patients/50 patients (20%) CC: 8 patients/57 patients (14%), P = 0.14</td>
<td>Per pregnancy L: 1 multiple pregnancy/10 pregnancies (10%) CC: 0 multiple pregnancies/8 multiple pregnancies (0%), P not reported</td>
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CC, clomiphene citrate; L, letrozole.
PCOS (including those who are therapy naïve, CC-resistant and those whose sensitivity to CC has not been reported), letrozole may be as effective as CC for pregnancy rate per patient (although one should note the difference in favour of letrozole), miscarriage rate per pregnancy, live birth rate per pregnancy and multiple pregnancy rate per pregnancy (Fig. 2). The meta-analysis for ovulation rate per patient demonstrated a higher ovulation rate per patient with letrozole; however, this meta-analysis was based on three RCTs that are of low to medium quality with moderate to high risk of bias (Fig. 1a). The meta-analysis for ovulation rate per cycle was based on two high-quality RCTs with low risk of bias and no statistical difference between letrozole and CC was observed (Fig. 1b). It should be noted that the RCTs in the meta-analysis inconsistently reported the status of sensitivity to CC. Two RCTs reported in the inclusion criteria that the participants were therapy naïve (Bayar et al., 2006; Dehbashi et al., 2009), one RCT included women who failed to ovulate when taking 100 mg/day of CC for 5 days in two consecutive cycles (Begum et al., 2009) and the remaining three RCTs did not specify whether the participants were therapy naïve or CC-resistant (Atay et al., 2006; Badawy et al., 2009a,b; Zeinalzadeh et al., 2010). Furthermore, all of the six RCTs were not powered a priori to detect a difference in ovulation or pregnancy rates. Findings of studies of moderate or high risk of bias should be interpreted with caution. The RCTs by Atay et al. (2006) and Zeinalzadeh et al. (2010) were both found to have a high risk of bias. The removal of these two RCTs from the meta-analysis during sensitivity analysis only marginally reduced heterogeneity and the effect estimate remained unaltered. Therefore, there is insufficient evidence to recommend letrozole over CC in infertile anovulatory women with PCOS in general.

A meta-analysis of four RCTs found that AIs were better than CC for pregnancy rate per patient [OR 2.0 (95% CI 1.1, 3.8) P = 0.025] and birth rate per patient [OR 2.4 (95% CI 1.2, 4.6) P = 0.011] (Polyzos et al., 2008). While there was no between-study heterogeneity observed, one of the included RCTs compared a combination of letrozole plus metformin with CC plus metformin in women with CC-resistant PCOS. Another RCT compared anastrozole plus FSH injections versus CC plus FSH injections. Eckmann and Kockler (2009) provided a descriptive systematic review of 11 prospective studies (including non-randomized studies) comparing AIs with CC in women with PCOS who were CC-resistant and treatment naïve and concluded that large comparative trials are necessary before AIs can be recommended routinely for ovulation induction. However, the authors went on to suggest that AIs may be of benefit in a subset of women with PCOS and infertility. This included those women who are not candidates for CC, gonadotrophins or GnRH analogues, providing that the risks and benefits have been discussed with the patient.

Two high-quality RCTs comparing letrozole with LOD over 6 months in women with CC-resistant PCOS, both with moderate sample sizes, found that there was no difference between the two interventions for all outcomes except ovulation rate per cycle, where the findings were conflicting (Abu Hashim et al., 2010a,b; Abdellah, 2011). Until further trials are conducted comparing these
interventions, there is insufficient evidence to recommend the use of letrozole over LOD.

The concern about the safety of the fetus in mothers who used letrozole was first raised in an oral abstract presentation at an American Society for Reproductive Medicine meeting in 2005 (Biljan et al., 2005). This Canadian retrospective observational study examined a relatively small number of babies (n = 150) born as a result of ovulation induction using either letrozole alone or in combination with gonadotrophins in women with unexplained infertility or PCOS and found that the use of letrozole for infertility treatment might be associated with a higher risk of congenital cardiac and ‘bone’ malformations in the newborns. However, two subsequent publications suggest that letrozole use for ovulation induction in infertility may not be associated with increased risk of fetal anomaly (Tulandi et al., 2006; Forman et al., 2007). The first Canadian retrospective observational study found no difference in the incidence of congenital malformations between 397 newborns arising from CC-induced pregnancies (4.8%) and 514 newborns arising from letrozole-induced pregnancies (2.4%). The authors concluded that the teratogenicity concerns with the use of letrozole for ovulation induction are unfounded (Forman et al., 2007). The second Canadian retrospective observational study found no difference in congenital malformations between 112 newborns from 94 letrozole-induced pregnancies, 271 newborns from 242 CC-induced pregnancies and 112 control newborns from spontaneous pregnancies (Tulandi et al., 2006). The authors concluded that the use of letrozole for ovulation induction does not appear to increase the risk of congenital malformations. In any case, AIs should be used with caution and patients should be adequately counselled about the potential safety concerns in newborns until this class of drugs have been further researched and approved for ovulation induction (Vause et al., 2010; PCOS Australian Alliance, 2011; Teede et al., 2011).

If the clinical decision is to use AIs, it remains unclear based on current evidence which type of AI to use. A high-quality RCT with low risk of bias found no statistical difference between letrozole and anastrozole (Badawy et al., 2008), whereas a low-quality RCT found that letrozole is better than anastrozole (Al-Omari et al., 2004). This effect may be overestimated in a study with high risk of bias and these results should be interpreted with caution. Only one RCT, performed in PCOS women with CC resistance, addressed the duration and dose of letrozole. The 10-day protocol using 2.5 mg/day appeared better than the shorter, 5-day protocol using 5 mg/day (Badawy et al., 2009a,b).

Evidence is insufficient to support the use of letrozole as first-line pharmacological therapy for infertility in women with PCOS. Therefore, in the absence of high-quality evidence about the effectiveness of AIs as first-line pharmacological therapy in this population, AIs should not be recommended as first-line treatment in women with PCOS who are anovulatory and infertile.

There is also insufficient evidence to date to recommend letrozole over CC in infertile anovulatory women with PCOS, in general or specifically in therapy naïve or CC-resistant women with PCOS. The evidence about the risk of congenital abnormalities with the use of AIs is unclear and these complications cannot be ruled out. However, under caution and with patient explanation and consent, either letrozole or anastrozole may be used if one is considering using AIs in women with PCOS who are CC-resistant, anovulatory and infertile with no other infertility factors. If using letrozole, it is preferable to treat for 10 days at a dose of 2.5 mg/day. Further methodologically rigorous, large trials are important to address the role of AIs in ovulation induction in women with PCOS, including in specific subgroups of women with PCOS such as those who are therapy naïve and CC-resistant.

Supplementary data

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

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Authors’ roles

M.L.M. contributed substantially to the design of the study; acquisition, analysis and interpretation of data; prepared, drafted and revised the article. J.L.A.W. contributed substantially to the conception of the study; interpretation of data and revised the article for important intellectual content and approved the final draft for publication. J.L.A.W. contributed substantially to the conception of the study; interpretation of data and revised the article for important intellectual content and approved the final draft for publication. H.J.T. contributed to the conception of the study; interpretation of data and revised the article for important intellectual content and approved the final draft for publication. L.R. contributed to the conception of the study; interpretation of data and revised the article for important intellectual content and approved the final draft for publication. A.M.M. contributed substantially to the design of the study; interpretation of data and revised the article for important intellectual content and approved the final draft for publication. F.C. contributed substantially to the conception of the study; interpretation of data and revised the article for important intellectual content and approved the final draft for publication.

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Conflict of interest

R.H. is a Medical Director of Fertility Specialists of WA, Medical Director of Fertility Specialists South, a member of the Fertility Advisory Board Schering Plough, a member of the Fertility Advisory Board Merck Serono, received grant from Merck Serono Australia Pty Ltd to fund ultrasound technician for testicular size measurement as part of NHMRC-supported prospective study in early life origins of adult testicular function. L.R. is a member of the Merck-Serono Australia Pty Ltd Advisory Board and the MSD–Schering Plough Pty Ltd Advisory Board. Both of these companies produce gonadotrophins—advice did not relate to currently available gonadotrophins—has ownership in an IVF company and received unconditional grants from Schering Plough Pty Ltd and Merck Serono Australia Pty Ltd, donated to Monash Research and Education Foundation. R.J.N. shares in Fertility SA, a company providing fertility and IVF services in Adelaide, received speaker fees from MSD Australia and Merck Serono Australia Pty Ltd., received honoraria from MSD–Schering Plough Pty Ltd and Merck Serono Australia Pty Ltd, and is a member of the MSD–Schering Plough Pty Ltd Advisory Board. M.F.C. shares in IVF Australia, received a grant from Schering Plough Pty Ltd in 2002 for research project unrelated to polycystic ovary syndrome. Schering Plough manufactures FSH injections for ovulation induction/ovarian stimulation, received sponsorship to attend and present at national and international scientific meetings on a broad range of topics determined by the individual conference organizing committees, from pharmaceutical companies (Serono and Schering Plough Pty Ltd) who have a commercial interest in PCOS treatment products or guide-
ces. The funders, the Australian Government Department of Health and Ageing, were not involved in the preparation of this manuscript or development of the guideline and have not influenced the scope or conclusions herein.

References


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