Aromatase inhibitors for subfertile women with polycystic ovary syndrome (Review)

Franik S, Kremer JAM, Nelen WLDM, Farquhar C

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Aromatase inhibitors for subfertile women with polycystic ovary syndrome

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Editorial group: Cochrane Menstrual Disorders and Subfertility Group.

Publication status and date: Edited (no change to conclusions), published in Issue 10, 2014.

Review content assessed as up-to-date: 18 September 2014.

Citation: Franik S, Kremer JAM, Nelen WLD, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD010287. DOI: 10.1002/14651858.CD010287.pub2.

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ABSTRACT

Background

Polycystic ovary syndrome (PCOS) is the most common cause of infrequent periods (oligomenorrhoea) and absence of periods (amenorrhoea). It affects about 4% to 8% of women worldwide and often leads to anovulatory subfertility. Aromatase inhibitors (AIs) are a novel class of drugs that were introduced for ovulation induction in 2001. Over the last ten years clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective as the first-line treatment clomiphene citrate (CC).

Objectives

To evaluate the effectiveness and safety of aromatase inhibitors for subfertile women with anovulatory PCOS.

Search methods

We searched the following sources from inception to September 2014 to identify relevant randomised controlled trials (RCTs): the Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO, Pubmed, LILACS, Web of Knowledge, the World Health Organisation (WHO) clinical trials register and Clinicaltrials.gov. Furthermore, we manually searched the references of relevant articles. The search was not restricted by language or publication status.

Selection criteria

We included all RCTs of aromatase inhibitors used alone or with other medical therapies for ovulation induction in women of reproductive age with anovulatory PCOS.

Data collection and analysis

Two review authors independently selected trials, extracted the data and assessed trial quality. Studies were pooled where appropriate using a fixed effect model to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs) for most outcomes and risk differences (RDs) for ovarian hyperstimulation syndrome (OHSS). The primary outcomes were live birth and OHSS. Secondary outcomes were pregnancy, miscarriage and multiple pregnancy. The quality of the evidence for each comparison was assessed using GRADE methods.

Main results

We included 26 RCTs (5560 women). In all studies the aromatase inhibitor was letrozole.

Live birth (12 RCTs)

One RCT compared letrozole with placebo in women who were clomiphene resistant and the results were inconclusive (OR 3.17, 95% CI 0.12 to 83.17, n=36)

Nine RCTs compared letrozole with clomiphene citrate (with or without adjuncts in one or both arms) followed by timed intercourse. The birth rate was higher in the letrozole group (OR 1.64, 95% CI 1.32 to 2.04, n=1783, I²=3%)

Two RCTs compared letrozole with laparoscopic ovarian drilling. There was no evidence of a difference between the groups in live birth rate (OR 1.19, 95% CI 0.76 to 1.86, n=407, I²=0%)

OHSS (16 RCTs)

There was no evidence of a difference in OHSS rates when letrozole (with or without adjuncts) was compared with placebo (one RCT, n=36), clomiphene citrate (with or without adjuncts) followed by timed intercourse (nine RCTs, n=2179) or intrauterine insemination (IUI) (two RCTs, n=1494), laparoscopic ovarian drilling (one RCT, n=260) or anastrozole (one RCT, n=220). Events were absent or very rare, and no study had more than 2 cases of OHSS.

Clinical pregnancy (25 RCTs)

One RCT compared letrozole versus placebo in women who were clomiphene resistant and the results were inconclusive (OR 3.17, 95% CI 0.12 to 83.17, n=36)

Fifteen RCTs compared letrozole versus clomiphene citrate (with or without adjuncts in one or both arms) followed by timed intercourse. The pregnancy rate was higher in the letrozole group (OR 1.40, 95% CI 1.18 to 1.65, n=2816, I²=26%)

Three RCTs compared letrozole versus clomiphene citrate (with or without adjuncts) followed by IUI. The pregnancy rate was higher in the letrozole group (OR 1.71, 95% CI 1.30 to 2.25, n=1597)

Three RCTs compared letrozole (with or without metformin) versus laparoscopic ovarian drilling. There was no evidence of a difference in the clinical pregnancy rate (OR 1.14, 95% CI 0.80 to 1.65, n=553, I²=0%)

Two RCTs compared letrozole versus anastrozole, one RCT compared a five day versus a 10 day administration protocol for letrozole and another RCT compared 5 mg of letrozole versus 7.5 mg of letrozole. There was no evidence of a difference in the clinical pregnancy rate in these comparisons.

The quality of the evidence was rated as low for live birth and pregnancy outcomes. The reasons for downgrading the evidence were poor reporting of study methods, possible publication bias and the tendency for studies that reported live birth to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth (suggesting that results might be somewhat less favourable to letrozole if all studies reported live birth).

Authors' conclusions

Letrozole appears to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to clomiphene citrate. The quality of this evidence is low and findings should be regarded with some caution. There appears to be no difference in effectiveness between letrozole and laparoscopic ovarian drilling, though there were few relevant studies. OHSS was a very rare event, with no occurrences in most studies.

PLAIN LANGUAGE SUMMARY

Aromatase inhibitors for subfertility treatment in women with polycystic ovary syndrome

Review question: Cochrane authors examined the evidence about aromatase inhibitors for subfertile women with polycystic ovary syndrome (PCOS).

Background: PCOS is the most common cause of infrequent or absent menstrual periods, and affects about 4% to 8% of women worldwide. It often causes anovulatory subfertility (subfertility related to failure to ovulate). Aromatase inhibitors are used to induce

ovulation. Over the last ten years clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective for treating subfertility as the most commonly used treatment, clomiphene citrate.

Study characteristics: The review included 26 randomised controlled trials (RCTs) with 5560 women. In all trials the aromatase inhibitor used was letrozole. Comparators included clomiphene citrate, which was used in 17 of the RCTs, and laparoscopic ovarian drilling, which was used in three RCTs. Several studies included co-treatments in one or both arms.

Key results: Letrozole appears to improve live birth and pregnancy rates compared to clomiphene citrate. However the quality of this evidence was low and findings should be regarded with some caution. There appeared to be no difference between letrozole and laparoscopic ovarian drilling, though there were few relevant studies. OHSS was a very rare event and there were no occurrences in most studies. The evidence is current to September 2014.

Quality of the evidence: The overall quality of the evidence ranged from low to moderate.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Aromatase inhibitors compared to clomiphene citrate with or without adjuncts for subfertile women with polycystic ovary syndrome						
Population: Subfertile women with polycystic ovary syndrome						
Intervention: Aromatase inhibitors compared to clomiphene citrate (with or without adjuncts in one or both arms) followed by timed intercourse						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Clomiphene citrate with or without adjuncts	Aromatase inhibitors (Letrozole) with or without adjuncts				
Live birth rate	188 per 1000	275 per 1000 (234 to 321)	OR 1.64 (1.32 to 2.04)	1783 (9 studies)	⊕⊕○○ low ¹	
Ovarian hyperstimulation syndrome rate	0 per 1000	0 per 1000 (0 to 0)	See comment	2179 (9 studies)	⊕⊕⊕○ moderate ²	Risks were calculated from pooled risk differences. Two events occurred in the clomiphene group in one study. The other eight studies reported no events in either arm.
Clinical pregnancy rate	202 per 1000	262 per 1000 (230 to 295)	OR 1.4 (1.18 to 1.65)	2816 (15 studies)	⊕⊕○○ low ^{2,3}	
Miscarriage rate per woman randomised	25 per 1000	33 per 1000 (23 to 46)	OR 1.32 (0.92 to 1.88)	2385 (12 studies)	⊕⊕⊕○ moderate ²	
Miscarriage rate per pregnancy	134 per 1000	123 per 1000 (86 to 174)	OR 0.91 (0.61 to 1.36)	696 (12 studies)	⊕⊕⊕○ moderate ²	

Multiple pregnancy rate	18 per 1000	7 per 1000 (3 to 15)	OR 0.38 (0.17 to 0.84)	2385 (11 studies)	⊕⊕⊕○ moderate ²
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*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Most studies failed to report their methods in adequate detail. Studies that reported live birth tended to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth, suggesting that results might be less favourable to letrozole if all studies reported live birth.

² Most studies failed to report their methods in adequate detail.

³ A funnel plot analysis strongly suggests that there might be more publications without a significant effect which were not published.

BACKGROUND

Description of the condition

Polycystic ovary syndrome (PCOS) is the most common cause of infrequent periods (oligomenorrhoea) and absence of periods (amenorrhoea), affecting about 4-8% of women worldwide in their fertile years [Abu 2012](#). Many of these women are subfertile, but for most of them it just takes longer to become pregnant naturally and only a small percentage needs fertility treatment.

The mechanisms causing PCOS are very complex and the exact pathogenesis remains unknown. But some of the symptoms are believed to be caused by abnormal levels of the pituitary hormones luteinizing hormone (LH) and of the male hormones (androgens) which interfere with the normal function of the ovaries.

The diagnosis can be made based on the "Rotterdam criteria 2003", jointly proposed by European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine [Rotterdam 2003](#). The woman must have two of the following three criteria to be diagnosed with PCOS:

- Oligoovulation (infrequent ovulation) and/or anovulation (absence of ovulation)
- High male hormone levels (hyperandrogenism) diagnosed either clinically (excessive hair growth, hirsutism) or biochemically (raised serum testosterone levels)
- Ovaries which appear to be polycystic on vaginal sonogram defined by the presence of 12 or more antral follicles in an ovary or an ovarian volume of >10mL. Antral follicles are defined as measuring between 2 and 9 mm in diameter.

Description of the intervention

There are many possible options for treatment of subfertility in women with anovulatory PCOS.

Clomiphene citrate (CC) is a selective oestrogen receptor modulator or SERM and is the most common medication used for treating the condition. It was first introduced in 1960 for treatment of WHO (World Health Organisation) type II anovulation (a type of subfertility where hormone levels remain to be normal) in subfertile women and it has been first line treatment ever since. CC is given orally and it is relatively safe and inexpensive, but there are also adverse effects found with CC such as negative changes in endometrium and cervical mucus due to the down-regulation of oestrogen receptors that might impair implantation after successful induction of ovulation [Casper 2006](#).

Aromatase inhibitors (AIs) are a newer class of drugs that were introduced for ovulation induction in 2001 by Mitwally and Casper [Mitwally 2001](#). Over the last ten years data from many clinical trials have been collected and there is evidence that the AI letrozole might be as effective as CC, but the outcome data vary. AIs are like

CC administered orally, but due to their short half-life elimination time of 48 hours there are fewer adverse effects on oestrogen target tissues such as endometrium and cervix compared to CC [Baruah 2009](#); [Jirge 2010](#); [Samani 2009](#). In 2005 a study published by Biljan et al. including 150 babies raised some concerns about teratogenicity of letrozole, but there were major methodological flaws in this study as the intervention group was not well controlled [Biljan 2005](#). Furthermore, two other large studies including 911 and 470 infants compared use of letrozole to CC and spontaneously conceiving women. Both reported no higher levels of minor or major congenital malformations or cardiac abnormalities in newborns after usage of letrozole for ovulation induction [Tulandi 2006](#); [Forman 2007](#). Additionally, due to the short half-life elimination time of letrozole it should be completely cleared out of the system before implantation takes place. Some authors recommend to test the blood levels of β -hCG prior to treatment with letrozole to exclude pregnancy [Casper 2011](#). CC and AIs are usually both given for five days starting on day 3 of the cycle. The doses for CC and letrozole range from 50mg to 150mg per day and 2.5mg to 7.5 mg per day, respectively [Lee 2011](#).

Since many patients with PCOS experience insulin resistance or impaired glucose tolerance, metformin and other insulin sensitising agents were thought to be a superior drug for treatment of ovulation induction [Velázquez 1997](#). However, the latest version of the Cochrane Review on oral agents for ovulation induction concluded that the use of metformin and other insulin sensitising agents as an adjunct is limited and might be favourable only in patients that are resistant to CC alone [Brown 2009](#).

Human menopausal gonadotrophins (hMG) were introduced into clinical practice in 1961 for ovulation induction. They exert a central role in ovulation induction in CC resistant subfertile normogonadotropic anovulatory women [Lunenfeld 2004](#). However, women with PCOS are at particular risk for complications such as OHSS and multiple pregnancies and a low-dose step-up protocol was introduced to reach the FSH (follicle stimulating hormone) threshold gradually in order to minimize the risk for OHSS and multiple pregnancies [White 1996](#).

Finally, another possible option for ovulation induction in cases of CC resistance is laparoscopic ovarian diathermy (or drilling), during which the damaging of localized areas in the ovarian cortex and stroma seem to have similar success rates compared with gonadotropin therapy [Farquhar 2002](#). However, it is not fully clarified how the partial destruction of the ovary results in follicle development and ovulation induction, and there are concerns on the long-term effects of the technique on ovarian function [Farquhar 2012](#).

How the intervention might work

AIs down-regulate the production of oestrogen by inhibiting the cytochrome P450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex [Cole 1990](#). They inhibit the negative feedback

loop of oestrogen in the hypothalamus and result in stronger gonadotropin releasing hormone (GnRH) pulses. The elevated levels of GnRH stimulate the pituitary gland to produce more follicle stimulating hormone (FSH), which induces development of follicles in the ovaries. Because AIs do not deplete oestrogen receptors, in contrast to CC, the central feedback mechanism remains intact and as the dominant follicle grows and oestrogen levels rise, normal negative feedback occurs centrally. This results in suppression of FSH and the smaller growing follicles will undergo atresia, leading to a single dominant follicle and monoovulation (ovulation of a single egg) in most cases [Casper 2006](#); [Lee 2011](#). Therefore, by leaving the central mechanism intact, the AIs might lower the risk of high multiple ovulation and OHSS compared to CC.

Why it is important to do this review

Because evidence for and against the effectiveness and safety of these agents has fluctuated over the last decade and new data based on recent randomised controlled trials have become available, a systematic Cochrane Review is necessary to provide up to date information for daily practice. Therefore, this review evaluates the effectiveness and safety of AIs compared to other agents for ovulation induction or laparoscopic ovarian drilling, to provide evidence as to whether AIs should be used as first-line treatment in subfertile women with PCOS.

OBJECTIVES

To evaluate the effectiveness and safety of aromatase inhibitors for subfertile women with anovulatory PCOS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) were considered for inclusion in the review. Not appropriately randomised (quasi-randomised) trials were excluded. Cross-over trials were excluded unless phase one data were available separately. Multi-centre trials were also considered for inclusion in the review.

Types of participants

Women of reproductive age with anovulatory PCOS (WHO type II anovulation in women with normogonadotropic normoestrogenic anovulation) diagnosed according to the Rotterdam Criteria

2003, the NIH consensus criteria or the AES criteria [Rotterdam 2003](#); [Zawadski 1992](#); [Azziz 2009](#).

Exclusion criteria

Women with hyperprolactinaemia or Cushing's syndrome, or both, were excluded and trials which report on women with these two conditions were excluded from the review. Trials containing women with WHO type I anovulation were also excluded (Hypogonadotropic hypogonadal anovulation: women in this group have amenorrhoea, low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH). Studies using methods other than ovulation induction followed by intercourse were also excluded, for example IUI or IVF.

Types of interventions

Aromatase inhibitors for ovulation induction (alone or in conjunction with medical adjuncts, e.g. metformin, FSH) followed by sexual intercourse in women with anovulatory subfertility were considered for inclusion in the review. AIs were compared to each other and to other choices of treatment, including CC, tamoxifen, recombinant and urinary gonadotropin (FSH), insulin-sensitizing agents such as metformin and laparoscopic ovarian drilling.

Types of outcome measures

Primary outcomes

Effectiveness:

1. Live birth rate per woman randomised, defined as delivery of a live fetus after twenty completed weeks of gestational age.

Adverse effects:

2. Ovarian hyperstimulation syndrome (OHSS) rate per woman randomised, defined according the definition adopted by the reporting authors.

Secondary outcomes

3. Clinical pregnancy rate per woman randomised, where clinical pregnancy was defined as the presence of a fetal heart on ultrasound scan at 7 weeks of gestation.

4. Miscarriage rate per woman randomised, where miscarriage was defined as the involuntary loss of a clinical pregnancy before 20 weeks gestation, including partial loss of a multiple pregnancy.

5. Miscarriage rate per pregnancies, where miscarriage was defined as the involuntary loss of a clinical pregnancy before 20 weeks gestation, including partial loss of a multiple pregnancy.

6. Multiple pregnancy rate per woman randomised, where multiple pregnancy was defined as more than one intrauterine pregnancy, confirmed by ultrasound or delivery.

Search methods for identification of studies

We searched for all published and unpublished RCTs studying use of AIs for ovulation induction in anovulatory women with PCOS. The following search strategy was used, without language restriction. The Cochrane Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator was consulted.

Electronic searches

1. Menstrual Disorders and Subfertility Group Specialised Register (MDSG) (inception to 9 September 2014, [Appendix 1](#))
2. The Cochrane Central Register of Controlled Trials (CENTRAL) (inception to 9 September 2014, [Appendix 2](#))
3. MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (inception to 9 September 2014, [Appendix 3](#))
4. EMBASE (inception to 9 September 2014, [Appendix 4](#))
5. PsycINFO (inception to 9 September 2014, [Appendix 5](#))

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in *The Cochrane Handbook of Systematic Reviews of Interventions* (Version 5.1.0 chapter 6, 6.4.11). The EMBASE search was combined with trial filters developed by The Scottish Intercollegiate Guidelines Network (SIGN) <http://www.sign.ac.uk/mehodology/filters.html#random>. There was no language restriction in these searches.

Searching other resources

The references of relevant systematic reviews and RCTs obtained by the search were looked through manually and experts in the field and manufacturers of aromatase inhibitors were contacted personally to pick up any additional, relevant data. Additionally, the databases of the WHO, clinicaltrials.gov, web of knowledge, PubMed and LILACS were also searched (up to September 2014).

Data collection and analysis

Data collection and analysis was conducted in accordance with *The Cochrane Handbook for Systematic Reviews of Interventions* [Higgins 2011](#).

Selection of studies

The trials to be included were independently selected by three review authors (SF, WN, CF) in accordance with the aforementioned criteria. Trials were excluded from the systematic review if they made comparisons other than those specified above. Studies from non-English language journals were translated if necessary. If a specific trial was published more than once we only included the most complete and up to date data. Authors of primary studies were contacted if papers contained insufficient information to

enable an accurate assessment of eligibility for inclusion. We provided a list of excluded studies and the reasons for exclusion are shown in the 'Characteristics of excluded studies' table.

Data extraction and management

The data obtained were extracted by three review authors independently and any disagreement between these review authors was resolved by a third party. Extraction of the data from eligible studies was done by using a data extraction form designed and piloted by the authors. All data collected for our analyses were dichotomous. If studies had multiple publications, only the main trial report was included. The review authors contacted study investigators to resolve any data queries, as required.

Assessment of risk of bias in included studies

Included studies were assessed for risk of bias, using the Cochrane risk of bias tool. Seven domains of possible biases were assessed, including:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias

The different types of biases were judged using the criteria from the Cochrane Handbook Table 8.5.d: Criteria for judging risk of bias in the 'Risk of bias' assessment tool [Higgins 2011](#). These domains of biases were evaluated by two authors (SF and CF or WN) independently and characterized as "high risk of bias", "low risk of bias" or "unclear risk of bias". The assessments were compared and any disagreements resolved by consensus or by discussion with a third review author (CF or WN). The conclusions are presented in the 'Risk of bias' table and were incorporated into the interpretation of review findings by means of sensitivity analyses.

Measures of treatment effect

Where dichotomous data measures were used, we have expressed the results in the control and intervention groups of each study as odds ratios (OR) with 95% confidence intervals (CIs). For the very rare outcome OHSS we have used a risk difference analysis to allow CIs for the difference in percentage points. Based on the specified outcomes there were no continuous data measures.

Unit of analysis issues

The primary analysis was per woman randomised. The secondary outcome miscarriage rate was also analysed per pregnancy. Authors of studies that used cycles as the denominator rather than women

were contacted for additional information or otherwise not included in the analysis. If there are multiple cycles then the unit of analysis is still per woman randomised. Only the first phase of crossover-trials was included in the analysis as successful treatment prevents a crossover. Multiple live births were treated as one event.

Dealing with missing data

If data were missing from included studies, the original investigators were contacted to request the relevant missing data. If this was not possible, we imputed individual values for the primary and secondary outcomes. In participants without a reported outcome we assumed that live births have not occurred. For other outcomes, only the available data were analysed. Any imputation that was undertaken was subjected to sensitivity analysis. The data was analysed on an intention-to-treat (ITT) basis, as far as possible.

Assessment of heterogeneity

The results of the included studies were tested for heterogeneity by measuring the scatter in the data points on the graph and the overlap in their CIs. This was done by using I^2 statistics which describe the percentage of total variation across the trials that is due to heterogeneity rather than chance [Higgins 2011](#). The values of the I^2 statistics lie between 0% (no heterogeneity) and 100% (heterogeneity). Values above 50% were taken to indicate moderate heterogeneity and were explored within a sensitivity and subgroup analysis.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. We compared all outcome measures stated in the methods section to the outcomes reported in the results section to ensure comparability. If there were more than 10 trials included in a comparison, a funnel plot was produced.

Data synthesis

A fixed-effect model to combine the data from the primary studies was used if the studies were sufficiently similar. Statistical analysis was performed with Review Manager 5 in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration [Higgins 2011](#).

Our comparisons were:

1. AIs compared to placebo;
2. AIs compared to other ovulation induction agents followed by intercourse
3. AIs compared to other ovulation induction agents followed by IUI

4. AIs compared to laparoscopic ovarian drilling;
5. Letrozole compared to anastrozole;
6. Five days administration compared to 10 days administration protocol of letrozole; and
7. Different doses of AIs

Increases in the odds of an outcome, either beneficial (e.g. live birth) or detrimental (e.g. OHSS) will be shown in the forest plots of the meta-analysis on the right of the centre-line.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was done for primary outcomes only to evaluate the evidence for a study population with an average BMI >25 compared to women with an average BMI <25 within their study group. We further did a subgroup analysis comparing women with no previous treatment for ovulation induction to women that were CC resistant. We intended to perform subgroup analyses on further parameters, such as age of the woman, duration of subfertility and the duration and doses of drugs administration, but that was not possible due to the lack of data. All the reported subgroup-characteristics of the different studies are shown in [Table 1](#).

Sensitivity analysis

A sensitivity analysis was conducted for the primary outcomes to evaluate whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis of studies. This analysis includes consideration of whether the review conclusions would have differed if:

1. Eligibility were restricted to studies without high or unclear risk of bias
2. A random effects model had been used
3. Alternative imputation strategies had been implemented
4. The summary effect measure was risk ratio instead of odds ratio.

Overall quality of the body of evidence: Summary of Findings Table

A Summary of findings table was generated using GRADEPRO software. This table evaluates the overall quality of the body of evidence for the main review outcomes, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) were justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The initial search yielded 341 articles, of which 52 were potentially eligible and retrieved in full text. Twenty six studies met our inclusion criteria, 11 studies were excluded and 8 studies are ongoing. Seven studies await assessment ([Figure 1](#)).

Figure 1. Study flow diagram.

See study tables: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

Included studies

Study design and setting

We included 26 parallel-designed randomised controlled trials (RCTs) in the review.

The studies were done in different parts of the world:

- Egypt ([Abdellah 2011](#); [Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Badawy 2008](#); [Badawy July 2009](#); [Badawy Sept 2009](#); [Elgafor 2013](#); [Selim 2012](#))
- India ([Begum 2009](#); [Ganesh 2009](#); [Kamath 2010](#); [Kar 2012](#); [Ray 2012](#); [Roy 2012](#); [Sh-El-Arab Elsedek 2011](#))
- Iraq ([Al-Omari 2004](#))
- Iran ([Davar 2011](#); [Dehbashi 2009](#); [Foroozanfard 2011](#); [Ramezanzadeh 2011](#); [Sohrabvand 2006](#); [Zeinalzadeh 2010](#))
- Turkey ([Atay 2006](#); [Bayar 2006](#); [Nazik 2012](#))
- USA ([Legro 2014](#))

The following different settings recruited women into the trials:

- Not stated ([Atay 2006](#); [Ray 2012](#); [Roy 2012](#); [Selim 2012](#))
- Subfertility clinic ([Begum 2009](#); [Davar 2011](#); [Dehbashi 2009](#); [Foroozanfard 2011](#); [Ganesh 2009](#); [Kar 2012](#); [Nazik 2012](#); [Ramezanzadeh 2011](#); [Sh-El-Arab Elsedek 2011](#); [Sohrabvand 2006](#); [Zeinalzadeh 2010](#))
- Outpatient department ([Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Badawy 2008](#); [Badawy July 2009](#); [Badawy Sept 2009](#); [Bayar 2006](#))
- Department of obstetrics and gynaecology ([Al-Omari 2004](#); [Elgafor 2013](#); [Legro 2014](#))
- Division of reproductive endocrinology ([Kamath 2010](#))
- Women's health institute ([Abdellah 2011](#))

It was confirmed by Abu Hashim and Badawy that their five studies conducted from 2008 till 2010 were independent and did not include the same women.

Participants

The studies included 5560 women who were subfertile due to anovulatory PCOS. The ages of the women ranged from 18 to 40 years.

Interventions

- 1/26 studies compared aromatase inhibitors versus placebo. ([Kamath 2010](#))
- 15/26 studies compared aromatase inhibitors to other ovulation induction agents followed by intercourse. ([Abu Hashim Sept 2010](#); [Atay 2006](#); [Badawy Sept 2009](#); [Bayar 2006](#); [Begum 2009](#); [Davar 2011](#); [Dehbashi 2009](#); [Foroozanfard 2011](#); [Legro 2014](#); [Nazik 2012](#); [Ray 2012](#); [Roy 2012](#); [Selim 2012](#); [Sh-El-Arab Elsedek 2011](#); [Sohrabvand 2006](#))

- 3/26 studies compared aromatase inhibitors to other ovulation induction agents followed by IUI ([Ganesh 2009](#); [Kar 2012](#); [Zeinalzadeh 2010](#))

- 3/26 studies compared aromatase inhibitors versus laparoscopic ovarian drilling. ([Abdellah 2011](#); [Abu Hashim June 2010](#); [Elgafor 2013](#))

- 2/26 studies compared letrozole versus anastrozole. ([Al-Omari 2004](#); [Badawy 2008](#))

- 1/26 studies compared a 5 versus 10 days administration protocol of letrozole. ([Badawy July 2009](#))

- 1/26 studies compared different doses of aromatase inhibitors. ([Ramezanzadeh 2011](#))

(See [Characteristics of included studies](#))

Outcomes

- 12/26 studies reported live birth rate per woman randomised. ([Abdellah 2011](#); [Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Bayar 2006](#); [Begum 2009](#); [Dehbashi 2009](#); [Foroozanfard 2011](#); [Legro 2014](#); [Kamath 2010](#); [Ray 2012](#); [Roy 2012](#); [Sohrabvand 2006](#))

- 16/26 studies reported OHSS rate per woman randomised. ([Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Badawy 2008](#); [Badawy July 2009](#); [Badawy Sept 2009](#); [Bayar 2006](#); [Begum 2009](#); [Foroozanfard 2011](#); [Ganesh 2009](#); [Kamath 2010](#); [Legro 2014](#); [Nazik 2012](#); [Ramezanzadeh 2011](#); [Roy 2012](#); [Selim 2012](#); [Zeinalzadeh 2010](#))

- 25/26 studies reported clinical pregnancy rate per woman randomised. ([Abdellah 2011](#); [Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Al-Omari 2004](#); [Atay 2006](#); [Badawy 2008](#); [Badawy July 2009](#); [Badawy Sept 2009](#); [Bayar 2006](#); [Begum 2009](#); [Davar 2011](#); [Dehbashi 2009](#); [Elgafor 2013](#); [Foroozanfard 2011](#); [Ganesh 2009](#); [Kamath 2010](#); [Kar 2012](#); [Nazik 2012](#); [Ramezanzadeh 2011](#); [Ray 2012](#); [Roy 2012](#); [Selim 2012](#); [Sh-El-Arab Elsedek 2011](#); [Sohrabvand 2006](#); [Zeinalzadeh 2010](#))

- 20/26 studies reported miscarriage rate per woman randomised and per pregnancies. ([Abdellah 2011](#); [Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Badawy 2008](#); [Badawy July 2009](#); [Badawy Sept 2009](#); [Bayar 2006](#); [Begum 2009](#); [Davar 2011](#); [Dehbashi 2009](#); [Elgafor 2013](#); [Foroozanfard 2011](#); [Ganesh 2009](#); [Kamath 2010](#); [Kar 2012](#); [Nazik 2012](#); [Ramezanzadeh 2011](#); [Ray 2012](#); [Roy 2012](#); [Sohrabvand 2006](#))

- 21/26 studies reported multiple pregnancy rate per woman randomised. ([Abdellah 2011](#); [Abu Hashim June 2010](#); [Abu Hashim Sept 2010](#); [Al-Omari 2004](#); [Atay 2006](#); [Badawy 2008](#); [Badawy July 2009](#); [Badawy Sept 2009](#); [Bayar 2006](#); [Begum 2009](#); [Dehbashi 2009](#); [Foroozanfard 2011](#); [Ganesh 2009](#); [Kamath 2010](#); [Kar 2012](#); [Legro 2014](#); [Nazik 2012](#); [Ramezanzadeh 2011](#); [Roy 2012](#); [Selim 2012](#); [Zeinalzadeh 2010](#))

(See [Characteristics of included studies](#))

Excluded studies

We excluded eleven studies from the review for the following reasons:

- 6/11 were not RCTs ([Anwary 2012](#); [Azargoon 2012](#); [Badawy 2009](#); [Mittal 2004](#); [Yang 2008](#); [Foroozanfard 2013](#))
- 3/11 were quasi-randomised (Randomisation was based on attendance order of the women) ([Baruah 2009](#); [Bigawy 2008](#); [Nahid 2012](#))
- 2/11 did not include women with anovulatory infertility due to PCOS ([Angel 2014](#); [Ozdemir 2013](#))
(See [Characteristics of excluded studies](#))

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdellah 2011	+	+	?	?	+	+	+
Abu Hashim June 2010	+	+	+	+	+	+	+
Abu Hashim Sept 2010	+	+	+	+	+	+	+
Al-Omari 2004	+	?	+	+	+	+	+
Atay 2006	?	?	?	?	+	?	+
Badawy 2008	+	?	?	?	+	+	+
Badawy July 2009	+	?	?	?	+	+	+
Badawy Sept 2009	+	+	+	+	+	+	+
Bayar 2006	+	?	?	?	+	+	+
Begum 2009	+	?	+	+	+	+	+
Davar 2011	+	?	?	?	+	+	+
Dehbashi 2009	?	?	+	+	+	+	+
Elgafor 2013	+	+	?	?	+	+	+
Foroozanfard 2011	+	+	+	+	+	+	+
Ganesh 2009	+	+	+	+	+	+	+
Kamath 2010	+	+	+	+	+	+	+
Kar 2012	?	?	?	?	+	+	+
Legro 2014	+	+	+	+	+	+	+
Nazik 2012	+	?	+	+	+	+	+
Ramezanzadeh 2011	+	?	?	?	+	+	+
Ray 2012	?	?	?	?	?	?	+
Roy 2012	+	?	?	?	+	+	+
Selim 2012	+	+	+	+	+	+	+
Sh-El-Arab Elseddek 2011	+	?	?	?	+	?	+
Sohrabvand 2006	+	?	+	+	+	+	+
Zeinalzadeh 2010	?	?	?	?	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Twenty one studies were at low risk of selection bias related to sequence generation. They used computer randomisation, a random numbers table or lottery. The remaining 5 studies did not further describe their method of randomisation and the contacted authors did not respond, therefore they were at unclear risk of this bias (Figure 2).

Ten studies were at low risk of selection bias related to allocation concealment. They used sequentially numbered, sealed (opaque) envelopes and the list was kept by a third party during the procedure. The other 16 studies did not describe allocation concealment sufficiently and the authors did not respond to e-mail, therefore they were at unclear risk of bias (Figure 2).

Blinding

We think that blinding is not likely to influence findings for the primary and secondary review outcomes (live birth, OHSS, miscarriage, pregnancy and multiple pregnancy). Four out of 26 studies described blinding of participants and personnel and were thus rated to be at low risk of performance bias. Thirteen studies did not mention blinding of participants of personnel and the authors did not respond to e-mail, therefore they were at unclear risk of bias. Nine studies stated that there was no blinding of participants and/or personnel and were at high risk of bias (Figure 2).

Six of 26 studies described that the outcome assessors were blinded

and were therefore at low risk of bias. Thirteen studies did not mention blinding of outcome assessors and the authors did not respond to e-mail contact, therefore they were at unclear risk of bias. Three studies were of high risk of detection bias because it was reported that the outcome assessors were not blinded. Another four studies were also of high risk of bias because the participants were not blinded and therefore it is not credible that the outcome assessors were blinded. (Figure 2).

Incomplete outcome data

Twenty four of 26 studies included all or nearly all women they had randomised (>90%) and were therefore at low risk of attrition bias. One study was of unclear risk of bias because they had peculiar group numbers and all the other biases were not addressed as well, so we tried to contact the authors, without success (Ray 2012). Another study was of high risk of bias because 13 of 80 women were not analysed. Four women were excluded after randomisation due to an ovarian cyst on sonography on day 3. Nine more women were lost to follow up without any reasons given (Ramezanzadeh 2011; Figure 2).

Selective reporting

Twenty three of the 26 studies we included in this review reported the outcomes they have stated in the methods section and were

therefore judged to be at low risk of bias. In 3 of 26 studies only a few outcomes were presented and the contacted authors did not respond, therefore they were at unclear risk of reporting bias (Figure 2).

Other potential sources of bias

In one study there were substantial baseline differences in age and duration of infertility between the two groups and the risk of bias was deemed high (Nazik 2012). We found no potential sources of within-study bias in the other 25 studies (Figure 2).

Effects of interventions

See: [Summary of findings for the main comparison Aromatase inhibitors compared to clomiphene citrate with or without adjuncts for subfertile women with polycystic ovary syndrome](#)

1. Aromatase inhibitors compared to placebo

Only one trial compared an aromatase inhibitor (letrozole) and placebo (Kamath 2010). This trial reported only one pregnancy, in the letrozole group, therefore although the trial showed no important difference we cannot conclude that there was no treatment effect. This was probably due to the small sample size (n=36) of the trial. There was no evidence to suggest a difference in live birth rate (OR 3.17 95% CI 0.12 to 83.17, Analysis 1.1). A risk difference analysis for OHSS rate showed no evidence of a difference in frequency of this adverse event (RR 0.00, 95% CI -0.10 to 0.10). Pregnancy rate was the same as live birth rate (OR 3.17, 95% CI 0.12 to 83.17, Analysis 1.2). Miscarriage rates and

multiple pregnancy rate were not estimable because there were no cases reported.

2. Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by intercourse

Fifteen trials including 2816 women compared the AI letrozole to CC with or without adjuncts (Abu Hashim Sept 2010; Atay 2006; Badawy Sept 2009; Bayar 2006; Begum 2009; Davar 2011; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Nazik 2012; Ray 2012; Roy 2012; Selim 2012; Sh-El-Arab Elseddek 2011; Sohrabvand 2006).

- Aromatase inhibitors (2.5mg to 7.5mg/day) versus clomiphene citrate (50mg to 150mg/day) either alone or in combination with metformin (1500mg daily) or 150 IU hMG in one or both arms.

Primary outcomes

2.1 Live birth

Nine studies including 1783 women compared the AI letrozole to CC (with or without adjuncts in one or both arms) and reported live birth (Abu Hashim Sept 2010; Bayar 2006; Begum 2009; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Ray 2012; Roy 2012; Sohrabvand 2006). Aromatase inhibitors resulted in an increased live birth rate compared to other agents for ovulation induction (OR 1.64, 95% CI 1.32 to 2.04, $I^2=3\%$, NNT = 10, Figure 4, Analysis 2.1)

Figure 4. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.1 Live birth rate.

Subgroup analysis showed no evidence to suggest a difference by BMI mean (P=0.81) or in study populations that were CC resistant or had no previous treatment for ovulation induction (P=0.50) (Analysis not shown). Sensitivity analysis excluding one study with high risk of detection bias (Begum 2009) showed no substantive influence on the conclusion of treatment effect. But a sensitivity analysis comparing studies with unclear and low risk for allocation bias suggested a difference in treatment effect between the two subgroups (P = 0.01), which might indicate an overestimation of treatment effect (analysis not shown).

An additional sensitivity analysis showed that studies that reported live birth tended to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth, suggesting that results might be less favourable to letrozole if all studies

reported live birth, with a more modest treatment effect.

2.2 Ovarian hyperstimulation syndrome

Nine studies including 2179 patients compared the AI letrozole to CC (with or without adjuncts in one or both arms) and reported the occurrence of ovarian hyperstimulation syndrome (Abu Hashim Sept 2010; Badawy Sept 2009; Bayar 2006; Begum 2009; Foroozanfard 2011; Legro 2014; Nazik 2012; Roy 2012; Selim 2012). Our risk difference analysis showed no evidence for a difference in frequency of this adverse event (RR 0.00, 95% CI -0.01 to 0.00, Figure 5, Analysis 2.7). A subgroup analysis showed no evidence to suggest a difference by BMI mean (P = 0.80) (analysis not shown).

Figure 5. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.6 Ovarian hyperstimulation syndrome rate.

Secondary outcomes

2.3 Clinical pregnancy

Clinical pregnancy rate was reported in fifteen studies, including 2816 women (Abu Hashim Sept 2010; Atay 2006; Badawy Sept 2009; Bayar 2006; Begum 2009; Davar 2011; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Nazik 2012; Ray 2012; Roy 2012; Sh-El-Arab Elseddek 2011; Sohrabvand 2006; Selim 2012). Use of letrozole resulted in a higher clinical pregnancy rate compared to clomiphene citrate (with or without adjuncts in one or both arms) (OR 1.40, 95% CI 1.18 to 1.65, n=2816, I²=26%; Figure 6, Analysis 2.9).

Figure 6. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.8 Clinical pregnancy rate.

2.4 Miscarriage rate per woman randomised and per pregnancy

Miscarriage rate was reported in twelve studies, including 2385 women (Abu Hashim Sept 2010; Badawy Sept 2009; Bayar 2006; Begum 2009; Davar 2011; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Nazik 2012; Ray 2012; Roy 2012; Sohrabvand 2006). The analysis of miscarriage rate per woman randomised showed no evidence of a difference between aromatase inhibitors and clomiphene citrate (with or without adjuncts in one or both arms) (OR 1.32, 95% CI 0.92 to 1.88, $I^2=0\%$, Analysis 2.11). The results of the analysis of miscarriage rate per pregnancy also showed no evidence of a difference between the groups (OR 0.91, 95% CI 0.61 to 1.36, $I^2=0\%$, Analysis 2.12).

2.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in eleven studies, including 2385 women (Abu Hashim Sept 2010; Atay 2006; Badawy Sept

2009; Bayar 2006; Begum 2009; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Nazik 2012; Roy 2012; Selim 2012). The analysis of multiple pregnancy rate per woman randomised showed evidence of a reduction in multiple pregnancies for aromatase inhibitors compared to other agents for ovulation induction (OR 0.38, 95% CI 0.17 to 0.84, $I^2=0\%$, Analysis 2.13).

Publication bias

A funnel plot was produced for the outcome pregnancy rate. Funnel plots for the primary outcomes live birth rate and ovarian hyperstimulation syndrome were not done because there were only nine studies in each outcome. The funnel plot for the secondary outcome pregnancy rate showed strong asymmetries with a gap on the left side Figure 7. This indicates that there were possibly some studies with significant effects in favour of CC which were not reported, and therefore the results of our meta-analysis might have overestimated the effect of aromatase inhibitors on pregnancy rate.

Figure 7. Funnel plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.8 Clinical pregnancy rate.

3. Aromatase inhibitors compared to other agents for ovulation induction followed by IUI

Three studies including 1597 women compared use of the aromatase inhibitor letrozole with or without adjuncts to other agents for ovulation induction (Ganesh 2009; Kar 2012; Zeinalzadeh 2010).

- Aromatase inhibitor (letrozole, 2.5mg - 5mg daily, cycle days 3 to 7 or 2 to 6) versus clomiphene citrate (50mg - 150mg daily, cycle days 3 to 7 or 2 to 6) with or without adjuncts or rFSH only (rFSH 75IU/100IU from day 2 until the day of hCG administration)

Primary outcomes

3.1 Live birth

No studies comparing letrozole to anastrozole reported live birth rate.

3.2 Ovarian hyperstimulation syndrome

Two studies reported ovarian hyperstimulation syndrome rate comparing use of letrozole to other agents for OI (Ganesh 2009; Zeinalzadeh 2010). Our risk difference analysis showed no evidence of a difference in frequency of this adverse event between the two treatment groups (RD 0.00, 95% CI -0.01 to 0.00, Analysis 3.1). Subgroup analyses were not possible because there were too few studies.

Secondary outcomes

3.3 Clinical pregnancy

Clinical pregnancy rate was reported in three studies comparing use of letrozole to other agents for OI (Ganesh 2009; Kar 2012; Zeinalzadeh 2010). There was no evidence of a difference between the two groups (OR 1.71, 95% CI 1.30 to 2.25, 3 RCTs, 1597 women, $I^2=0\%$, Analysis 3.2).

3.4 Miscarriage rate per woman randomised and per pregnancies

Miscarriage rate was reported in two studies comparing use of letrozole to other agents for OI (Ganesh 2009; Kar 2012). There was no evidence of a difference between the two groups for miscarriage rate per woman randomised (OR 1.22, 95% CI 0.62 to 2.40, 2 RCTs, 1490 women, $I^2=0\%$, Analysis 3.3) or per pregnancies (0.76, 95% CI 0.37 to 1.57, 2 RCTs, 1490 women, $I^2=30\%$, Analysis 3.4).

3.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in three studies comparing use of letrozole to clomiphene citrate with or without adjuncts (Ganesh 2009; Kar 2012; Zeinalzadeh 2010). There was no evidence of a difference between the two groups (OR 1.03, 95% CI 0.49 to 2.13, $I^2=0\%$) (Analysis 3.5).

4. Aromatase inhibitors compared to laparoscopic ovarian drilling

Three studies including 553 women compared use of the aromatase inhibitor letrozole with or without metformin to laparoscopic ovarian drilling (Abdellah 2011; Abu Hashim June 2010; Elgafor 2013).

- Aromatase inhibitor (letrozole, 2.5mg - 5mg daily, cycle days 3 to 7) with or without metformin (850mg to 1700mg daily for 6-8 weeks) versus laparoscopic ovarian drilling

Primary outcomes

4.1 Live birth

Live birth rate was reported in two studies comparing use of an aromatase inhibitor to laparoscopic ovarian drilling (Abdellah 2011; Abu Hashim June 2010). Our analysis did not show evidence of a difference in live birth rate between the treatment groups (OR 1.19, 95% CI 0.76 to 1.86, 2 RCTs, 407 women, $I^2=0\%$, Figure 8, Analysis 4.1). Subgroup analyses were not possible because there were only two studies.

Figure 8. Forest plot of comparison: 3 Aromatase inhibitors compared to laparoscopic ovarian drilling, outcome: 3.1 Live birth rate.

Footnotes

- (1) Clomiphene resistant women; Letrozole 5 mg/day versus LOD
(2) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

4.2 Ovarian hyperstimulation syndrome

Only one study reported ovarian hyperstimulation syndrome rate comparing use of letrozole to laparoscopic ovarian drilling (Abu Hashim June 2010). Our risk difference analysis showed no evidence of a difference in frequency of this adverse event for the two treatment groups (RD 0.00, 95% CI -0.01 to 0.01, Analysis 4.2).

Secondary outcomes

4.3 Clinical pregnancy

Clinical pregnancy rate was reported in three studies comparing use of letrozole with or without metformin to laparoscopic ovarian drilling (Abdellah 2011; Abu Hashim June 2010; Elgafor 2013). There was no evidence of a difference between the two groups (OR 1.14, 95% CI 0.80 to 1.65, 3 RCTs, 553 women, I²=0%, Analysis 4.3).

4.4 Miscarriage rate per woman randomised and per pregnancies

Miscarriage rate was reported in three studies comparing use of letrozole with or without metformin to laparoscopic ovarian drilling (Abdellah 2011; Abu Hashim June 2010; Elgafor 2013). There was no evidence of a difference between the two groups for miscarriage rate per woman randomised (OR 0.91, 95% CI 0.38 to 2.19, 3 RCTs, 553 women, I²=0%, Analysis 4.4) and per pregnancies (OR 0.81, 95% CI 0.32 to 2.01, 3 RCTs, 553 women, I²=0%, Analysis 4.5).

4.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in two studies comparing use of letrozole to laparoscopic ovarian drilling (Abdellah 2011; Abu

Hashim June 2010). However, no cases of multiple pregnancies occurred and therefore an analysis was not possible.

5. Letrozole compared to anastrozole

Two studies including 270 women compared use of the aromatase inhibitor letrozole to the aromatase inhibitor anastrozole (Al-Omari 2004; Badawy 2008).

- Letrozole, 2.5mg/day versus anastrozole, 1mg/day for five days starting on cycle day three.

Primary outcomes

5.1 Live birth

No studies comparing letrozole to anastrozole reported live birth rate.

5.2 Ovarian hyperstimulation syndrome

Only one study comparing letrozole to anastrozole reported the occurrence of ovarian hyperstimulation syndrome (Badawy 2008). A risk difference analysis showed no evidence of a difference between the two treatment groups (RD 0.00, 95% CI -0.02 to 0.02, Analysis 5.1)

Secondary outcomes

5.3 Clinical pregnancy

Clinical pregnancy rate was reported in two studies comparing letrozole to anastrozole (Al-Omari 2004; Badawy 2008). There was no evidence of a difference between the two groups (OR 0.85, 95% CI 0.51 to 1.43, 2 RCTs, 260 women, I²=3%, Analysis 5.2)

5.4 Miscarriage rate per woman randomised

Miscarriage rate was reported only in one study comparing letrozole to anastrozole (Badawy 2008). There was no evidence of a difference between the two groups for miscarriage rate per woman randomised (OR 0.98, 95% CI 0.24 to 4.03, Analysis 5.3) or per pregnancies (OR 1.19, 95% CI 0.27 to 5.13, Analysis 5.4).

5.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in two studies comparing letrozole to anastrozole (Al-Omari 2004; Badawy 2008). One study did not report any cases of multiple pregnancy rate and an odds ratio was therefore not estimable (Al-Omari 2004). The other study reported no evidence to suggest a difference between the two treatment groups (OR 5.00, 95% CI 0.24 to 105.35; Badawy 2008, Analysis 5.5)

6. Five days compared to 10 days administration protocol of aromatase inhibitors

There was only one trial comparing a 5 day letrozole administration protocol to a 10 day letrozole administration protocol (Badawy July 2009). This study did not report live birth rate. A risk difference analysis on OHSS rate showed no evidence to suggest a difference in occurrence of OHSS between the two treatment groups (RD 0.00, 95% CI -0.02 to 0.02, Analysis 6.1). The analysis showed furthermore no evidence of a difference between the groups in clinical pregnancy rate (OR 0.63, 95% CI 0.35 to 1.13, Analysis 6.2), miscarriage rate per woman randomised (OR 0.69, 95% CI 0.21 to 2.24, Analysis 6.3), miscarriage rate per pregnancies (OR 0.96, 95% CI 0.27 to 3.42, Analysis 6.4) or multiple pregnancy rate (OR 0.32, 95% CI 0.01 to 8.05, Analysis 6.5).

7. Dosage studies of letrozole

There was only one trial comparing a 5mg/daily administration of letrozole to a 7.5mg/daily administration protocol (Ramezanzadeh 2011). This study did not report on live birth rate. A risk difference analysis on OHSS rate showed no evidence to suggest a difference in occurrence of OHSS between the two treatment groups (RD 0.00, 95% CI -0.05 to 0.05, Analysis 7.1). Their results show furthermore no evidence of a difference between the groups in clinical pregnancy rate (OR 1.00, 95% CI 0.32 to 3.17, Analysis 7.2), miscarriage rate per woman randomised (OR 0.33, 95% CI 0.01 to 8.22, Analysis 7.3), miscarriage rate per pregnancies (OR 0.29, 95% CI 0.01 to 8.39, Analysis 7.4) or multiple pregnancy rate (OR 1.00, 95% CI 0.06 to 16.56, Analysis 7.5).

DISCUSSION

Summary of main results

Aromatase inhibitors compared to placebo

Only one trial compared Letrozole to placebo Kamath 2010. It showed no evidence of a difference in rates for live birth, ovarian hyperstimulation syndrome, pregnancy, miscarriage or multiple pregnancy. But the sample size might have been too small to show any effects because there were only 18 women in each group. However, based on the studies comparing letrozole to clomiphene citrate in women with no previous treatment for ovulation induction, which show that letrozole is equally effective as clomiphene citrate, further research comparing letrozole to placebo is unnecessary and might even be unethical Badawy Sept 2009; Bayar 2006; Dehbashi 2009; Nazik 2012; Sh-El-Arab Elsedek 2011.

Aromatase inhibitors compared to clomiphene citrate followed by timed intercourse

The results of our analysis of fifteen trials comparing letrozole to CC followed by timed intercourse suggests that letrozole improves live birth rate and pregnancy rate compared to CC Summary of findings for the main comparison.

However, we noted that studies that reported live birth tended to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth, with no evidence of a difference in miscarriage rates. This suggests that findings might be less favourable to letrozole if all studies reported live birth. Moreover in subgroup analysis comparing studies with low and unclear risk of bias for the outcome of live birth, the studies with unclear methods of allocation concealment tended to be more favourable to letrozole. Therefore, our findings on live birth rate should be regarded with some caution as they may overestimate the benefits of letrozole relative to CC.

Furthermore, the funnel plot for clinical pregnancy rate (Figure 7) was asymmetrical, suggesting that our findings might be influenced by publication bias. A second funnel plot, investigating the impact of possible allocation bias on clinical pregnancy rate (Figure 9) also showed strong asymmetry with a gap on the left side, suggesting that the results might be influenced by allocation bias.

Figure 9. Funnel plot of comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, outcome: 2.10 Impact of allocation bias for clinical pregnancy rate.

Risk difference analysis suggested that letrozole and clomiphene citrate are equally safe in terms of ovarian hyperstimulation and miscarriage. On the other hand, there was moderate quality evidence that fewer multiple pregnancies occurred in the letrozole group ([Summary of findings for the main comparison](#)).

All analyses had absent or low levels of statistical heterogeneity ($I^2 < 25\%$).

Five of our fifteen studies in this analysis included women that were resistant to clomiphene citrate ([Abu Hashim Sept 2010](#); [Begum 2009](#); [Davar 2011](#); [Foroozanfard 2011](#); [Sohrabvand 2006](#)), the other ten studies included women that were not resistant to clomiphene citrate ([Badawy Sept 2009](#); [Bayar 2006](#); [Dehbashi 2009](#); [Legro 2014](#); [Nazik 2012](#); [Sh-El-Arab Elseddek 2011](#)) or it was not mentioned ([Atay 2006](#); [Selim 2012](#); [Ray 2012](#); [Roy 2012](#)).

Our subgroup analyses did not show evidence of a difference in effectiveness related to BMI, though there were too few trial in some subgroups to allow comparison, or the study sizes were too small with low, or zero, event rates. Furthermore, two studies excluded women with a high BMI. Therefore, our subgroup analyses of BMIs were inconclusive. Subgroup analysis by CC resistance showed no evidence for a difference in treatment effect for live birth.

In sensitivity analyses findings for live birth were not influenced by use of a random effects model, alternative imputation strategies, or risk ratio rather than odds ratio.

Unpublished data, apparently based on preliminary findings from [Legro 2014](#), found that the interventions had comparable treatment costs. This suggests that given its higher effectiveness Letrozole is more cost-effective than clomiphene citrate ([Reproductive Medicine Network 2013](#)).

Aromatase inhibitors compared to other agents for ovulation induction followed by IUI

Three trials compared letrozole to clomiphene citrate for ovulation induction followed by IUI [Ganesh 2009](#); [Kar 2012](#); [Zeinalzadeh 2010](#). None reported live birth. Two reported OHSS: only 3 cases occurred and there was no evidence of a difference despite a study population of 1494 women. Clinical pregnancy rates were increased in women treated with letrozole, compared to CC and FSH. We found no evidence of a difference in rates of miscarriage or multiple pregnancy.

Aromatase inhibitors compared to laparoscopic ovarian drilling

Three trials compared letrozole to laparoscopic ovarian drilling in clomiphene citrate resistant women [Abdellah 2011](#); [Abu Hashim June 2010](#); [Elgafor 2013](#). OHSS was reported only in [Abdellah 2011](#), but no cases of OHSS were found despite a study population of 260 women. We found no evidence of a difference in rates of live birth, pregnancy or miscarriage. Multiple pregnancy rate was reported in two studies, but with zero events. More and larger studies are needed in this area.

Letrozole compare to anastrozole

Letrozole was compared to anastrozole in two studies including 260 women [Al-Omari 2004](#); [Badawy 2008](#). Neither study reported live birth and OHSS was only reported in [Badawy 2008](#) but with zero events, so further research is needed. Rates of clinical pregnancy and multiple pregnancies were compared in both trials, but we found no evidence of difference. Miscarriage rates were reported only in the study of [Badawy 2008](#), with no difference between the groups.

Five days compared to 10 days letrozole administration protocol

A single study including 218 women compared a 5 days administration protocol to a 10 days administration protocol for letrozole [Badawy July 2009](#). There was no evidence of increased effectiveness or reduced side effects for any of our outcomes. Additionally, there might be some concern about the longer administration protocol because of the possible teratogenic effects of letrozole. In combination with a 10 day protocol, letrozole might not be completely removed from the human body by the time of implantation of the embryo. Therefore, further research is needed to investigate whether a long term protocol for letrozole is beneficial or even harmful for treatment of subfertility.

Dosage studies of letrozole

We intended to analyse different doses of letrozole in the range from 2.5 to 5 mg/day, but only one study including 80 women was published comparing a dosage of 5mg/day to 7.5mg/day [Ramezanzadeh 2011](#). There was no evidence of a difference in effectiveness as seven pregnancies were reported in each group. There was also no evidence of a difference in adverse events, but the size of the study population might have been too small because only one or zero cases were reported in each group for OHSS, miscarriage and multiple pregnancy rate. Therefore, further research is needed to find out more about dosage of letrozole.

Overall completeness and applicability of evidence

Although we cannot give a definite answer on the likelihood of the occurrence of OHSS in the different treatment groups we compared, further research is unlikely to give a conclusive answer since OHSS is a very rare event and only very few or no cases were reported even in the bigger studies. For our main comparison of aromatase inhibitors compared to other agents for ovulation induction, we found sufficient studies for our analysis to tentatively answer our research question, but additional studies are likely to have an impact on the effect estimate.

It might be unethical to compare letrozole to placebo because the efficiency of letrozole is proven in comparison to clomiphene citrate or laparoscopic ovarian drilling, but additional studies are needed for all the other comparisons to give a more conclusive answer, since our analyses were based on one to three published studies.

Another point of concern was that almost all of our studies included were conducted in Egypt or the Middle East. Therefore, the overall results might vary if the trials were conducted elsewhere.

Quality of the evidence

We included 26 studies with in total 5560 women. The overall quality of the evidence varied and was rated as low to moderate (see [Summary of findings for the main comparison](#)). The reasons for downgrading the evidence included poor reporting of study methods (especially with respect to allocation concealment and blinding) and possible publication bias. Moreover there was a tendency for studies that reported live birth to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth, suggesting that results might be somewhat less favourable to letrozole if all studies reported live birth. Our conclusions therefore require cautious interpretation, as additional studies may alter the effect estimates.

Many comparisons included only one or two studies, and more research is needed.

Potential biases in the review process

We conducted a comprehensive search with the help of an experienced trials search coordinator and, in addition, extensive manual searching, in an effort to minimise the risk of publication bias. However, we generated a funnel plot for the outcome pregnancy rate in the comparison of aromatase inhibitors to other ovulation induction agents, which indicated that there might be some studies not published that reported results in favour of clomiphene citrate. There are several studies awaiting classification which could also have an influence on our results. Therefore, there might be some publication bias in this review.

We followed the guidelines of the Cochrane Collaboration to select studies, extract data and assess the quality and potential risk of different types of biases in all our included studies, in order to minimise the chance of reviewer error and bias.

Agreements and disagreements with other studies or reviews

Our meta analysis shows some evidence for increased live birth rates in favour of letrozole when compared to clomiphene citrate in women with PCOS. This differs from a previous review, which did not report a difference (Misso 2012). Our review showed no evidence for a difference in effect between letrozole and laparoscopic ovarian drilling for subfertility treatment in women who are resistant to clomiphene citrate, which is in agreement with the results of an earlier meta-analysis (Misso 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest that letrozole is superior to clomiphene citrate for the treatment of subfertility in women with PCOS who have had no previous treatment for ovulation induction or are resistant to clomiphene citrate. However, this conclusion should be

regarded with some caution because the quality of the evidence was low.

Implications for research

Further research including large studies is needed to compare letrozole with CC specifically in women with PCOS who have had no previous treatment for ovulation induction to help determine whether letrozole or CC should be first line medical ovulation induction agent in anovulatory PCOS women.

Further research including large studies is needed to investigate the effect of different doses of aromatase inhibitors and whether either letrozole or anastrozole should be used.

More randomised clinical trials investigating a 5 or 10 days administration protocol of letrozole could also be conducted, but with caution due to the concerns of teratogenic effects of letrozole.

ACKNOWLEDGEMENTS

We would like to thank Marian Showell (Trials Search Coordinator) for writing and running the search, Vanessa Jordan for assistance with methodological questions, Helen Nagels (Managing Editor of MDSG) for helping us to develop the protocol and answering our questions and Julie Brown for assistance on writing the full review.

REFERENCES

References to studies included in this review

Abdellah 2011 {published data only}

Abdellah MS. Reproductive outcome after letrozole versus laparoscopic ovarian drilling for clomiphene-resistant polycystic ovary syndrome. *International Journal of Gynecology and Obstetrics* 2011;**113**:218–21.

Abu Hashim June 2010 {published data only}

Abu Hashim H, Mashaly AM, Badawy A. Letrozole versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. *Archives of Gynecology and Obstetrics* 2010;**282**:567–71.

Abu Hashim Sept 2010 {published data only}

Abu Hashim H, Shokeir T, Badawy A. Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. *Fertility and Sterility* 2010;**94**:1405–9.

Al-Omari 2004 {published data only}

Al-Omari WR, Sulaiman WR, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-

resistant polycystic ovary syndrome. *International Journal of Gynecology & Obstetrics* 2004;**85**:289–91.

Atay 2006 {published data only}

Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *Journal of International Medical Research* 2006;**34**:73–6.

Badawy 2008 {published data only}

Badawy A, Mosbah A, Shady M. Anastrozole or letrozole for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome: a prospective randomized trial. *Fertility and Sterility* 2008;**89**:1209–12.

Badawy July 2009 {published data only}

Badawy A, Mosbah A, Tharwat A, Eid M. Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol. *Fertility and Sterility* 2009;**92**:236–9.

Badawy Sept 2009 {published and unpublished data}

Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. *Fertility and Sterility* 2009;**92**:849–52.

Bayar 2006 {published data only}

Bayar U, Basaran M, Kiran S, Coskun A, Gezer S. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. *Fertility and Sterility* 2006;**86**:1447–51.

Begum 2009 {published and unpublished data}

Begum MR, Ferdous J, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *Fertility and Sterility* 2009;**92**:853–7.

Davar 2011 {published data only}

Davar R, Javedani M, Fallahzadeh MH. Metformin-letrozole in comparison with Metformin-clomiphene citrate in clomiphene-resistance PCOS patients undergoing IUI. *Iranian Journal of Reproductive Medicine* 2011;**9**:31–6.

Dehbashi 2009 {published data only}

Dehbashi S, Kazerooni T, Robati M, Alborzi S, Parsanezhad ME, Shadman A. Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome. *Iranian Journal of Medical Sciences* 2009;**34**:23–8.

Elgafor 2013 {published data only}

Elgafor IA. Efficacy of combined metformin-letrozole in comparison with bilateral ovarian drilling in clomiphene-resistant infertile women with polycystic ovarian syndrome. *Archives of Gynecology and Obstetrics* 2013;**288**:119–123. [DOI: 10.1007/s00404-013-2714-2]

Foroozanfard 2011 {published data only}

Foroozanfard F, Mahdian M, Mousavi GI, Pejmanmanesh M, Soleimani A. Use of letrozole versus clomiphene citrate combined with gonadotropins in patients with clomiphene resistant polycystic ovarian syndrome: A comparative study. *Pakistan Journal of Medical Sciences* 2011;**27**:967–70.

Ganesh 2009 {published data only}

Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B. Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. *Journal of assisted reproduction and genetics* 2009;**26**(1): 19–24.

Kamath 2010 {published and unpublished data}

Kamath MS, Aleyamma TK, Chandy A, George K. Aromatase inhibitors in women with clomiphene citrate resistance: a randomized, double-blind, placebo-controlled trial. *Fertility and Sterility* 2010;**94**:2857–9.

Kar 2012 {published data only}

Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial. *Journal of Human Reproductive Sciences* 2012;**5**(3):262–265. [DOI: 10.4103/0974-1208.106338]

Legro 2014 {published and unpublished data}

Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD et al for the NICHD Reproductive Medicine Network.

Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *NEJM* 2014;**371**(2):119–29.

Legro RS, Kunselman AR, Brzyski RG, Casson PR, Diamond MP, Schlaff WD, Christman GM, Coutifaris C, Taylor HS, Eisenberg E, Santoro N, Zhang H. Effect of Letrozole versus Clomiphene on live birth in women with anovulatory infertility due to Polycystic Ovary Syndrome (PCOS): A randomized double-blind multi-center trial. *ASRM 2013 conference abstract* 2013:S51.

Nazik 2012 {published data only}

Nazik H, Kumtepe Y. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction for women with polycystic ovarian syndrome. *HealthMED* 2012;**6**: 879–83.

Ramezanzadeh 2011 {published data only}

Ramezanzadeh F, Nasiri R, Yazdi MS, Baghrei M. A randomized trial of ovulation induction with two different doses of Letrozole in women with PCOS. *Archives of Gynecology and Obstetrics* 2011;**284**(4):1029–34.

Ray 2012 {published data only}

Ray PB, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. *Archives of Gynecology and Obstetrics* 2012;**285**(3):873–7.

Roy 2012 {published data only}

Roy K, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, Goyal M. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *Journal of Human Reproductive Sciences* 2012;**5**:20–5.

Selim 2012 {published data only}

Selim MF, Borg TF. Letrozole and Clomiphene Citrate Effect on Endometrial and Subendometrial Vascularity in Treating Infertility in Women with Polycystic Ovary Syndrome. *Journal of Gynaecologic Surgery* 2012;**28**(6): 405–410. [DOI: 10.1089/gyn.2012.0033]

Sh-El-Arab Elsedek 2011 {published data only}

Sheikh-El-Arab Elsedek M, Elmaghraby HAH. Predictors and characteristics of letrozole induced ovulation in comparison with clomiphene induced ovulation in anovulatory PCOS women. *Middle East Fertility Society Journal* 2011;**16**:125–30.

Sohrabvand 2006 {published data only}

Sohrabvand F, Ansari SH, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. *Human Reproduction* 2006;**21**:1432–5.

Zeinalzadeh 2010 {published data only}

Zeinalzadeh M, Basirat Z, Esmailpour M. Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome. *The Journal of reproductive medicine* 2010;**55**: 36–40.

References to studies excluded from this review

Angel 2014 {published data only}

Angel M, Ghose S, Gowda M. A randomized trial comparing the ovulation induction efficacy of clomiphene citrate and letrozole. *Journal of Natural Science Biology & Medicine* 2014;**5**(2):450–452.

Anwary 2012 {published data only}

Anwary SA, Alfazzaman M, Bar, N, Islam MR. Outcome of Metformin Treatment in Polycystic Ovary Syndrome. *Mymensingh Medical Journal* 2012;**21**(1):60–65.

Azargoon 2012 {published data only}

Azargoon A, Toussy JA, Darbanan FF. Pregnancies following the use of sequential treatment of metformin and incremental doses of letrozole in clomiphene-resistant women with polycystic ovary syndrome. *Iranian Journal of Reproductive Medicine* 2012;**10**(1):33–40.

Badawy 2009 {published data only}

Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or anastrozole for ovulation induction in women with polycystic ovary syndrome? A prospective controlled trial. *Fertility and Sterility* 2009;**92**:860–3.

Baruah 2009 {published data only}

Baruah J, Roy KK, Rahman SM, Kumar S, Sharma JB, Karmakar D. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. *Archives of Gynecology & Obstetrics* 2009;**279**:31–4.

Bigawy 2008 {published data only}

El Bigawy AF, Fouda UMF, Wahab HAE. A randomized trial of letrozole versus clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome (PCOS). *Middle East Fertility Society Journal* 2008;**13**:52–6.

Foroozanfard 2013 {published data only}

Foroozanfard F, Saberi H, Moravvegi A, Kazemi M. Pregnancy rate following luteal phase support in polycystic ovarian syndrome using combination therapies for ovulation induction: A randomized clinical trial.. Conference abstracts: 29th Annual Meeting of the European Society of Human Reproduction and Embryology. June 2013.

Mittal 2004 {published data only}

Mittal S, Kamthane VP, Goswami SK, Ghosh S, Chakravarty BN. Comparative evaluation of different stimulation protocols in CC resistant P.C.O women undergoing IUI. Abstracts of the 20th Annual Meeting of the ESHRE, Berlin, Germany, 27–30 June 2004. 2004:i122.

Nahid 2012 {published data only}

Nahid L, Sirous K. Comparison of the effects of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome. *Minerva Ginecologica* 2012;**64**:253–8.

Ozdemir 2013 {published data only}

Ozdemir U, Ozaksit G, Cakir Gungor AN, Aydogan M. Letrozole usage adjuvant to gonadotropins for ovulation induction for patients with clomiphene citrate failure. *Archives of Gynecology and Obstetrics* 2013;**288**(2):445–448.

Yang 2008 {published data only}

Yang M, Quan S, Li H, Song Y, Xing F. Effect of two different doses of letrozole in promoting ovulation in infertile women with polycystic ovarian syndrome. *Journal of Southern Medical University* 2008;**28**(11):2060–2062.

References to studies awaiting assessment

Aygen 2007 {published data only}

Aygen EM, Guzel Z, Ozgun T, Atakul T, Sahin Y. [The use of letrozole for ovulation induction in infertile women with polycystic ovarian syndrome]. *Erciyes Tip Dergisi* 2007;**29**: 195–200.

Hazlina 2012 {published data only}

Study On The Effects of Letrozole And Clomiphene Citrate For Induction of Ovulation In Polycystic Ovarian Syndrome(PCOS). <https://clinicaltrials.gov/ct2/show/NCT01577017?term=ovulation+induction+and+aromatase&rank=1>.

Lorzadeh 2011 {published data only}

Lorzadeh N, Kazemirad S, Mohammadi Z. Comparison of effects letrozole and clomiphene citrate for ovulation induction in women with polycystic ovary syndrome. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2011; **14**(3):13–19.

Parihar 2008 {published data only}

Parihar. An Open, Randomized, Parallel-Group, Multicentric, Comparative Study of Letrozole With Clomiphene Citrate for Induction of Ovulation in Anovulatory Infertility.. <https://clinicaltrials.gov/ct2/show/NCT00610077?term=ovulation+induction+and+aromatase&rank=8>. [: NCT00610077]

Safdarian 2012 {published data only}

Safdarian L, Dibazar NS, Ahmadzadeh A, Yekta BG. Comparing two ovulation induction methods by brachial artery ultrasonography in infertile women with polycystic ovary syndrome. *Tehran University Medical Journal* 2012; **70**:242–9.

Sharma 2010 {published data only}

Sharma S, Goswami SK, Rajani S, et al. Efficacy of letrozole-gonadotropin, clomiphene-gonadotropin and only gonadotropin in clomiphene and letrozole resistant PCOS women undergoing IUI. *Human Reproduction* 2010;**25** suppl 1:i46.

Shirin 2009 {published data only}

Shirin G, Mehran A, Maryam B, Maryam G, Masoumeh M. Comparing the effects of clomiphene-HMG and letrozole-HMG on ovulation Induction in infertile women. *Journal of Reproduction and Infertility* 2009;**10**:156.

References to ongoing studies

Ali 2012 {published data only}

Letrozole or combined clomiphene citrate metformin as a first line treatment in women with polycystic ovary syndrome (PCO). Ongoing study January 2009.

Amer 2007 {published data only}

Letrozole versus clomiphene citrate for Ovulation induction. Ongoing study 2007.

Feng 2011 {published data only}

the ovulation-induced therapy for polycystic ovary syndrome. Ongoing study 2011.

Ghanem 2013 {published data only}

Clomiphene Citrate Plus hPFSH Versus Letrozole Plus hPFSH in Clomid Resistant Infertile PCOS Women. Ongoing study March 2013.

Hou 2011 {published data only}

Letrozole Versus Chinese Herbal Compound on Polycystic Ovary Syndrome. Ongoing study September 2011.

Li 2013 {published data only}

Letrozole and Berberine in Infertile PCOS Patients. Ongoing study October 2009.

Philihawadana 2008 {published data only}

A study on anti-oestrogen clomifene citrate and aromatase inhibitor letrozole in induction of ovulation, in WHO group II anovulatory subjects, and in augmentation of ovulation in ovulatory infertility. Ongoing study 2008.

Sarvi 2010 {published data only}

The effect of metformin in different phenotypes of polycystic ovary syndrome according to Rotterdam criteria criteria. Ongoing study 2010.

Additional references

Abu 2012

Abu Hashim H. Clomiphene citrate alternatives for the initial management of polycystic ovary syndrome: an evidence-based approach. *Archives of Gynecology and Obstetrics* 2012;**285**:1737–45.

Azziz 2009

Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF, Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and Sterility* 2009;**91**(2):456. [PUBMED: 18950759]

Biljan 2005

Biljan, MM, Hemmings, R, Brassard, N. The Outcome of 150 Babies Following the Treatment With Letrozole or Letrozole and Gonadotropins. *Fertility and Sterility* 2005; **84**:95.

Brown 2009

Brown j, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD002249.pub4]

Casper 2006

Casper RF, Mitwally MF. Review: aromatase inhibitors for ovulation induction. *Journal of Clinical Endocrinology and Metabolism* 2006;**91**:760–71.

Casper 2011

Casper, RF, Mitwally, MF. Use of the aromatase inhibitor letrozole for ovulation induction in women with polycystic ovarian syndrome. *Clinical Obstetrics and Gynaecology* 2011; **54**:685–95.

Cole 1990

Cole PA, Robinson CH. Mechanism and inhibition of cytochrome P-450 aromatase. *Journal of Medical Chemistry* 1990;**33**:2933–2944.

Farquhar 2002

Farquhar, CM, Williamson, K, Gudex, G, Johnson, NP, Garland, J, Sadler, L. A randomized controlled trial of laparoscopic ovarian diathermy versus gonadotropin therapy for women with clomiphene citrate-resistant polycystic ovary syndrome. *Fertility and Sterility* 2002;**78**(2):404.

Farquhar 2012

Farquhar C, Brown J, Marjoribanks J. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD001122.pub4]

Forman 2007

Forman R, Gill S, Moretti M, Tulandi T, Koren G, Casper R. Fetal safety of letrozole and clomiphene citrate for ovulation induction.. *Journal of obstetrics and gynaecology Canada* 2007;**29**(8):668.

Higgins 2011

Julian PT Higgins, Sally Green. *Cochrane Handbook for Systematic Reviews of Interventions*. Vol. **5.1.0**, The Cochrane Collaboration, March 2011.

Jirge 2010

Jirge PR, Patil RS. Comparison of endocrine and ultrasound profiles during ovulation induction with clomiphene citrate and letrozole in ovulatory volunteer women. *Fertility and Sterility* 2010;**93**:174–83.

Lee 2011

Lee VC, Ledger W. Aromatase inhibitors for ovulation induction and ovarian stimulation. *Clinical Endocrinology* 2011;**74**:537–46.

Lunenfeld 2004

Lunenfeld, B. Historical perspectives in gonadotrophin therapy. *Human Reproduction Update* 2004;**10**:453.

Misso 2012

Misso ML, Wong JLA, Teede HJ, Hart R, Rombauts L, Melder AM Norman RJ, Costello MF. Aromatase inhibitors for PCOS: a systematic review and meta-analysis. *Human Reproduction Update* 2012;**18**(3):301–312.

Mitwally 2001

Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. *Fertility and Sterility* 2001; **75**:305–9.

Reproductive Medicine Network 2013

Letrozole versus clomiphene citrate in anovulatory PCOS women: A cost-effectiveness analysis.. Conference Abstract:

International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and the 69th Annual Meeting of the American Society for Reproductive Medicine, IFFS-ASRM 2013 Boston, MA United States.

Rotterdam 2003

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction* 2004;**19**(1):41.

Samani 2009

Samani FG, Farzadi L, Nezami N, Tarzamni MK, Soleimani F. Endometrial and follicular development following letrozole intervention in unexplained infertile patients failed to get pregnant with clomiphene citrate. *Archives of Gynecology and Obstetrics* 2009;**280**:201–5.

Tulandi 2006

Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, Librach C, Greenblatt E, Casper RF. Congenital malformations among 911 newborns conceived after

infertility treatment with letrozole or clomiphene citrate. *Fertility and Sterility* 2006;**85**(6):1761.

Velázquez 1997

Velázquez E, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. *Obstetrics and Gynecology* 1997;**90**(3):392.

White 1996

White DM, Polson DW, Kiddy D, Sagle P, Watson H, Gilling-Smith C, Hamilton-Fairley D, Franks S. Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. *Journal of Clinical Endocrinology and Metabolism* 1996;**81**(11):3821.

Zawadski 1992

Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc., Boston 1992:377.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdellah 2011

Methods	Randomised controlled trial
Participants	<p>Inclusion criteria: All patients met the Rotterdam consensus criteria for the diagnosis of PCOS. Other inclusion criteria included primary or secondary infertility because of anovulation for at least 1 year and clomiphene resistance. Clomiphene resistance was defined as lack of ovulation after 6 consecutive induction cycles with 50mg of CC, then with 150 mg of CC each day for 5 days in each cycle. The male partner of each participant was required to have a normal result on semen analysis and each woman was required to have patent tubes on hysterosalpingography or on a diagnostic laparoscopy</p> <p>Exclusion criteria: Exclusion criteria included age below 20 years or above 35 years; hormonal treatment within 3 months prior to the study; hyperprolactinaemia (morning plasma prolactin concentration 30ng/mL or more); any other endocrine, hepatic, or renal disorder; presence of an organic pelvic mass; and a history of abdominal surgery that might have caused pelvic factor infertility</p> <p>Number of women randomised: 147, 74 in the letrozole group and 73 in the LOD group.</p> <p>Number of women analysed: 70 in the letrozole group and 70 in the LOD group.</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 7 women were lost to follow up.</p> <p>Number of centres: One, Women's Health Center, Assiut University, Assiut</p> <p>Age (y): Group A letrozole: 23.9±3.2, Group B LOD: 23.6±3.2</p> <p>BMI (kg/m²): Group A letrozole: 27.3±2.6, Group B LOD: 27.1±2.6</p> <p>Duration of infertility (y): Group A letrozole: 4.2±1.7, Group B LOD: 4.2±1.7</p> <p>Country: Egypt</p>
Interventions	<p>Group A: Letrozole, 5mg/day given orally for 5 days during cycle days 3-7 for up to 6 cycles</p> <p>Group B: LOD, triple-puncture laparoscopy, monopolar diathermy, needle electrode set at 40W pressed against border of ovary for 4 sec to achieve penetration depths of 7-8mm, punctured at 4-6 points</p>
Outcomes	<p>Primary outcomes: Ovulation rate</p> <p>Secondary outcomes: endometrial thickness on the day of hCG injection, rates of clinical pregnancy, spontaneous abortion, live birth and multiple pregnancies</p>
Notes	<p>Ethical approval: Yes, the study was approved by Mansoura University Hospital Research Ethics Committee</p> <p>Informed consent: Yes, all participants gave informed consent before inclusion in the trial</p> <p>Source of funding: No, but "Conflict of interest statement: We declare that we have no conflict of interest"</p> <p>Authors contacted about information on OHSS</p> <p>Power calculation: "The sample size required to detect a 25% difference between the 2 groups with a power of 80% was estimated to be 68 patients per group."</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated random numbers table
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved using serially numbered opaque envelopes that were only opened once the interventions were assigned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 women lost to follow up, but similar (3 vs 4) in both groups; losses due to noncompliance
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	not stated

Abu Hashim June 2010

Methods	Randomised controlled clinical trial
Participants	<p>Inclusion criteria: Infertile women with CC-resistance and PCOS based on the Rotterdam criteria 2003. Patent fallopian tubes proved by hysterosalpingography and normal semen analysis for their partners according to the modified criteria of WHO</p> <p>Exclusion criteria: Other causes of infertility, age over 40 years, BMI > 35, contraindication to general anaesthetic, previous history of LOD and women who had received metformin, gonadotropin, oral contraceptives or other hormonal drugs during the preceding 6 months. Women who intended to start a diet or a specific program of physical activity were also excluded</p> <p>Number of centres: Two, Outpatient clinic in Mansoura University hospitals and a private practice setting</p> <p>Number of women randomised: 260, 128 in the letrozole group and 132 in the LOD group</p> <p>Number of women analysed: 128 in the letrozole group and 132 in the LOD group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: None</p> <p>Age (y): Group A letrozole: 27.3±2.6, Group B LOD: 26.4±2.4</p> <p>BMI (kg/m²): Group A letrozole: 26.4±3.3, Group B LOD: 26.6±3.6</p> <p>Duration of infertility (y): Group A letrozole: 4.3±1.11, Group B LOD: 4.5±1.24</p> <p>Country: Egypt</p>

Interventions	<p>Group A: Letrozole, 2.5mg/day orally given for 5 days starting from day 3 of the cycle</p> <p>Group B: LOD, laparoscopy was performed using three-puncture technique. Each ovary was cauterized at four points, each for 4s at 40W for a depth of 4mm with a mixed current, using a monopolar electrosurgical needle</p>
Outcomes	<p>Primary outcome: Ovulation rate</p> <p>Secondary outcomes: midcycle endometrial thickness (mm), biochemical pregnancy/cycle, clinical pregnancy/patient, biochemical miscarriage/cycle, clinical miscarriage/patient and live birth rates</p>
Notes	<p>Ethical approval: Yes, the study was approved by Mansoura University Hospital Research Ethics Committee</p> <p>Informed consent: Yes, all participants gave informed consent before inclusion in the trial</p> <p>Source of funding: No, but “Conflict of interest statement: We declare that we have no conflict of interest”</p> <p>Power calculation: “Sample size was calculated based on the fact that with an expected rate of ovulation of 70% in the LOD group we needed 244 women to show an absolute increase of 15% in ovulation rate in the letrozole group, with a power of 80% at confidence interval of 95% using a two tailed chi-square test with a 5% significance level (type alfa error)</p> <p>We had contact with Prof. Abu Hashim, all questions were answered in detail</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomised according to a computer-generated random numeric table prepared by an independent statistician
Allocation concealment (selection bias)	Low risk	Concealment of treatment allocation was done by using sealed opaque envelopes that were given to a third party (nurse) who assigned patients to study arms
Blinding of participants and personnel (performance bias) All outcomes	High risk	“Once allocated, the treatment was revealed to both the investigator and the patient.”
Blinding of outcome assessment (detection bias) All outcomes	High risk	“Once allocated, the treatment was revealed to both the investigator and the patient.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Other bias	Low risk	not stated
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Abu Hashim Sept 2010

Methods	Randomised controlled clinical trial	
Participants	<p>Inclusion criteria: Infertile women with PCOS based on the Rotterdam 2003 criteria. Additionally, diagnosed as CC resistant, patent fallopian tubes proved by hysterosalpin-gography and normal semen analysis for their partners according to the modified criteria of WHO 1999</p> <p>Exclusion criteria: None stated</p> <p>Number of centres: Two, Outpatient clinic in Mansoura University hospitals and a private practice setting</p> <p>Number of women randomised: 250, 123 in the letrozole group and 127 in the CC+Met group</p> <p>Number of women analysed: 123 in the letrozole group and 127 in the CC+Met group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A letrozole: 28.3±2.7, Group B CC+Met: 26.2±2.2</p> <p>BMI (kg/m²): Group A letrozole: 29.1±3.2, Group B CC+Met: 30.1±2.3</p> <p>Duration of infertility (y): Not stated</p> <p>Country: Egypt</p>	
Interventions	<p>Group A: Letrozole, 2.5mg/day for 5 days from cycle days 3 to 7</p> <p>Group B: Metformin HCl, 500mg thrice daily for 6-8 weeks, followed by 150mg of CC orally given for 5 days starting on day 3 of menstruation</p> <p>Patients continued treatment for three successive cycles using the same protocol</p>	
Outcomes	<p>Primary outcomes: Ovulation rate, number of growing and mature follicles, serum E2, serum P and endometrial thickness</p> <p>Secondary outcomes: Pregnancy and miscarriage rates, multiple pregnancies and cases of ovarian hyperstimulation syndrome</p>	
Notes	<p>Ethical approval: Yes, the study was approved by the local Research Ethics Committee</p> <p>Informed consent: Yes, all participants gave informed consent before inclusion in the trial</p> <p>Source of funding: No, but “All authors have nothing to disclose”</p> <p>Power calculation: The sample size was based on the fact that for an expected rate of ovulation of 70% in the combined metformin-CC group we needed 244 women to show an absolute increase of 15% in ovulation rate in the letrozole group, with a power of 80% at confidence interval of 95% using a two-tailed x² test with a 5% significance level</p> <p>We had contact with Prof. Abu Hashim, all questions were answered in detail</p>	
Risk of bias		
Bias	Authors’ judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Computer generated random table
Allocation concealment (selection bias)	Low risk	"Dark, sealed envelopes containing the intervention and taken from a computer-generated random numeric table were prepared by a third party (independent statistician) not involved in the allocation process."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"patients were not blinded because of the difference in shape, colour and size of letrozole, CC and metformin tablets" (E-mail with Prof. Abu Hashim)
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is not credible that outcome assessors were blinded if participants were not
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	not stated

Al-Omari 2004

Methods	Randomised, double blind, clinical trial
Participants	<p>Inclusion criteria: Non-fertile clomiphene-resistant women with PCOS</p> <p>Exclusion criteria: Tubal, peritoneal and uterine causes of infertility were excluded by laparoscopic hysterosalpingogram or by ultrasonography. Specific endocrine abnormalities and male factor causes for infertility were also excluded. Patients had to receive clomiphene treatment at least 2 months before enrolment</p> <p>Number of centres: "The study was done in the Baghdad teaching hospital/ Medical city which is a tertiary ref. hospital affiliated with Baghdad Med college/ University of Baghdad." (E-mail)</p> <p>Number of women randomised: 22 in the letrozole group and 18 in the anastrozole group</p> <p>Number of women analysed: 22 in the letrozole group and 18 in the anastrozole group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A letrozole: 28.4±5.18, group B anastrozole: 25.56±6.26</p> <p>BMI (kg/m²): Group A let: 29.95±3.73, group B anastrozole: 27.90±5.29</p> <p>Duration of infertility (y): Group A let: 3.95±2.70, group B anastrozole: 4.50±3.61</p> <p>Country: Iraq</p>
Interventions	<p>Group A: Letrozole 2.5mg/day orally given for 5 days during cycle days 3-7</p> <p>Group B: Anastrozole 1mg/day orally given for 5 days during cycle days 3-7</p>

	Treatment was continued for three months. When ovulation or pregnancy did not occur, the same treatment protocol was used with the doubling of the first dose for a maximum of two treatment cycles	
Outcomes	Primary outcomes: Ovulation rate/cycle, endometrial thickness (mm) measured on day of hCG administration Secondary outcomes: Multiple pregnancy rate, pregnancy rate/cycle, E2 (pmol/l), Progesterone (nmol/l), LH (U/l), Number and size of follicles, Pulsatility index, Day of hCG administration	
Notes	Ethical approval: “Ethical approval was obtained from the Iraqi Board for medical specialization/ Scientific committee” (E-mail contact) Informed consent: “written consent was obtained from all patients” (email contact) Source of funding: “The study was partially funded by the Iraqi Board for medical specialization as well as the Drug Scientific Office of the Iraqi Ministry of Health.” Power calculation: Not stated We had E-mail contact with Dr. Al-Omari, but there was no further information available about the outcomes	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Actually, we just put all envelopes in a box, mixing them then the patient herself selected one.” (E-mail with Dr. Al-Omari)
Allocation concealment (selection bias)	Unclear risk	“My associate informed me that for randomisation we distributed blank envelopes containing the medications at our Gyn.clinic on twice weekly basis.” (e-mail with Dr. Al-Omari)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is not credible that outcome assessors were blinded if participants were not
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Not stated

Methods	Randomised controlled clinical trial	
Participants	Inclusion criteria: Women with primary infertility and PCOS with no other known cause of infertility were enrolled into the study. All patients had a history of oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2-10mm in diameter and hyperechogenic stroma Exclusion criteria: None declared Number of centres: Setting unknown, tried to contact authors via e-mail Number of women randomised: 51 in the letrozole group and 55 in the CC group Number of women analysed: 51 in the letrozole group and 55 in the CC group Number of withdrawals/exclusions/loss to follow up and reasons: 0 Age (y): Group A letrozole: 27.1±0.9, group B CC: 26.2±1.1 BMI (kg/m²): Group A let: 26.1±1.91, group B CC: 25.8±1.77 Duration of infertility (y): Group A let: 2.2±0.7, group B CC: 2.4±0.9 Country: Turkey	
Interventions	Group A: Letrozole, 2.5mg/day orally given for 5 days starting on cycle day 3 Group B: Clomiphene citrate, 100mg/day orally given for 5 days starting on cycle day 3	
Outcomes	Outcomes: Number of mature follicles, endometrial thickness (mm), day of hCG administration, ovulation rate, pregnancy rate, multiple pregnancies	
Notes	Ethical approval: Yes, the study protocol was approved by the institutional ethics committee Informed consent: Yes, informed consent was obtained from all study participants Source of funding: No, but “Conflicts of interest: No conflicts of interest were declared in relation to this article” Power calculation: Not stated We contacted Dr. V Atay via e-mail about the study setting, about how randomisation and allocation was done, blinding and if data is available on OHSS, miscarriage rate and live birth rate, but no response	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how it was done exactly
Allocation concealment (selection bias)	Unclear risk	Unclear how it was done exactly
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Atay 2006 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Unclear risk	Protocol of the study was not available
Other bias	Low risk	not stated

Badawy 2008

Methods	Randomised controlled trial	
Participants	<p>Inclusion criteria: Diagnosis of PCOS based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS. All women were previously treated with 100mg of CC daily for 5 days per cycle, for two to three cycles with persistent anovulation or ovulate with very thin endometrium <5mm at the time of hCG administration. They had patent fallopian tubes proved by hysterosalpingography and normal semen analysis for their partners according to the modified criteria of WHO</p> <p>Exclusion criteria: No exclusion criteria stated.</p> <p>Number of centres: 2, Outpatient clinic in Mansoura University Hospitals and a private practice setting</p> <p>Number of women randomised: 111 in the letrozole group and 109 in the anastrozole group</p> <p>Number of women analysed: 111 in the letrozole group and 109 in the anastrozole group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Letrozole: 28.2±2.8, Group B Anastrozole: 26.3±2.5</p> <p>BMI (kg/m²): Group A Let: 29.1±3.1, Group B Anastrozole: 30.1±2.1</p> <p>Duration of infertility (y): Not stated</p> <p>Country: Egypt</p>	
Interventions	<p>Group A: Letrozole 2.5mg/day orally given for 5 days during cycle days 3-7</p> <p>Group B: Anastrozole 1mg/day orally given for 5 days during cycle days 3-7</p> <p>Treatment was continued for three months.</p>	
Outcomes	<p>Primary Outcomes: Number of growing and mature follicles, serum E2 (pg/ml), serum P (ng/mL), and endometrial thickness (mm)</p> <p>Secondary Outcomes: Pregnancy rate, miscarriage rate, multiple pregnancy rate, ovarian hyperstimulation syndrome rate</p>	
Notes	<p>Ethical approval: Yes, the study was approved by the hospital ethics research committee</p> <p>Informed consent: Yes, all participants gave informed consent before inclusion in the trial</p> <p>Source of funding: Not stated</p> <p>Power calculation: Not stated</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Badawy 2008 (Continued)

Random sequence generation (selection bias)	Low risk	Patients were randomly allocated using a computer-generated random table into two treatment groups
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	not stated

Badawy July 2009

Methods	Randomised controlled study
Participants	<p>Inclusion criteria: Infertile women with clomiphene- resistant PCOS, diagnosis of PCOS based on the 2003 Rotterdam Criteria. Normal serum PRI, TSH and 17OH-P</p> <p>Exclusion criteria: Infertility caused by fallopian tube problems, infertility problems caused by male partner</p> <p>Number of centres: 2, Outpatient clinic in Mansoura University Hospitals and a private practice setting</p> <p>Number of women randomised: 110 in the short letrozole group and 108 in the long letrozole group</p> <p>Number of women analysed: 110 in the short letrozole group and 108 in the long letrozole group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A short Letrozole: 25.1±3.2, Group B long Let: 25.3±3.0</p> <p>BMI (kg/m²): Group A short Let: 33.9±3.1, Group B long Let: 34.2±2.6</p> <p>Duration of infertility (y): Not stated</p> <p>Country: Egypt</p>
Interventions	<p>Group A: Letrozole orally given, 5mg/day for 5 days, from cycle days 3-7</p> <p>Group B: Letrozole orally given, 2.5mg/day for 10 days, from cycle days 3-12</p>
Outcomes	<p>Primary Outcomes: Number of growing and mature follicles, serum E2 (pg/mL), serum P (ng/mL), and endometrial thickness (mm)</p> <p>Secondary Outcomes: Pregnancy rate, miscarriage rate, Multiple pregnancies, ovarian hyperstimulation syndrome rate</p>

Notes	Ethical approval: Yes, the study was approved by the hospital ethics research committee Informed consent: Yes, all participants gave informed consent before inclusion in the trial Source of funding: No, but Conflicts of Interest: "All authors have nothing to disclose" Power calculation: "Sample size calculation, using StatCalc 3.02 computer package 8Acastat software, Leesburg, VA), showed that each arm should contain at least 103 patients to have 80% power of the study at 95% confidence interval (CI) Authors were contacted, but information on live birth was not collected	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated into two treatment groups using a computer-generated random table: short letrozole group and long letrozole group
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported
Other bias	Low risk	not stated

Badawy Sept 2009

Methods	Prospective randomised trial
Participants	<p>Inclusion criteria: Diagnosis of PCOS based on the 2003 Rotterdam Criteria. All women had patent fallopian tubes proved by hysterosalpingography and their partners had normal semen analysis parameters according to the modified criteria of the WHO. All patients had normal serum prolactin, thyroid stimulating hormone (TSH) and 17-OH progesterone</p> <p>Exclusion criteria: Not stated</p> <p>Number of centres: Multiple, University teaching hospital and private practices</p> <p>Number of women randomised: 218 in the Letrozole group and 220 in the Clomiphene Citrate group</p> <p>Number of women analysed: 218 in the Letrozole group and 220 in the Clomiphene</p>

	Citrate group Number of withdrawals/exclusions/loss to follow up and reasons: 0 Age (y): Group A Letrozole: 27.1±3.2, Group B Clomiphene Citrate: 29.3±2.9 BMI (kg/m²): Group A Let: 28.1±3.2, Group B CC: 27.1±3.1 Duration of infertility (y): Not reported Country: Egypt
Interventions	Group A: Letrozole orally given 5mg/day for 5 days from cycle days 3-7 Group B: Clomiphene Citrate orally given 100mg/day for 5 days from cycle days 3-7
Outcomes	Primary Outcomes: Number of growing and mature follicles, the concentrations of serum E2 (pg/mL) and progesterone (ng/mL), and the endometrial thickness (mm) Secondary Outcomes: Ovulation rate, Ovarian hyperstimulation rate, pregnancy rate, miscarriage rate, Multiple pregnancy rate
Notes	Ethical approval: Yes, the study was approved by the hospital research ethics committee Informed consent: Yes, all participants gave informed consent before inclusion in the trial Source of funding: The study was self-funded Power calculation: Not stated Authors were contacted via e-mail and gave all information, but they did not measure the live birth

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated using a computer generated random table into two groups
Allocation concealment (selection bias)	Low risk	"Allocation concealment was done by sequentially numbered opaque sealed envelopes opened by the chief nurse" (via e-mail contact with authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, e-mail with Prof. Badawy
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is not credible that outcome assessors were blinded if participants were not
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported, LB was not measured
Other bias	Low risk	Not stated

Bayar 2006

Methods	Randomised controlled study	
Participants	Inclusion criteria: Anovulatory PCOS patients diagnosed by using 2003 Rotterdam criteria Exclusion criteria: Tubal, peritoneal and uterine cause of infertility. Male factor infertility. Specific endocrine abnormalities (Cushings disease/syndrome, hypothyroidism, hyperthyroidism, prolactinoma) Number of centres: One, Outpatient clinics of the Infertility and Reproductive Medicine Unit of the Zonguldak Karaelmas University Hospital (Zonguldak, Turkey) Number of women randomised: 80, 40 in Group A Let and 40 in Group B CC Number of women analysed: 38 in Group A Let and 36 in Group B CC Number of withdrawals/exclusions/loss to follow up and reasons: 6 lost to follow up, no reasons given Age (y): Group A Letrozole: 32.2±3.9, Group B Clomiphene Citrate: 30.6±4.0 BMI (kg/m²): Not stated Duration of infertility (y): Group A Letrozole: 5 (1-10), Group B Clomiphene Citrate: 3 (3-11) Country: Turkey	
Interventions	Group A: Letrozole, 5mg/day orally given for 5 days during cycle days 3-7 Group B: Clomiphene citrate, 100mg/day orally given for 5 days during cycle days 3-7	
Outcomes	Outcomes: Ovulation rate per cycle, pregnancy rate per cycle, delivery rate per cycle, miscarriage rate, multiple pregnancy rate, endometrial thickness on the day of hCG (mm), No. of follicles sized >15 mm in diameter on the day of hCG, E2 level on the day of hCG (pg/mL), E2 per follicle sized >15 mm in diameter on the day of hCG (pg/mL)	
Notes	Ethical approval: Yes, the study was approved by the institutional ethics committee of karelmal university Informed consent: Not stated Source of funding: No funding source or conflicts of interest stated. Power calculation: Sample-size determination was based on the difference between the median number of follicles sized >15 mm and E2 concentration on hCG day. A sample size of 60 patients (30 patients in each group) was targeted to be able to detect a difference of at least one follicle or of 200 pmol/L between the two groups, with alfa (type I error) set at 0.05 and 80% power Dr. Bayar was contacted via e-mail for additional information, but he did not respond	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation performed by a computer
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was achieved by using central consultation for treatment of eligible patients

Bayar 2006 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double blind not it is not clear who is actually blinded and how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind not it is not clear who is actually blinded and how this was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 Patients lost to follow up, 4 and 2 respectively
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Not stated

Begum 2009

Methods	Randomised not blinded, controlled trial
Participants	<p>Inclusion criteria: Infertile female women with PCOS diagnosed by the Rotterdam criteria 2003 who failed to ovulate by taking 100mg of CC/day for 5 days in two consecutive cycles</p> <p>Exclusion criteria: Patients with hyperprolactinaemia, thyroid disorder, male factor infertility, known or suspicious tubal factor infertility (endometriosis and pelvic inflammatory disease), and unexplained infertility were excluded from the study</p> <p>Number of centres: One, private infertility care setting</p> <p>Number of women randomised: 32 in each group</p> <p>Number of women analysed: 32 in each group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Letrozole: 25.47±3.98, Group B Clomiphene Citrate: 26.09±3.62</p> <p>BMI (kg/m²): Group A Letrozole: 22.72±2.77, Group B Clomiphene Citrate: 23.63±3.23</p> <p>Duration of infertility (y): Group A Letrozole: 2.66±1.11, Group B Clomiphene Citrate: 2.58±1.10</p> <p>Country: India</p>
Interventions	<p>Group A: Letrozole, 7.5mg/day orally given for 5 days from cycle days 3 to 7</p> <p>Group B: Clomiphene Citrate, 150mg/day orally given for 5 days from cycle days 3 to 7</p>
Outcomes	<p>Primary Outcomes: Ovulation and pregnancy rate</p> <p>Secondary Outcomes: Follicular development by day 16 (mm), Serum E2 on day of hCG (pg/mL), Endometrial development by day 16 (mm), Serum P on day 21 (ng/mL), Multiple pregnancies, ovarian hyperstimulation syndrome cases. Live birth rate was provided via email contact</p>
Notes	<p>Ethical approval: Yes, the study protocol was approved by the institutional review board (IRB) of Dhaka medical college</p>

	<p>Informed consent: Yes, patients were counselled and informed consent was obtained before recruitment</p> <p>Source of funding: The study was self-funded</p> <p>Power calculation: A study population of 57 women was calculated considering an average of 60% of PCOS women are associated with insulin resistance, allowing an alfa value of 0.05</p> <p>Authors were contacted via e-mail, additional information was provided</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by lottery method. They put the name of letrozole and CC in a sealed unleveled envelope. By calculating sample size they made 64 pieces of paper. 32 for letrozole and 32 for CC
Allocation concealment (selection bias)	Unclear risk	"All unleveled envelop were put together and the patients drew one piece of envelop from them. Then we opened the envelop to see the name of the drug." (via e-mail contact with Prof. Rashida)
Blinding of participants and personnel (performance bias) All outcomes	High risk	"There was no blinding" (via e-mail contact with Prof. Rashida)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"There was no blinding" (e-mail with Prof. Rashida)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	not stated

Davar 2011

Methods	Single blind randomised clinical trial
Participants	<p>Inclusion criteria: Patients who received 150mg cc daily for 3 cycles and failed to become pregnant, and were diagnosed with anovulatory PCOS based on Rotterdam 2003</p> <p>Exclusion criteria: "We excluded patients with liver and kidney dysfunction, cardiovascular disease, diabetics, and those who use metformin or drugs affecting insulin secretion and clomiphene citrate in recent 2 cycles."</p>

	<p>Number of centres: One, Research and clinical centre for infertility, shahid sadoughi University of medical sciences, Yazd</p> <p>Number of women randomised: 100 women, 50 in Group A Met-Let, 50 in Group B Met-CC</p> <p>Number of women analysed: 48 in Group A Met-Let, 50 in Group B Met-CC</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 2, experienced side effects with metformin before Let was started</p> <p>Age (y): Group A Metformin-Letrozole: 28.54±3.13, Group B Metformin-Clomiphene Citrate: 29.55±3.47</p> <p>BMI (kg/m²): Group A Met-Letrozole: 28.98±3.83, Group B Met-Clomiphene Citrate: 29.21±2.92</p> <p>Duration of infertility (y): Group A Met-Letrozole: 3.81, Group B Met-Clomiphene Citrate: 3.76</p> <p>Country: Iran</p>	
Interventions	<p>Group A: Metformin 1500mg daily for 6-8 weeks, followed by 5mg letrozole daily orally given for 5 days during cycle days 3-7 if pregnancy did not occur</p> <p>Group B: Metformin 1500mg daily for 6-8 weeks, followed by 100mg CC daily orally given for 5 days during cycle days 3-7 if pregnancy did not occur</p>	
Outcomes	E2 (pg/mL) on day of hCG administration, Number of follicles >18mm in diameter, Endometrial thickness on day of hCG administration (mm), clinical pregnancy rate, miscarriage rate	
Notes	<p>Ethical approval: Yes, the study was approved by ethical board of shahid sagoughi university of medical sciences, yazd</p> <p>Informed consent: No, at least nothing written about it - authors contacted</p> <p>Source of funding: “the study was fully supported and funded by shahid sadoughi university of medical sciences, yazd, iran”</p> <p>Power calculation: “In this study, 50 cases were needed in each group so as to gain a significant difference of 22% in pregnancy rate at a significant level of 5% and a power of 80%”</p> <p>Dr Davar was contacted via e-mail to get additional information, but we did not get a response</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done using a random numbers table
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated who was blinded in this single blinded trial

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated who was blinded in this single blinded trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients lost to follow up due to side effects experienced with metformin before letrozole was started
Selective reporting (reporting bias)	Low risk	All outcomes reported stated in the protocol
Other bias	Low risk	not stated

Dehbashi 2009

Methods	Double blind randomised study	
Participants	Inclusion criteria: Infertility for at least one year, diagnosis of PCOS by the rotterdam criteria 2003, having patent tubes on hysterosalpingogram, and normal semen analysis of the patients husbands Exclusion criteria: Patients must not have received any other medication for ovulation induction before enrolment to the study Number of centres: One, outpatient infertility clinics at Shiraz University of Medical Scieces Number of women randomised: 100 women, 50 in each group Number of women analysed: 100 women, 50 in each group Number of withdrawals/exclusions/loss to follow up and reasons: 0 Age (y): Group A Letrozole: 23.62±2.92, Group B CC: 24.32±3.43 BMI (kg/m²): Group A Let: 27.45±4.61, Group B CC: 27.09±3.61 Duration of infertility (y): Group A Let: 2.00±1.34, Group B CC: 2.30±1.85 Country: Iran	
Interventions	Group A: Letrozole, 5mg/day orally given for 5 days during cycle days 3-7 Group B: Clomiphene Citrate, 100mg/day orally given for 5 days during cycle days 3-7	
Outcomes	Total number of follicles with diameter ≥14 mm, endometrial thickness on the day of hCG injection, pregnancy rate, miscarriage rate, multiple pregnancy rate, live birth rate	
Notes	Ethical approval: Yes, “The study was approved by the Institutional Ethics Committee of the University.” Informed consent: Yes, “An informed written consent was obtained from each patient” Source of funding: No, but “Conflicts of interest: None declared” Power calculation: Not stated Authors contacted about randomisation, allocation, and information about OHSSr	
Risk of bias		
Bias	Authors’ judgement	Support for judgement

Dehbashi 2009 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not stated how it was done exactly
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only the pharmacist knew the name of the medication that had been taken by the patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only the pharmacist knew the name of the medication that had been taken by the patients
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients excluded or lost to follow up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	not stated

Elgafor 2013

Methods	Randomised controlled trial
Participants	<p>Inclusion criteria: Clomiphene citrate resistant women with infertility due to PCOS, diagnosed according to the Rotterdam 2003 criteria. Clomiphene citrate resistance was defined as failure to achieve adequate follicular maturation after 3 consecutive induction cycles with CC at 150 mg/day for 5 days</p> <p>Exclusion criteria: Exclusion criteria includes women with other causes of infertility as male factor or tubal factor, those with endocrine disorders as thyroid dysfunction and hyperprolactinaemia, women who received hormonal treatment or ovulation induction drugs 3 months before the study</p> <p>Number of centres: One, Zagazig University Hospital, Egypt</p> <p>Number of women randomised: 146 women, 73 in each group</p> <p>Number of women analysed: 146 women, 73 in each group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Metformin + Letrozole: 24.7±1.8, Group B LOD: 25.1±2.1</p> <p>BMI (kg/m²): Group A Metformin + Letrozole: 31.5±3.3, Group B LOD: 32.4±4.4</p> <p>Duration of infertility (y): Group A Metformin + Letrozole: 3.4±0.9, Group B LOD: 3.9±1.1</p> <p>Country: Egypt</p>
Interventions	<p>Group A: Metformin 850 to 1700mg daily for 6-8 weeks, followed by 5mg letrozole daily orally given for 5 days during cycle days 3-7 if pregnancy did not occur</p> <p>Group B: LOD, laparoscopy was performed using three-puncture technique</p>
Outcomes	Cycle regularity, ovulation rate, clinical pregnancy rate, miscarriage rate

Notes	Ethical approval: Yes, “Ethics Committee of Zagazig University approved the study” Informed consent: Yes, “written informed consent was obtained from each patient at the start of the study” Source of funding: No, but “Conflicts of interest: None” Power calculation: Not stated	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participant women were randomised according to a computer-generated random numeric table
Allocation concealment (selection bias)	Low risk	The random allocation sequence was concealed in sealed dark envelopes, then patients were assigned randomly into group 1 (n = 73) received metformin plus letrozole, and group 2 (n = 73) underwent LOD
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Not stated

Foroozanfar 2011

Methods	Randomised controlled clinical trial
Participants	Inclusion criteria: Our inclusion criteria were age 20-35 years, infertility for at least one year and resistance to Clomiphene (at least 3 cycles Clomiphene usage, 150mg/day with no ovulatory response) Exclusion criteria: Exclusion criteria were BMI >27, endocrine disorders such as hypothyroidism, hyperprolactinemia, infertility due to male factors, uterine factors and adhesive diseases due to pelvic surgery Number of centres: One, outpatient infertility clinic in Kashan Number of women randomised: 60 in each group Number of women analysed: 60 in each group Number of withdrawals/exclusions/loss to follow up and reasons: 0

	Age (y): Group A Let+Gon: 25.8±3.75, Group B CC+Gon: 25.33±4.14 BMI (kg/m²): Group A Let+Gon: 24.12±2.33, Group B CC+Gon: 24.87±2.00 Duration of infertility (y): Group A Let+Gon: 2.76±2.27, Group B CC+Gon: 2.60±2.07 Country: Iran	
Interventions	Group A: Letrozole, 5mg/day orally given for 5 days from cycle days 3-7 + 150 IU hMG intramuscularly during cycle days 5-8 Group B: Clomiphene citrate, 100mg/day orally given for 5 days from cycle days 3-7 + 150 IU hMG intramuscularly during cycle days 5-8	
Outcomes	Life birth rate, ovarian hyperstimulation syndrome rate, pregnancy rate, miscarriage rate, multiple birth rate, number of dominant follicles, endometrial thickness (mm), ectopic pregnancies	
Notes	Ethical approval: Yes,” approval was obtained from the Institute Research Board to perform this study. “ Informed consent: Yes, “All patients were informed about possible side effects ad also off label use of letrozole for the purpose of inducing ovulation and written consent were obtained for all participants.” Source of funding: Yes, “Authors acknowledge the research deputy of Kashan University of Medical Sciences for providing the financial support.” Power calculation: Not stated Authors contacted via e-mail, all information provided.	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was performed by a computer .
Allocation concealment (selection bias)	Low risk	Via sequentially numbered opaque sealed envelopes (e-mail with authors)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Before commence of the study all patients were informed of the study and were told about this issue that it is possible to be enrolled in letrozole or clomiphene group but none of them knew which group she allocated to and the researcher was blinded also to patients’ treatment approach. (e-mail contact with authors)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Not stated

Ganesh 2009

Methods	Randomised controlled trial	
Participants	<p>Inclusion criteria: 1387 women with PCOS diagnosed by the Rotterdam criteria who had previously failed to conceive or ovulate with cc treatment and undergoing IUI were included in the study. Specific inclusion criteria for the study were normal TSH and prolactin levels and normozoospermic male partners as per WHO guidelines</p> <p>Exclusion criteria: Patients with pre-existing ovarian cyst on day 3 and previous history of ovarian drilling were carefully identified and excluded</p> <p>Number of centres: One, a tertiary infertility care unit, Institute of Reproductive Medicine, Kolkata, India</p> <p>Number of women randomised: 1378 in total</p> <p>Number of women analysed: 1378 in total</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Let: 30.25±4.90, Group B CC: 30.38±5.18, Group C rFSH: 30.82±4.56</p> <p>BMI (kg/m²): Group A Let: 24.49±3.83, Group B CC: 24.75±4.05, Group C rFSH: 24.08±3.43</p> <p>Duration of infertility (y): Not reported.</p> <p>Country: India</p>	
Interventions	<p>Group A: Letrozole, 5mg/day orally given for 5 days from cycle days 3-7</p> <p>Group B: Clomiphene citrate, 100mg/day orally given for 5 days from cycle days 3-7 + 75 or 100 IU rFSH during cycle days 3 and 8</p> <p>Group C: One ampoule rFSH 75IU/100IU from day 2 until the day of hCG administration</p>	
Outcomes	The primary outcome measures including ovulation rate, cancellation rate, miscarriage rate and pregnancy rate were compared amongst the three groups. Secondary outcomes were OHSS rate and multiple pregnancy rate	
Notes	<p>Ethical approval: Yes, approval was obtained from the institutional Research ethics board</p> <p>Informed consent: Yes, “Written informed consent was taken from all women included in this study.”</p> <p>Source of funding: No, but ”This study was not funded by any funding agency.”</p> <p>Power calculation: Not stated</p> <p>Authors contacted via e-mail, all information provided.</p>	
Risk of bias		
Bias	Authors’ judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"The subjects recruited for the study were randomly and blindly assigned to one of the treatment protocols. The procedure was carried out by requesting the patient to pick up randomly an opaque, sealed envelope. Each envelope contained a piece of paper with one of the three protocols written on it. Many such sealed envelopes were prepared and placed randomly. Once the patient picked the envelope, the seal was opened in front of the patient and the coordinator, the content showed and the protocol allocated." (Information via email from the author)
Allocation concealment (selection bias)	Low risk	"the allocation was done using sealed envelopes where the person allocating was blinded to the type of protocol received by the patients."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Only researcher was blinded and the patient aware of the protocol followed since the route of administration was different in all the three groups."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Only researcher was blinded and the patient aware of the protocol followed since the route of administration was different in all the three groups."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Not stated

Kamath 2010

Methods	A randomised, double-blind, placebo-controlled trial
Participants	<p>Inclusion criteria: Women with PCOS and clomiphene resistance who were being treated with ovulation induction were invited to participate. Additionally, women had to have normal hormone profile and a male partner with normal semen parameters by WHO criteria. Normal hormone profile was defined as a FSH level of <12IU/L, serum prolactin level of <25ng/mL, and a thyroid-stimulating hormone (TSH) value between 0.3 and 4.5µIU/mL</p> <p>Exclusion criteria: Women with other endocrine disorders such as Cushing syndrome and congenital adrenal hyperplasia were excluded</p> <p>Number of centres: One, Reproductive medicine unit, Christian Medical college, Vellore, Tamil Nadu, India</p> <p>Number of women randomised: 18 in each group</p> <p>Number of women analysed: 17 in each group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 2 lost to follow up before treatment started</p>

	Age (y): Group A Letrozole: 25.61±3.58, Group B Placebo: 25.72±3.72 BMI (kg/m²): Group A Letrozole: 26.06±3.73, Group B Placebo: 24.67±4.17 Duration of infertility (y): Group A Letrozole: 5.17±3.17, Group B Placebo: 3.56±2.15 Country: India	
Interventions	Group A: Letrozole, orally given 2.5mg/day for 5 days from cycle days 2 to 6 Group B: Placebo, also given for 5 days from cycle days 2 to 6	
Outcomes	Primary Outcome: Ovulation rate Secondary Outcomes: Live birth rate, ovarian hyperstimulation syndrome rate, pregnancy rate, miscarriage rate, multiple pregnancy rate, endometrial thickness (mm), day 21 serum progesterone (nmol/L), number of patients with mature follicle (%)	
Notes	Ethical approval: Yes, the protocol of the study was approved by the institutional review board Informed consent: Yes, written informed consent was obtained from each patient Source of funding: No, but Conflicts of interest stated:. “The Authors have nothing to disclose” Power calculation: “Our literature pointed to a 75% ovulation rate when 2.5 mg of letrozole was used in women with PCOS who had clomiphene resistance. We hypothesized an ovulation rate of 60& with letrozole and 10% with placebo. On this basis, a sample size of 17 women in each arm (80% and alpha .05 for a two-sided test) was calculated.” Contacted authors about OHSS rate and how randomisation and allocation concealment was done in detail. All information provided	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly distributed using a computer-generated randomisation sequence in blocks of six, into two groups
Allocation concealment (selection bias)	Low risk	Allocation concealment was done by using consecutively numbered sealed opaque envelopes containing the treatment packets
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The randomisation code was maintained by the pharmacy department, which revealed the group assignments at the end of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The code was revealed after the statistical analysis had been performed

Incomplete outcome data (attrition bias) All outcomes	Low risk	One women in each group was lost to follow up, after randomisation and before treatment started
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Not stated

Kar 2012

Methods	Randomised controlled trial	
Participants	<p>Inclusion criteria: “PCOS was diagnosed according to Rotterdam criteria. All women were treatment-naïve i.e. had not undergone any significant treatment for infertility/ovulation induction earlier.”</p> <p>Exclusion criteria: “Patients with hyperprolactinaemia, thyroid disorder, male factor, suspected tubal factor, endometriosis, unexplained infertility were not included in the study.”</p> <p>Number of centres: “This study was conducted at a private hospital with a large gynecological practice.”</p> <p>Number of women randomised: 103 women, 52 in the Let group and 51 in the CC group.</p> <p>Number of women analysed: 103 women, 52 in the Let group and 51 in the CC group.</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Letrozole: 26.26±2.41, Group B CC: 26.27±2.47</p> <p>BMI (kg/m²): Group A Letrozole: 25.91±3.57, Group B Placebo: 25.95±3.31</p> <p>Duration of infertility (y): Group A Letrozole: 3.08±1.92, Group B CC: 3.14±2.16</p> <p>Country: India</p>	
Interventions	<p>Group A: Letrozole, 5mg/day orally given for 5 days from cycle days 2-6</p> <p>Group B: Clomiphene citrate, 100mg/day orally given for 5 days from cycle days 2-6</p>	
Outcomes	<p>Primary outcomes: ovulation rate, endometrial thickness, mono vs. multi-follicular rate, and days to ovulation</p> <p>Secondary outcomes: pregnancy and miscarriage rate</p>	
Notes	<p>Ethical approval: Yes, “Study protocol was approved by the institutional ethics committee.”</p> <p>Informed consent: Not stated.</p> <p>Source of funding: “Nil”</p> <p>Power calculation: Not reported.</p>	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Patients were randomized by lottery”

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Not stated

Legro 2014

Methods	A randomized, double-blind multi-center trial
Participants	<p>Inclusion criteria: Women with PCOS defined by the Rotterdam criteria and at least 1 patent fallopian tube and normal uterine cavity and a male partner with sperm concentration of more than 14 million/mL</p> <p>Exclusion criteria: “We will exclude subjects with medical conditions that represent contraindications to CC, letrozole and/or pregnancy or who are unable to comply with the study procedures.”</p> <p>Number of centres: Multi-center trial</p> <p>Number of women randomised: 750, 374 in the Let group and 376 in the CC group</p> <p>Number of women analysed: 750, 374 in the Let group and 376 in the CC group</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Let: 29±5, Group B CC: 28±4</p> <p>BMI (kg/m²): Group A Let: 35±10, Group B CC: 35±9</p> <p>Duration of infertility (y): Not reported</p> <p>Country: USA</p>
Interventions	<p>Group A: Letrozole, orally given 2.5mg/day for 5 days during cycle days 3-7</p> <p>Group B: Clomiphene Citrate, orally given 100mg/day for 5 days during cycle days 3-7</p>
Outcomes	Live birth, ovulation rate, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate
Notes	<p>Ethical approval:</p> <p>Informed consent:</p> <p>Source of funding: The study is funded through a cooperative agreement by the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD)</p> <p>Power calculation: A sample size of 300 subjects in each arm of the randomization</p>

Legro 2014 (Continued)

	yields 81% statistical power to prospectively demonstrate a 0.10 absolute difference in live birth proportions between treatment arms (0.20 for CC and 0.30 for letrozole) using the Pearson's chi-square test with a two-sided significance level of 0.05	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Almac statisticians will generate the randomization scheme for the study
Allocation concealment (selection bias)	Low risk	third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In order to maintain the double-blind, CC and letrozole will be overencapsulated and packaged in identically appearing numbered study kits (using Almac Clinical Services, Durham NC) which will then be directly shipped to each clinical site
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In order to maintain the double-blind, CC and letrozole will be overencapsulated and packaged in identically appearing numbered study kits (using Almac Clinical Services, Durham NC) which will then be directly shipped to each clinical site. The randomization scheme (including block size) will be disclosed to the DCC data manager, but not to any RMN investigators or staff, including the Protocol Lead Investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Not stated

Nazik 2012

Methods	A partly randomised controlled clinical trial.
Participants	Inclusion criteria: Infertile patients with PCOS, diagnosis based on the 2003 Rotterdam criteria Exclusion criteria: Patients who had ovarian or adnexal surgery, hypothyroidism, hyperprolactinaemia, bilateral tubal occlusion diagnosed with hysterosalpingography and unexplained infertility were excluded from the study, as were patients with follicles greater than 10mm

	Number of centres: One, Infertility Polyclinic of Atatürk University Medical Faculty Erzurum Number of women randomised: 31 in Group A, 33 in Group B Number of women analysed: 31 in Group A, 33 in Group B Number of withdrawals/exclusions/loss to follow up and reasons: 0 Age (y): Group A Letrozole: 25.55±4.45, Group B CC: 27.80±6.18 BMI (kg/m²): Group A Letrozole: 24.66±3.57, Group B CC: 24.90±4.80 Duration of infertility (y): Group A Letrozole: 3.40±3.04, Group B CC: 4.40±3.58 Country: Turkey	
Interventions	Group A: Letrozole, orally given 2.5mg/day for 5 days during cycle days 3-7 Group B: Clomiphene Citrate, orally given 100mg/day for 5 days during cycle days 3-7	
Outcomes	Primary Outcomes: Ovulation rate and pregnancy rate Secondary Outcomes: Ovarian hyperstimulation syndrome rate, Miscarriage rate, Multiple Pregnancy rate, number of follicles on day of hCG (≥17mm), E2 (pg/mL) on hCG day, endometrial thickness (mm), other side effects	
Notes	Ethical approval: Yes, “Ethical approval was obtained from the institutional review board of Atatürk University Medical Faculty in order to conduct this study.” Informed consent: “Instead of written consent verbal approval was obtained from the patients prior to study begin and treatment” - correspondence with Dr. Hakan Nazik Source of funding: “This study was done by researchers without any funding” Power calculation: Not stated All questions were answered by Dr. Hakan Nazik	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“The patients were randomly allocated using a computer random list into first and second groups”
Allocation concealment (selection bias)	Unclear risk	“The patients were randomly allocated using a computer random list into first and second groups”
Blinding of participants and personnel (performance bias) All outcomes	High risk	“There was no blinding in our study” (E-mail with Dr. Hakan Nazik)
Blinding of outcome assessment (detection bias) All outcomes	High risk	“There was no blinding in our study” (E-mail with Dr. Hakan Nazik)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Patients in Group 2 Letrozole were significantly Younger and had a significantly shorter duration of infertility

Ramezanzadeh 2011

Methods	Randomised controlled trial
Participants	<p>Inclusion criteria: PCOS patients with infertility who underwent ovulation induction and timed intercourse for the first time. PCOS was diagnosed by the Rotterdam 2003 criteria. Participants were less than 35 years old with at least one year of infertility with no other infertility factor</p> <p>Exclusion criteria: Ovarian cysts on cycle day 3 found by transvaginal ultrasound examination</p> <p>Number of centres: One, an infertility clinic of a tertiary referral centre</p> <p>Number of women randomised: 80; Group A letrozole 5mg: 40, Group B letrozole 7.5mg: 40</p> <p>Number of women analysed: Group A letrozole 5mg: 30, Group B letrozole 7.5mg: 37</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 4 Excluded in group A due to a cyst before treatment, 6 lost to follow up in Group A and 3 lost to follow up in group B</p> <p>Age (y): Group A letrozole 5mg: 28.27±4.98, Group B letrozole 7.5mg: 28.22±4.45</p> <p>BMI (kg/m²): Group A letrozole 5mg: 25.87±4.19, Group B letrozole 7.5mg: 26.69±3.60</p> <p>Duration of infertility (y): Group A letrozole 5mg: 3.64±2.30, Group B letrozole 7.5mg: 4.74±3.16</p> <p>Country: Iran</p>
Interventions	<p>Group A: Letrozole orally given, 5mg/day for 5 days from cycle days 3-7</p> <p>Group B: Letrozole orally given, 7.5mg/day for 5 days from cycle days 3-7</p>
Outcomes	Number and size of follicles and endometrial thickness on days 12-14, the number of days to reach mature follicle, day 7 testosterone level, day 21 progesterone level, ovulation rate, pregnancy rate, miscarriage rate, multiple pregnancy rate, ovarian hyperstimulation syndrome rate
Notes	<p>Ethical approval: Yes, the hospital research ethics board approved the study.</p> <p>Informed consent: All participants gave informed consent before inclusion in trial</p> <p>Source of funding: No, but "Conflict of interest: All of the authors do not have any conflict of interest"</p> <p>Power calculation: "Using PASS software and based on two previous studies, a sample size of 30 subjects in each group would provide 80% power to detect a significant difference in the number of mature follicles and duration of stimulation between two groups with a significant level of 0.05."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated using computer-generated random table into two Letrozole treatment groups
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	4 patients excluded due to ovarian cyst on day 3 sonography. 9 patients lost to follow up, 6 in Group A and 3 in Group B without reasons given
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Not stated

Ray 2012

Methods	A comparative, randomised, phase III, open labelled trial study
Participants	<p>Inclusion criteria: Infertile females aged 20-35 with PCOS diagnosis based on the Rotterdam criteria 2003</p> <p>Exclusion criteria: Patients who had hyperprolactinaemia, thyroid disorder, male factor infertility, known or suspicious tubal factor infertility (endometriosis and pelvic inflammatory disease) were excluded from the study. Exclusion also include patients with a history of liver and kidney failure, cardiovascular diseases, diabetes or patients who consumed metformin or drugs effecting insulin secretion or CC in the previous 2 months</p> <p>Number of centres: One, Eden Hospital, Medical College Kolkata</p> <p>Number of women randomised: 147; Group A Let: 69, Group B CC: 78</p> <p>Number of women analysed: Group A Let: 69, Group B CC: 78</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 0</p> <p>Age (y): Group A Let: 28 (19-35), Group B CC: 29 (20-35)</p> <p>BMI (kg/m²): Group A Let: 28.8 (23.2-34.6), Group B CC: 28.5 (24.2 - 33.6)</p> <p>Duration of infertility (y): Group A Let: 2.2, Group B CC: 2.4 (Std or range not given)</p> <p>Country: India</p>
Interventions	<p>Group A: Letrozole, 2.5mg/day given orally for 5 days from cycle day 3 to 7</p> <p>Group B: Clomiphene Citrate, 100mg/day given orally for 5 days from cycle day 3 to 7</p>

Outcomes	Primary Outcomes: Ovulation rate, average follicular diameter on day 16, number of mature follicles produced per cycle, mean estradiol level on the day of hCG administration, mean endometrial thickness, pregnancy rate Secondary Outcomes: miscarriage rate, live birth rate,	
Notes	Ethical approval: Yes, the study protocol was approved by the ethical committee of Medical college Kolkata Informed consent: Yes, Patients were counselled and informed consent was obtained before recruitment Source of funding: “Conflict of interest: the authors hereby declare that they have not received any financial support for this study and there is no conflict of interest.” Power calculation: Not stated Dr. Ray was contacted via e-mail about Randomisation, allocation, blinding, MPR and OHSSr, but he did not respond	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how randomisation was done exactly
Allocation concealment (selection bias)	Unclear risk	Unclear how allocation was done exactly
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported if anyone was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported if anyone was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No patients stated as lost, but 147 Patients is an odd number to start with, so are the groups of 69 and 78 respectively, authors contacted for protocol
Selective reporting (reporting bias)	Unclear risk	All expected outcomes were reported, but contacted authors for protocol
Other bias	Low risk	Not stated

Methods	Randomised clinical trial	
Participants	<p>Inclusion criteria: The inclusion criteria include patients in the age group of 20-35 years having infertility for more than one year, body mass index (BMI) <28, and patients of anovulatory PCOS based on the Rotterdam 2003 criteria.</p> <p>Exclusion criteria: In all patients, a comprehensive infertility work-up was done. This included a tubal patency test, pelvic ultrasonography, husband semen analysis, and serum hormone measurements (FSH, LH, prolactin, estradiol, progesterone, and testosterone) on the 2nd to 5th day of the cycle. Patients having abnormality in any of these tests, which may be responsible for reproductive failure, were excluded from the study</p> <p>Number of centres: One, a tertiary care hospital in India</p> <p>Number of women randomised: 212 women; Group A Let: 104, Group B CC: 108</p> <p>Number of women analysed: Letrozole group: 98, Clomiphene group: 106</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 8 lost to follow up</p> <p>Age (y): Group A Letrozole: 26.1±1.8, Group B CC: 26.5±1.3</p> <p>BMI (kg/m²): Group A Letrozole: 25.8±2.1, Group B CC: 25.4±1.56</p> <p>Duration of infertility (y): Group A Letrozole: 6.4±3.8, Group B CC: 5.8±3.1</p> <p>Country: India</p>	
Interventions	<p>Group A: Letrozole, orally given in doses of 2.5mg/day and 5mg/day for 5 days during cycle days 3-7</p> <p>Group B: Clomiphene Citrate, orally given in doses of 50mg/day and 100mg/day for 5 days during cycle days 3-7</p> <p>Treatment was continued for 3 months.</p>	
Outcomes	The mean number of follicles, endometrial thickness, ovulatory cycle rate, conception rate, pregnancy outcome, miscarriage rate, multiple pregnancies and ovarian hyperstimulation syndrome rate were compared in both groups	
Notes	<p>Ethical approval: Yes, the necessary ethical approval was taken from Institutional Review Board to conduct this study</p> <p>Informed consent: Yes, the patients were counselled, and informed consent was taken before randomisation</p> <p>Source of funding: “Source of support: Nil, Conflict of interest: None declared.”</p> <p>Power calculation: “On basis of previous studies, to achieve a statistically valid comparison of pregnancy rates in the two groups, with a type I error of 0.05 and a power of 80%, a sample size of at least 40 women in each arm was required.”</p> <p>We contacted Dr. Roy via e-mail to get additional information, but unfortunately he did not respond</p>	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	They used online software to generate a random number table (www.randomization.com).

Allocation concealment (selection bias)	Unclear risk	"Randomisation codes (A, B) were packed into sealed opaque envelopes by an individual not involved in enrolment, treatment and follow-up of subjects to ensure concealment of allocation. One resident had the responsibility for dispensing the trial drugs to the patient based on the unique randomization code. At the end of allocation, the resident provided us with a randomization list."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 losses to follow up of 112 patients
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Not stated

Selim 2012

Methods	Randomised controlled trial
Participants	<p>Inclusion criteria: Diagnosis of PCOS relied on Rotterdam criteria provide that anovulation is one of the two required criteria</p> <p>Exclusion criteria: Exclusion criteria included hyperprolactinaemia, congenital adrenal hyperplasia, thyroid disease, other causes of amenorrhoea such as premature ovarian failure, and clinically suspected Cushing's syndrome or androgen-secreting neoplasm. Exclusion criteria also included all women who had received metformin or ovarian drilling in the previous 6 months. Other causes of infertility were excluded by documentation of a normal uterine cavity and at least one patent fallopian tube, and each woman's current partner had a semen concentration of at least $2 \cdot 10^7/\text{mL}$</p> <p>Number of centres: Not reported</p> <p>Number of women randomised: 220; Group A Let: 110, Group B CC: 110</p> <p>Number of women analysed: Group A Let: 102, Group B CC: 99</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: "In the letrozole group, eight women were excluded because of missed follow-up visits (three women), treatment suspension (two women), and homogenous not triple-line endometrial pattern (three women). In the CC group, 11 women were excluded because of missed follow-up visits (four women), treatment suspension (two women), and homogenous not triple-line endometrial pattern (five women)."</p> <p>Age (y): Group A Let: 26.0 ± 2.7, Group B CC: 25.1 ± 3.1</p> <p>BMI (kg/m^2): Group A Let: 24.4 ± 4.3, Group B CC: 23.8 ± 3.7</p> <p>Duration of infertility (y): Group A Let: 2.9 ± 0.6, Group B CC: 2.6 ± 0.7</p>

	Country: Not reported, Saudi Arabia or Egypt	
Interventions	Group A: 110 patients who were treated with 5 mg/day of letrozole (Femara; Novartis, Switzerland) in two divided doses from cycle day 3 to 7 Group B: 110 patients who were treated with 100 mg/day of CC (Clomid; Sanofi Aventis, France) in two divided doses from cycle day 3 to 7	
Outcomes	“The mean number of follicles, endometrial thickness, the Doppler study of endometrial and sub endometrial vasculatures, ovulation rate, and pregnancy rate were compared in both groups.”	
Notes	Ethical approval: “approval was obtained from the Institutional Review Board of Jeddah Clinic Hospital, Jeddah, Saudi Arabia.” Informed consent: Yes, “all participants gave verbal and written informed consent.” Source of funding: “No competing financial interests exist.” Power calculation: Not stated	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated to the letrozole group or CC group by means of a series of blind envelopes numbered from 1 to 220
Allocation concealment (selection bias)	Low risk	Each patient was invited to choose an envelope and was placed by the clinic secretary in either the letrozole group or the CC group
Blinding of participants and personnel (performance bias) All outcomes	High risk	“The patients were not blinded about the treating drug in either group.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	To remove any inter observational bias, ultrasound in all patients was demonstrated by a single observer (MF Selim) who was blinded to the treating drug
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts were reported, reasons given.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	Not stated

Methods	Randomised controlled double blind trial
Participants	<p>Inclusion criteria: Diagnosis of PCOS relied on Rotterdam criteria provide that anovulation is one of the two required criteria</p> <p>Exclusion criteria: Exclusion criteria were BMI>35, presence of other causes of infertility, >5 years infertility duration and known poor response to either drugs in previous cycles. Cases found to have baseline ovarian cysts or endometrial pathology were also excluded</p> <p>Number of centres: One, an infertility unit of a university hospital</p> <p>Number of women randomised: 124; Group A Let: 62, Group B CC: 62</p> <p>Number of women analysed: Group A Let: 59, Group B CC: 57</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 3 in the Let and 5 in the CC group were reported as lost to follow up, but no further explanation given</p> <p>Age (y): Group A Letrozole: 24.95±3.11, Group B CC: 25±3.59</p> <p>BMI (kg/m²): Group A Let: 27.7±3.48, Group B CC: 29.18±3.47</p> <p>Duration of infertility (y): Not reported</p> <p>Country: India</p>
Interventions	<p>Group A: Letrozole, 5mg/day orally given for 5 days, cycle days not given</p> <p>Group B: Clomiphene citrate, 100mg/day orally given for 5 days, cycle days not given</p>
Outcomes	Pregnancy rate, ovulation rate, endometrial thickness (mm), mid luteal progesterone level (ng/mL), number of follicles ≥ 12 mm
Notes	<p>Ethical approval: Yes, institutional review board (IRB) approval was obtained for the study</p> <p>Informed consent: Yes, informed consent was taken from all included cases</p> <p>Source of funding: Not reported, also no conflicts of interest given.</p> <p>Power calculation: Not stated</p> <p>Dr. Sheik-el-Arab Elsedeeek was contacted via e-mail about allocation concealment, blinding of outcome assessors, information on LBR, MR, OHSSr, MP_r and funding/COI, but he did not respond</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised using computer generated tables to undergo one cycle of CC or let induction."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if personnel was blinded and how the patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Both patients and sonographers were blinded to this allocation." - Unclear if the

		other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 Patients lost to follow up, reasons unknown
Selective reporting (reporting bias)	Unclear risk	Only pregnancy was reported, authors contacted to get study protocol
Other bias	Low risk	Not stated

Sohrabvand 2006

Methods	Single blinded randomised clinical trial
Participants	<p>Inclusion criteria: PCOS patients who had failed to become pregnant after three courses of 150 mg clomiphene citrate (considered as clomiphene resistant), whereas the values of hormonal tests were normal. (Tests: thyroid function, prolactin level, hysterosalpingography and husband's sperm analysis)</p> <p>Exclusion criteria: Exclusion criteria included patients with a history of liver and kidney failure, cardiovascular disease, diabetes (based on criteria set by the American diabetic association) or patients who consumed metformin or drugs effecting insulin secretion or clomiphene citrate in the previous 2 month</p> <p>Number of centres: One, infertility clinic of Vali-e-Asr Hospital Tehran</p> <p>Number of women randomised: 60; Group A Met-Let: 30, Group B Met-CC: 30</p> <p>Number of women analysed: Group A Met-Let: 29, Group B Met-CC: 30</p> <p>Number of withdrawals/exclusions/loss to follow up and reasons: 1 because she got pregnant after met treatment before let was started</p> <p>Age (y): Group A Met-Letrozole: 28.24±3.11, Group B Met-CC: 29.55±3.47</p> <p>BMI (kg/m²): Group A Met-Let: 29.98±4.83, Group B Met-CC: 30.21±3.92</p> <p>Duration of infertility (y): Group A Met-Let: 3.78, Group B Met-CC: 3.81</p> <p>Country: Iran</p>
Interventions	<p>Group A: Metformin 500mg three times a day for 6-8 weeks. If pregnancy did not occur, 2.5mg letrozole from cycle days 3-7 was given orally</p> <p>Group B: Metformin 500mg three times a day for 6-8 weeks. If pregnancy did not occur, 100mg CC from cycle days 3-7 was given orally</p> <p>Treatment was continued for 2 cycles.</p>
Outcomes	Endometrial thickness on day of hCG administration (cm), Number of follicles >18 mm in diameter, Mean total estradiol level on day of hCG administration (pM/L), mean estradiol level per mature follicle (pM/l), regular menses after metformin, adverse effects of metformin, live birth rate, pregnancy rate, miscarriage rate
Notes	<p>Ethical approval: Yes, consent from the deputy of research and the medical ethics committee of Tehran university of medical sciences</p> <p>Informed consent: Not obtained because "it was the routine treatment protocol and it was just put in the frame of a structured study" (E-mail with Dr Farnaz Sohrabvand)</p> <p>Source of funding: "No funding was necessary" (E-mail with Dr Farnaz Sohrabvand)</p> <p>Power calculation: Not stated</p>

	Authors were contacted about Or, OHSSr, MPr per woman randomised, Informed consent, funding. No data available on OR, OHSSr and MPr, information retrieved about informed consent and funding. (E-mail with Dr Farnaz Sohrabvand)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A series of blind envelopes numbered from 1 to 60 had been prepared. Each patient was invited to pull out an envelope and was placed by the clinic secretary in either the metformin-letrozole group (number 1-30) or in the metformin-CC group (31-60)."
Allocation concealment (selection bias)	Unclear risk	"A series of blind envelopes numbered from 1 to 60 had been prepared. Each patient was invited to pull out an envelope and was placed by the clinic secretary in either the metformin-letrozole group (number 1-30) or in the metformin-CC group (31-60)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is not credible that outcome assessors were blinded if participants were not
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient was excluded due to pregnancy after start of metformin treatment
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	Not stated

Zeinalzadeh 2010

Methods	Randomised controlled trial
Participants	<p>Inclusion criteria: Patients with primary infertility, documented PCOS, age <35y, <5y infertility and BMI between 19-26. PCOS was defined on the basis of ultrasonography findings, oligomenorrhoea and an increased luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio (>3)</p> <p>Exclusion criteria: Moderate or severe case of OHSS during trial, infertility resulting from male factors, tubular factors and endometriosis</p> <p>Number of centres: One, Fatemeh Zahra Infertility Center, Babol</p> <p>Number of women randomised: 107; Group A Let: 50, Group B CC: 57</p>

	Number of women analysed: 107; Group A Let: 50, Group B CC: 57 Number of withdrawals/exclusions/loss to follow up and reasons: 0 Age (y): Group A Letrozole: 23.8±3.6, Group B CC: 23.1±3.6 BMI (kg/m²): Not reported Duration of infertility (y): Group A Let: 2.4±1, Group B CC: 2.6±1.2 Country: Iran	
Interventions	Group A: 5mg letrozole from cycle days 3-7 was given orally. Group B: 100mg CC from cycle days 3-7 was given orally.	
Outcomes	Ovulation rate, pregnancy rate, number of follicles >17, OHSS rate, multiple pregnancy rate, endometrial thickness	
Notes	Ethical approval: Yes, “The study protocol was approved by the ethics committee of Babol Medical University Informed consent: Yes, ”All the patients signed a written consent form as to be enrolled in the study“ Source of funding: No, but ”Financial disclosure: The authors have no connection to any companies or products mentioned in this article” Power calculation: Not stated Authors were contacted for additional information, but they did not respond	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“The participants were assigned to two groups using systematic randomization method”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Not stated

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Angel 2014	RCT, but not about women with PCOS
Anwary 2012	Not a RCT
Azargoon 2012	Not a RCT
Badawy 2009	Not a RCT
Baruah 2009	Quasi-randomised trial ("Based on attendance order, patients with odd numbers were given letrozole and those with even numbers were given CC")
Bigawy 2008	Quasi-randomised trial
Foroozanfard 2013	Not randomized for clomiphene or letrozole
Mittal 2004	Not a RCT
Nahid 2012	Suspected quasi-randomisation based on attendance order
Ozdemir 2013	RCT, but not about women with PCOS
Yang 2008	Not a RCT ("the allocation depended on the patients' choice" - translated by Prof Taixiang Wu)

Characteristics of studies awaiting assessment [ordered by study ID]**Aygen 2007**

Methods	Randomised clinical study
Participants	15 infertile patients with polycystic ovarian syndrome
Interventions	Patients were randomised into three treatment groups: In group 1, continuous metformin was used at the dose of 850mg/tid/day for six months; afterwards, daily 2.5mg letrozole between 3 and 7 days of the menstrual cycle was added to the metformin therapy Group 2 patients received only daily 2.5 mg letrozole between days 3 and 7 of the menstrual cycle Group 3 patients received daily 100mg clomiphene citrate only between days 3 and 7 of the menstrual cycle
Outcomes	Unclear
Notes	The article was written in Turkish, unfortunately we were not able to have it translated properly

Hazlina 2012

Methods	Open label randomized controlled trial
Participants	150 women Inclusion criteria: Age > 18 years but < 40 years old Was diagnosed PCOS Normal husband's seminal fluid analysis (SFA) Exclusion criteria : Not having medical problems eg- renal disease, thyroid disorder, hyperprolactinemia, liver disease Other causes of anovulatory infertility
Interventions	Women in group C will assigned CC 100mg and those in L assigned Letrozole 2.5 mg. Both drugs will be given from days 5 to 9 of menses
Outcomes	Primary outcomes: Ovulation induction Secondary outcomes: Pregnancy rate, endometrial thickness
Notes	No study results published yet

Lorzadeh 2011

Methods	Randomised clinical trial
Participants	100 infertile women with polycystic ovary syndrome referred to asali hospital and private clinic in 2008
Interventions	The women were randomised into two groups of 50 that were treated with 5 mg letrozole or 100 mg clomiphene citrate from day 3 to 7 of the menstrual cycle
Outcomes	Outcomes: Pregnancy rate
Notes	The article was written in Persian, unfortunately we were not able to have it translated properly

Parihar 2008

Methods	Open lable Randomised clinical trial
Participants	55 females with anovulatory infertility aged 20-38 years. Inclusion Criteria: Females with anovulatory infertility 20-38 years of age. Diagnosis of anovulatory infertility as established by standard criteria. Normal Pelvic USG and bilateral tubal patency Willingness and giving written Informed Consent Exclusion Criteria: Uterine and adnexal pathology e.g. leiomyomata Ovarian cyst Hyperprolactinaemia Hyperthyroidism or Hypothyroidism* FSH >9mIU/ml (during early follicular phase).* (As per Chemoluminescence method) Previous surgery related to genital tract as per history Appendicitis, peritonitis, genital tuberculosis as per history and/or having an abnormal pelvic anatomy Impaired hepatic /renal function Diabetes mellitus/Random blood sugar- > 140mg/dl Drugs likely to interfere with ovulation Alcohol intake as per history History of hypersensitivity to the study drug or to its excipients Planned travel outside the study area for a substantial portion (>5 days) of the study period by potential participants Lack of willingness to give informed written consent Participation in any clinical study within the preceding 1 month

Parihar 2008 (Continued)

Interventions	Letrozole 2.5 mg once a day for 5 days for 3 cycles Clomiphene citrate 100 mg or 150 mg once a day for 5 days in 3 cycles
Outcomes	Primary outcomes: ovulation rate Secondary outcomes: pregnancy rate, endometrial thickness, safety
Notes	No published data found, last updated on clinicaltrials.gov in 2008

Safdarian 2012

Methods	Double-blind randomised clinical trial
Participants	59 infertile women who had the inclusion criteria for PCoS were evaluated in the Infertility Clinic of Shariati Hospital in Tehran, Iran in 2010-2011
Interventions	The patients were assigned to two letrozole and one letrozole plus HMG groups
Outcomes	Reported no outcomes of our interest.
Notes	The article was written in Persian, unfortunately we were not able to have it translated properly

Sharma 2010

Methods	Randomised controlled trial
Participants	557 women with PCOS resistant to clomiphene citrate and letrozole undergoing IUI were randomised by simple randomisation
Interventions	Group A received clomiphene citrate (100mg daily from day 3 to day 7) and u-fSh from day onwards Group B received letrozole (5mg daily from day 3 to day 7) plus u-FSH from day 5 onwards Group C received continuous u-FSH from day 3 onwards until hCG injection
Outcomes	The number of follicles, endometrial thickness, terminal estradiol (E2) levels, pregnancy rate per cycle, cancellation rates, multiple pregnancy and miscarriage rate were compared between the three groups
Notes	Only conference abstract available, full article could not be found. Contact address of authors unknown

Shirin 2009

Methods	Randomised clinical trial, "The cases were assigned assigned to two groups through simple random sampling"
Participants	100 infertile, 20-35 year old women with PCOD attending Vali-e-Asr Infertility Clinic from April 2003 to April 2007
Interventions	Group A received clomiphene citrate plus HMG, Group B received Loetrozole plus HMG

Shirin 2009 (Continued)

Outcomes	Primary outcomes: none Secondary outcomes: pregnancy, miscarriage and multiple pregnancy rates
Notes	The article was written in Persian, unfortunately we were not able to have it translated properly

Characteristics of ongoing studies [ordered by study ID]**Ali 2012**

Trial name or title	Letrozole or combined clomiphene citrate metformin as a first line treatment in women with polycystic ovary syndrome (PCO)
Methods	Randomised clinical trial
Participants	200 infertile women with PCOS
Interventions	Letrozole versus combined metformin - clomiphene citrate
Outcomes	Primary outcome: Ovulation rate Secondary outcomes: Pregnancy and miscarriage rate
Starting date	January 2009
Contact information	Ahmed Ali, Principle investigator, Assiut university
Notes	Study should be finished, authors were contacted by an e-mail found via google because no contact information was written in the study protocol: abd_ellah98@yahoo.com

Amer 2007

Trial name or title	Letrozole versus clomiphene citrate for Ovulation induction
Methods	Double-blind Cross-over randomised controlled trial
Participants	Unknown number of infertile women with PCOS
Interventions	Letrozole versus clomiphene citrate
Outcomes	Primary outcome: Pregnancy rate Secondary outcomes: ovulation rate, number of growing and mature follicles during treatment, miscarriage rate, live-birth rate, multiple pregnancy rate, endometrial thickness
Starting date	2007
Contact information	Authors e-mail address: saad.amer@nottingham.ac.uk

Notes	I have contacted the authors, but the study is still ongoing (start date: 2007) The study is double blind, therefore no data available until ~April 2013
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Feng 2011

Trial name or title	the ovulation-induced therapy for polycystic ovary syndrome
Methods	Randomised controlled trial
Participants	<p>Still recruiting; but aimed to be 4 groups of each 67 patients</p> <p>Inclusion criteria: 1 Patients who are diagnosed as PCOS based on the Revised 2003 consensus diagnostic criteria for PCOS.</p> <p>2 The PCoS patients who want to give birth to a baby.</p> <p>3 patients with clinical and/or biochemical signs of hyperandrogenism and/or insulin resistance. And those patients need to receive a 3-6 months anti-androgen and/or anti-insulin therapy before included in until above symptoms have been relieved.</p> <p>Exclusion criteria: 1) with other factors affecting pregnancy: 1 dysfunction of ovarian ducts: hydrosalpinx, obstructions, stenosis. 2 uterine abnormalities, such as submucous myoma in submucosa or cornua, uterine malformation, intrauterine adhesions, chocolate cyst. 3 abnormal serum PRL or thyroidal dysfunction 4 a positive pulmonary or pelvic TB history. 5 abnormal semen.</p> <p>2) clinical and/or biochemical signs of hyperandrogenism</p> <p>3) BMI>30kg/m²</p> <p>4) age>35 years old</p> <p>Age minimum: 20 years old</p> <p>Age maximum: 35 years old</p> <p>Gender: Female</p>
Interventions	<p>Group A: 5g letrozole qd from the 3rd day of menstruation for 5 days</p> <p>Group B: 50-150mg clomiphene qd from the 3rd day of menstruation for 5 days</p> <p>Group C: 500mg metformin tid immediately and 50-150mg clomiphene qd from the 3rd day of menstruation for 5 days. Medication was discontinued when pregnancy was confirmed</p> <p>Group D: 500mg metformin tid immediately and 5mg letrozole qd from the 3rd day of menstruation for 5 days. Medication was discontinued when pregnancy was confirmed</p>
Outcomes	<p>Primary outcomes: ovulation rate, pregnancy rate, live birth rate</p> <p>Secondary outcomes: pregnancy lost rate, multiple pregnancy rate, OHSS morbidity</p>
Starting date	2011
Contact information	<p>Guimei Feng,</p> <p>17 3rd section, Renmin south road, Chengdu, Chia 610041</p> <p>Telephone: +8613551344177</p> <p>Email: guimei.feng@163.com</p> <p>Wei Huang, West China Women's and Childrens Hoospital S.C.U</p> <p>Telephone: +86 028 85501073</p> <p>Email: weihuang64@163.com</p>

Notes	
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Ghanem 2013

Trial name or title	Clomiphene Citrate Plus HPuFSH Versus Letrozole Plus HPuFSH in Clomid Resistant Infertile PCOS Women
Methods	Radomized controlled trial
Participants	Approximately 160 infertile clomiphene-resistend women with PCOS Inclusion Criteria: <ul style="list-style-type: none"> • CC resistant PCOS • Infertile • Females • Age 18-38 Exclusion Criteria: <ul style="list-style-type: none"> • Hyperprolactinaemia • Cushing syndrome • Adult onset adrenal hyperplasia • Age > 38 • Other infertility factors in the couple than PCOS: male factor,tubal factor,edometriosis
Interventions	Control: clomiphene citrate 50 mg tablets twice /day for 5 days plus 37.5 IU uFSH IM injections daily for 10 days Experimental: letrozole tablets 5 mg /day for days 3-7 plus intramuscular injections of uFSH 37.5 IU/day for days 3-12
Outcomes	Primary outcomes: Ovulation rate Secondary outcomes: endometrial thickness, ongoing cycle pregnancy rate
Starting date	March 2013
Contact information	Mohamad E Ghanem, MD Mansoura Integrated fertility center Mansoura, Dekahlia, Egypt E-mail: meghanem87@gmail.com
Notes	

Hou 2011

Trial name or title	Letrozole Versus Chinese Herbal Compound on Polycystic Ovary Syndrome
Methods	Randomised, double blind parallel study
Participants	160 infertile women with PCOS, diagnosed using the 2003 Rotterdam criteria Exclusion criteria are Tubal or male factor infertility or sub-fertility, suspected peritoneal factor infertility and

Hou 2011 (Continued)

	neoplastic, metabolic, hepatic, and cardiovascular disorders or other concurrent
Interventions	Chinese herbal compound versus Chinese herbal compound placebo versus letrozole
Outcomes	Primary outcome(s): Live birth rate Secondary outcome(s): ovulation rate, pregnancy rate
Starting date	September 2011
Contact information	Lihui Hou Telephone: +86 451 82130049 E-mail: houlahui2007@hotmail.com
Notes	

Li 2013

Trial name or title	Letrozole and Berberine in Infertile PCOS Patients
Methods	Randomised, double blinded clinical trial
Participants	660 infertile women with PCOS diagnosis based on the 2003 Rotterdam criteria Exclusion criteria are Tubal or male factor infertility or sub-fertility, suspected peritoneal factor infertility and neoplastic, metabolic, hepatic, and cardiovascular disorders or other concurrent
Interventions	Berberine versus letrozole versus berberine + letrozole
Outcomes	Primary outcome: Live birth rate Secondary outcome: Ovulation rate, pregnancy rate
Starting date	October 2009
Contact information	Xiaoke Wu, MD. PhD Telephone: +86 451 8213 0094 E-mail: xiaokewu2002@vip.sina.com
Notes	

Philihawadana 2008

Trial name or title	A study on anti-estrogen clomifene citrate and aromatase inhibitor letrozole in induction of ovulation, in WHO group II anovulatory subjects, and in augmentation of ovulation in ovulatory infertility
Methods	Randomised controlled trial
Participants	Inclusion criteria: Phase I: participants with WHO group II anovulatory infertility Phase II: Participants with unexplained infertility Exclusion criteria: 1. Previous ovarian surgery 2. Endocrinopathies (other than PCOS) giving rise to anovu-

Philihawadana 2008 (Continued)

	lation
Interventions	In phase one: ovulation induction with clomifene citrate followed by letrozole in patients with anovulatory infertility In phase two: Subjects with unexplained infertility would undergo augmentation of ovulation with either clomifene citrate or letrozole randomly followed by other agent after a three month drug free interval
Outcomes	Primary outcomes phase 1: Ovulation rate, endometrial characteristics Phase 2: Monofollicle development rate, endometrial characteristics Secondary outcomes phase 2: Follicular phase and luteal phase endocrinological changes Secondary outcomes: Follicular phase and luteal phase endocrinological changes
Starting date	2008
Contact information	Dr. Thilina S Paliawadana Faculty of Medicine, No 6, Thalagolla Road, Ragama; paliawadana_t@sltnet.lk
Notes	

Sarvi 2010

Trial name or title	The effect of metformin in different phenotypes of poly cystic ovary syndrome according to Rotterdam criteria criteria
Methods	Randomised controlled trial
Participants	Infertile women were included in the patients attending the outpatient clinic of the Infertility Research Centre of Shariati Hospital. The diagnosis of PCOD was based on the Rotterdam criteria, age between 18 to 35 years, normal thyroid, liver and kidney, normal sperm count according to WHO criteria, taking no metformin in previous 8 weeks, normal hysterosalpingography
Interventions	Intervention 1: metformin tablet 500 mg TDS from two months before starting ovulation induction, then ovulation induction started on day 2-6 of menstrual cycle with Letrozole 2.5 mg twice per day, when dominant follicle reached 18 mm, human chorionic gonadotropin 10000 IU was injected. Intervention 2: In control groups: no drug used before starting ovulation induction, then ovulation induction started on day 2-6 of menstrual cycle with Letrozole tablet 2.5 mg twice per day, when dominant follicle reached 18 mm, human chorionic gonadotropin 10000 IU was injected
Outcomes	Primary outcomes: none Secondary Outcomes: clinical pregnancy rate
Starting date	2010
Contact information	Fatemeh Sarvi, E-mail: fsarvi@razi.tums.ac.ir; sarvi.fateme@yahoo.com
Notes	Authors were contacted about availability of information, but did not respond

DATA AND ANALYSES

Comparison 1. Aromatase inhibitors compared to placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Ovarian hyperstimulation syndrome rate	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
3 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Miscarriage rate per woman randomised	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Miscarriage rate per pregnancies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	9	1783	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [1.32, 2.04]
1.1 AIs versus clomiphene citrate	6	1353	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [1.40, 2.33]
1.2 AI versus clomiphene + metformin	1	250	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.60, 1.81]
1.3 Aromatase inhibitor + metformin compared to clomiphene + metformin	1	60	Odds Ratio (M-H, Fixed, 95% CI)	4.5 [1.09, 18.50]
1.4 Aromatase inhibitor + FSH compared to clomiphene + FSH	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.53, 2.61]
2 Live birth rate per BMI	8	1703	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [1.32, 2.06]
2.1 BMI > 25	6	1519	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [1.31, 2.11]
2.2 BMI < 25	2	184	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.81, 2.93]
3 Live birth rate per first or second line treatment	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 No previous Ovulation induction	2	180	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.68, 3.24]
3.2 CC resistant women	1	64	Odds Ratio (M-H, Fixed, 95% CI)	2.6 [0.83, 8.13]
3.3 Unclear or mixed study population	2	359	Odds Ratio (M-H, Fixed, 95% CI)	2.31 [1.42, 3.76]
4 Impact of allocation bias for live birth rate	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Unclear risk of allocation	6	663	Odds Ratio (M-H, Fixed, 95% CI)	2.22 [1.53, 3.23]
4.2 Low risk of allocation	2	370	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.69, 1.71]

5 Impact of detection bias for live birth rate	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 High risk of detection	1	64	Odds Ratio (M-H, Fixed, 95% CI)	2.6 [0.83, 8.13]
5.2 Low risk of detection	4	530	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.90, 1.97]
5.3 Unclear risk of detection	3	439	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [1.33, 3.24]
6 Impact of attrition bias for live birth rate	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Unclear risk of attrition	1	147	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.93, 4.50]
6.2 Low risk of attrition	7	886	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [1.19, 2.19]
7 Ovarian hyperstimulation syndrome rate	9	2179	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
7.1 AIs versus clomiphene citrate	7	1809	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
7.2 AI versus clomiphene + metformin	1	250	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.02, 0.02]
7.3 Aromatase inhibitor + hMG versus clomiphene + hMG	1	120	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
8 Ovarian hyperstimulation syndrome rate per BMI	8		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
8.1 BMI > 25	4	1650	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
8.2 BMI < 25	4	449	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.02, 0.02]
9 Clinical pregnancy rate	15	2816	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [1.18, 1.65]
9.1 AIs versus clomiphene citrate	11	2286	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [1.20, 1.73]
9.2 AI versus clomiphene + metformin	1	250	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.60, 1.71]
9.3 Aromatase inhibitor + metformin versus clomiphene + metformin	2	160	Odds Ratio (M-H, Fixed, 95% CI)	2.88 [0.99, 8.36]
9.4 Aromatase inhibitor + FSH versus clomiphene + FSH	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.55, 2.45]
10 Impact of allocation bias for clinical pregnancy rate	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Unclear risk of allocation	10	1057	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.41, 2.54]
10.2 Low risk of allocation	4	1009	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.29]
11 Miscarriage rate per woman randomised	12	2385	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.92, 1.88]
11.1 AIs versus clomiphene citrate	8	1855	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [1.00, 2.20]
11.2 AI versus clomiphene + metformin	1	250	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.25, 4.23]
11.3 Aromatase inhibitor + metformin versus clomiphene + metformin	2	160	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.19]
11.4 Aromatase inhibitor + FSH versus clomiphene + FSH	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.27, 3.65]
12 Miscarriage rate per pregnancy	12	696	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.36]
12.1 AIs versus clomiphene citrate	8	549	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.64, 1.60]

12.2 AI versus clomiphene + metformin	1	85	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.24, 4.40]
12.3 Aromatase inhibitor + metformin versus clomiphene + metformin	2	20	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.77]
12.4 Aromatase inhibitor + FSH versus clomiphene + FSH	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.21, 3.65]
13 Multiple pregnancy rate	11	2385	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.84]
13.1 AIs versus clomiphene citrate	9	2015	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.17, 1.01]
13.2 AI versus clomiphene + metformin	1	250	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.82]
13.3 Aromatase inhibitor + FSH versus clomiphene + FSH	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.04, 5.57]

Comparison 3. Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ovarian hyperstimulation syndrome rate	2	1494	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
1.1 AI versus Clomiphene	1	107	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
1.2 AI versus Clomiphene +rFSH and rFSH only	1	1387	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
2 Clinical pregnancy rate	3	1597	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [1.30, 2.25]
2.1 AI versus Clomiphene	2	210	Odds Ratio (M-H, Fixed, 95% CI)	2.09 [0.97, 4.53]
2.2 AI versus Clomiphene +rFSH and rFSH only	1	1387	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [1.23, 2.22]
3 Miscarriage rate per woman randomised	2	1490	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.62, 2.40]
3.1 AI versus Clomiphene	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.06]
3.2 AI versus Clomiphene +rFSH and rFSH only	1	1387	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.66, 2.65]
4 Miscarriage rate per pregnancies	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.37, 1.57]
4.1 AI versus Clomiphene	1	15	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.00, 3.09]
4.2 AI versus Clomiphene +rFSH and rFSH only	1	245	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.40, 1.79]
5 Multiple pregnancy rate	3	1597	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.49, 2.13]
5.1 AI versus Clomiphene	2	210	Odds Ratio (M-H, Fixed, 95% CI)	3.48 [0.14, 87.49]
5.2 AI versus Clomiphene +rFSH and rFSH only	1	1387	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.44, 2.03]

Comparison 4. Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	2	407	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.76, 1.86]
2 Ovarian hyperstimulation syndrome rate	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
3 Clinical pregnancy rate	3	553	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.80, 1.65]
3.1 AI versus LOD	2	407	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
3.2 AI + metformin versus LOD	1	146	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.60, 2.39]
4 Miscarriage rate per woman randomised	3	553	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.38, 2.19]
4.1 AI versus LOD	2	407	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.26, 2.20]
4.2 AI + metformin versus LOD	1	146	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.29, 6.27]
5 Miscarriage rate per pregnancies	3	167	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.32, 2.01]
5.1 AI versus LOD	2	118	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.22, 2.03]
5.2 AI + metformin versus LOD	1	49	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.24, 6.09]
6 Multiple pregnancy rate	2	407	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Letrozole compared to anastrozole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ovarian hyperstimulation syndrome rate	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical pregnancy rate	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.51, 1.43]
3 Miscarriage rate per woman randomised	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Miscarriage rate per pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Multiple pregnancy rate	2	260	Odds Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 105.35]

Comparison 6. Five days compared to 10 days administration protocol of letrozole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ovarian hyperstimulation syndrome rate	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Miscarriage rate per woman randomised	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

4 Miscarriage rate per pregnancies	1	Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Multiple pregnancy rate	1	Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. Dosage studies of letrozole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ovarian hyperstimulation syndrome rate	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.1 5mg vs 7.5mg letrozole	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 5mg vs 7.5mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Miscarriage rate per woman randomised	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 5mg vs 7.5mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Miscarriage rate per pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 5mg vs 7.5mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 5mg vs 7.5mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Aromatase inhibitors compared to placebo, Outcome 1 Live birth rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 1 Aromatase inhibitors compared to placebo

Outcome: 1 Live birth rate

Study or subgroup	Letrozole n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kamath 2010	1/18	0/18			3.17 [0.12, 83.17]
Subtotal (95% CI)	0	0			0.0 [0.0, 0.0]
Total events: 1 (Letrozole), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
0.01 0.1 10 100					
Favours Placebo Favours Letrozole					

Analysis 1.2. Comparison 1 Aromatase inhibitors compared to placebo, Outcome 2 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 1 Aromatase inhibitors compared to placebo

Outcome: 2 Ovarian hyperstimulation syndrome rate

(1) Clomiphene resistant women; Letrozole, 2.5mg/day versus placebo

Analysis 1.3. Comparison 1 Aromatase inhibitors compared to placebo, Outcome 3 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 1 Aromatase inhibitors compared to placebo

Outcome: 3 Clinical pregnancy rate

(1) Clomiphene resistant women; Letrozole, 2.5mg/day versus placebo

Analysis 1.4. Comparison 1 Aromatase inhibitors compared to placebo, Outcome 4 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 1 Aromatase inhibitors compared to placebo

Outcome: 4 Miscarriage rate per woman randomised

Study or subgroup	Letrozole n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Kamath 2010 (1)	0/18	0/18		Not estimable

(1) Clomiphene resistant women; Letrozole, 2.5mg/day versus placebo

Analysis 1.6. Comparison 1 Aromatase inhibitors compared to placebo, Outcome 6 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 1 Aromatase inhibitors compared to placebo

Outcome: 6 Multiple pregnancy rate

Study or subgroup	Letrozole n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Kamath 2010 (1)	0/18	0/18		Not estimable

(1) Clomiphene resistant women; Letrozole, 2.5mg/day versus placebo

Analysis 2.1. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 1 Live birth rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 1 Live birth rate

- (1) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (2) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (3) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (4) Cumulative live birth rate
- (5) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (6) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (7) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day with metformin, 1500mg/day
- (8) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day
- (9) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Analysis 2.2. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 2 Live birth rate per BMI.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 2 Live birth rate per BMI

(1) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day with metformin, 1500mg/day

(2) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day

(3) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day

(4) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day

(5) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day

(6) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day

(7) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Analysis 2.3. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 3 Live birth rate per first or second line treatment.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 3 Live birth rate per first or second line treatment

Analysis 2.4. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 4 Impact of allocation bias for live birth rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 4 Impact of allocation bias for live birth rate

(1) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day

(2) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day

(3) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day

(4) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day

(5) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day

(6) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day

(7) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day with metformin, 1500mg/day

(8) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Analysis 2.5. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 5 Impact of detection bias for live birth rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 5 Impact of detection bias for live birth rate

- (1) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (2) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day with metformin, 1500mg/day
- (3) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (4) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
- (5) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day
- (6) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (7) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (8) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day

Analysis 2.6. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 6 Impact of attrition bias for live birth rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 6 Impact of attrition bias for live birth rate

(Continued ...)

- (1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (2) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day with metformin, 1500mg/day
- (3) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (4) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (5) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (6) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
- (7) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (8) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day

Analysis 2.7. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 7 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 7 Ovarian hyperstimulation syndrome rate

- (1) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (2) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (3) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (4) Cumulative live birth rate
- (5) No previous ovulation induction; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (6) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (7) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (8) 30% of the women were CC-resistant
- (9) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Analysis 2.8. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 8 Ovarian hyperstimulation syndrome rate per BMI.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 8 Ovarian hyperstimulation syndrome rate per BMI

(Continued ...)

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Study or subgroup	Aromatase inhibitor n/N	Other agents for OI n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Selim 2012 (8)	0/102	0/99		44.8 %	0.0 [-0.02, 0.02]
Subtotal (95% CI)	225	224		100.0 %	0.0 [-0.02, 0.02]
Total events: 0 (Aromatase inhibitor), 0 (Other agents for OI)					
Heterogeneity: Chi ² = 0.0, df = 3 (P = 1.00); I ² = 0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Chi ² = 0.06, df = 1 (P = 0.80), I ² = 0.0%					

-1 -0.5 0 0.5 1
Favours aromatase inhib Favours other OI agents

- (1) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day with metformin, 1500mg/day
- (2) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (3) Cumulative live birth rate
- (4) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (5) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (6) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
- (7) No previous ovulation induction; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (8) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus clomiphene, 100mg/day

Analysis 2.9. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 9 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 9 Clinical pregnancy rate

(Continued ...)

- (1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 100mg/day
- (2) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (3) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (4) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (5) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (6) No previous ovulation induction; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (7) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (8) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (9) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (10) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (11) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day
- (12) Clomiphene resistant women; Letrozole, 5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
- (13) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day
- (14) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Analysis 2.10. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 10 Impact of allocation bias for clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 10 Impact of allocation bias for clinical pregnancy rate

- (1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 100mg/day
- (2) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (3) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (4) Clomiphene resistant women; Letrozole, 5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
- (5) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (6) No previous ovulation induction; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (7) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (8) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (9) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (10) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day
- (11) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day
- (12) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (13) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
- (14) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus clomiphene, 100mg/day

Analysis 2.11. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 11 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 11 Miscarriage rate per woman randomised

Analysis 2.12. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 12 Miscarriage rate per pregnancy.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 12 Miscarriage rate per pregnancy

Analysis 2.13. Comparison 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse, Outcome 13 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 2 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts, followed by timed intercourse

Outcome: 13 Multiple pregnancy rate

- (1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 100mg/day
- (2) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (3) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (4) CC-resistant women; Letrozole, 7.5 mg/day versus clomiphene, 150mg/day
- (5) No previous ovulation induction; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (6) Cumulative live birth
- (7) No previous ovulation induction; Letrozole, 2.5 mg/day versus clomiphene, 100mg/day
- (8) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5-5 mg/day versus clomiphene, 50-100mg/day
- (9) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus clomiphene, 100mg/day
- (10) 30% of the women were CC-resistant; Letrozole, 2.5mg/day versus clomiphene, 150mg/day
- (11) Clomiphene resistant women; Letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Analysis 3.1. Comparison 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI, Outcome 1 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI

Outcome: 1 Ovarian hyperstimulation syndrome rate

(... Continued)

Analysis 3.2. Comparison 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI, Outcome 2 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI

Outcome: 2 Clinical pregnancy rate

(Continued ...)

(... Continued)

Study or subgroup	Aromatase inhibitors n/N	Other agents for OI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 108 (Aromatase inhibitors), 170 (Other agents for OI)					
Heterogeneity: $\chi^2 = 1.06$, $df = 2$ ($P = 0.59$); $I^2 = 0.0\%$					
Test for overall effect: $Z = 3.84$ ($P = 0.00012$)					
Test for subgroup differences: $\chi^2 = 0.31$, $df = 1$ ($P = 0.58$), $I^2 = 0.0\%$					
			0.2 0.5 1 2 5		
			Favours other OI agents	Favours Aromatase inhib	

Analysis 3.3. Comparison 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI, Outcome 3 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI

Outcome: 3 Miscarriage rate per woman randomised

Study or subgroup	Aromatase inhibitors n/N	Other agents for OI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 AI versus Clomiphene					
Kar 2012	0/52	1/51		10.4 %	0.32 [0.01, 8.06]
Subtotal (95% CI)	52	51		10.4 %	0.32 [0.01, 8.06]
Total events: 0 (Aromatase inhibitors), 1 (Other agents for OI)					
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.69$ ($P = 0.49$)					
2 AI versus Clomiphene +rFSH and rFSH only					
Ganesh 2009	12/372	25/1015		89.6 %	1.32 [0.66, 2.65]
Subtotal (95% CI)	372	1015		89.6 %	1.32 [0.66, 2.65]
Total events: 12 (Aromatase inhibitors), 25 (Other agents for OI)					
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.78$ ($P = 0.44$)					
Total (95% CI)	424	1066		100.0 %	1.22 [0.62, 2.40]
Total events: 12 (Aromatase inhibitors), 26 (Other agents for OI)					
Heterogeneity: $\chi^2 = 0.71$, $df = 1$ ($P = 0.40$); $I^2 = 0.0\%$					
Test for overall effect: $Z = 0.56$ ($P = 0.57$)					
Test for subgroup differences: $\chi^2 = 0.71$, $df = 1$ ($P = 0.40$), $I^2 = 0.0\%$					
			0.2 0.5 1 2 5		
			Favours Aromatase inhib	Favours other OI agents	

Analysis 3.4. Comparison 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI, Outcome 4 Miscarriage rate per pregnancies.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI

Outcome: 4 Miscarriage rate per pregnancies

Analysis 3.5. Comparison 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI, Outcome 5 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 3 Aromatase inhibitors compared to clomiphene citrate with or without adjuncts followed by IUI

Outcome: 5 Multiple pregnancy rate

Analysis 4.1. Comparison 4 Aromatase inhibitors compared to laparoscopic ovarian drilling, Outcome 1 Live birth rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 4 Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome: 1 Live birth rate

(1) Clomiphene resistant women; Letrozole 5 mg/day versus LOD

(2) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

Analysis 4.2. Comparison 4 Aromatase inhibitors compared to laparoscopic ovarian drilling, Outcome 2 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 4 Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome: 2 Ovarian hyperstimulation syndrome rate

(1) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

Analysis 4.3. Comparison 4 Aromatase inhibitors compared to laparoscopic ovarian drilling, Outcome 3 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 4 Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome: 3 Clinical pregnancy rate

(1) Clomiphene resistant women; Letrozole 5 mg/day versus LOD

(2) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

Analysis 4.4. Comparison 4 Aromatase inhibitors compared to laparoscopic ovarian drilling, Outcome 4 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 4 Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome: 4 Miscarriage rate per woman randomised

(1) Clomiphene resistant women; Letrozole 5 mg/day versus LOD

(2) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

Analysis 4.5. Comparison 4 Aromatase inhibitors compared to laparoscopic ovarian drilling, Outcome 5 Miscarriage rate per pregnancies.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 4 Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome: 5 Miscarriage rate per pregnancies

(1) Clomiphene resistant women; Letrozole 5 mg/day versus LOD

(2) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

Analysis 4.6. Comparison 4 Aromatase inhibitors compared to laparoscopic ovarian drilling, Outcome 6 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 4 Aromatase inhibitors compared to laparoscopic ovarian drilling

Outcome: 6 Multiple pregnancy rate

Study or subgroup	Aromatase inhibitor n/N	LOD n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Abdellah 2011 (1)	0/74	0/73			Not estimable
Abu Hashim June 2010 (2)	0/128	0/132			Not estimable
Total (95% CI)	202	205			Not estimable
Total events: 0 (Aromatase inhibitor), 0 (LOD)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

(1) Clomiphene resistant women; Letrozole 5 mg/day versus LOD

(2) Clomiphene resistant women; Letrozole 2.5 mg/day versus LOD

Analysis 5.1. Comparison 5 Letrozole compared to anastrozole, Outcome 1 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 5 Letrozole compared to anastrozole

Outcome: 1 Ovarian hyperstimulation syndrome rate

Study or subgroup	Letrozole n/N	Anastrozole n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
Badawy 2008 (1)	0/111	0/109		0.0 [-0.02, 0.02]

(1) Clomiphene resistant women; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

Analysis 5.2. Comparison 5 Letrozole compared to anastrozole, Outcome 2 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 5 Letrozole compared to anastrozole

Outcome: 2 Clinical pregnancy rate

(1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

(2) Clomiphene resistant women; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

Analysis 5.3. Comparison 5 Letrozole compared to anastrozole, Outcome 3 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 5 Letrozole compared to anastrozole

Outcome: 3 Miscarriage rate per woman randomised

(1) Clomiphene resistant women; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

Analysis 5.4. Comparison 5 Letrozole compared to anastrozole, Outcome 4 Miscarriage rate per pregnancies.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 5 Letrozole compared to anastrozole

Outcome: 4 Miscarriage rate per pregnancies

(1) Clomiphene resistant women; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

Analysis 5.5. Comparison 5 Letrozole compared to anastrozole, Outcome 5 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 5 Letrozole compared to anastrozole

Outcome: 5 Multiple pregnancy rate

(1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

(2) Clomiphene resistant women; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

Analysis 6.1. Comparison 6 Five days compared to 10 days administration protocol of letrozole, Outcome 1 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 6 Five days compared to 10 days administration protocol of letrozole

Outcome: 1 Ovarian hyperstimulation syndrome rate

(1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus 2.5 mg/day

Analysis 6.2. Comparison 6 Five days compared to 10 days administration protocol of letrozole, Outcome 2 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 6 Five days compared to 10 days administration protocol of letrozole

Outcome: 2 Clinical pregnancy rate

(1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus 2.5 mg/day

Analysis 6.3. Comparison 6 Five days compared to 10 days administration protocol of letrozole, Outcome 3 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 6 Five days compared to 10 days administration protocol of letrozole

Outcome: 3 Miscarriage rate per woman randomised

(1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus 2.5 mg/day

Analysis 6.4. Comparison 6 Five days compared to 10 days administration protocol of letrozole, Outcome 4 Miscarriage rate per pregnancies.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 6 Five days compared to 10 days administration protocol of letrozole

Outcome: 4 Miscarriage rate per pregnancies

(1) Unknown if primary fertility treatment or CC-resistant; Letrozole, 5 mg/day versus 2.5 mg/day

Analysis 6.5. Comparison 6 Five days compared to 10 days administration protocol of letrozole, Outcome 5 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 6 Five days compared to 10 days administration protocol of letrozole

Outcome: 5 Multiple pregnancy rate

Analysis 7.1. Comparison 7 Dosage studies of letrozole, Outcome 1 Ovarian hyperstimulation syndrome rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 7 Dosage studies of letrozole

Outcome: 1 Ovarian hyperstimulation syndrome rate

Analysis 7.2. Comparison 7 Dosage studies of letrozole, Outcome 2 Clinical pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 7 Dosage studies of letrozole

Outcome: 2 Clinical pregnancy rate

(I) No previous ovulation induction treatment

Analysis 7.3. Comparison 7 Dosage studies of letrozole, Outcome 3 Miscarriage rate per woman randomised.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 7 Dosage studies of letrozole

Outcome: 3 Miscarriage rate per woman randomised

(I) No previous ovulation induction treatment

Analysis 7.4. Comparison 7 Dosage studies of letrozole, Outcome 4 Miscarriage rate per pregnancies.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 7 Dosage studies of letrozole

Outcome: 4 Miscarriage rate per pregnancies

(I) No previous ovulation induction treatment

Analysis 7.5. Comparison 7 Dosage studies of letrozole, Outcome 5 Multiple pregnancy rate.

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 7 Dosage studies of letrozole

Outcome: 5 Multiple pregnancy rate

(I) No previous ovulation induction treatment

ADDITIONAL TABLES

Table 1. Subgroup characteristics for aromatase inhibitors versus other ovulation induction agents

Study	LBR (AI versus other)	CPR (AI versus other)	Age in years (AI group vs other group)	Exclusion criteria on age	BMI (AI group versus other group)	Exc. crit. on BMI	Duration of infertility in years (AI group versus other group)	Exc. crit. on duration of infertility
Abu Hashim Sept 2010	36/123 vs 36/127	42/123 vs 43/127	28.3±2.7 vs 26.2±2.2	None stated	29.1±3.2 vs 30.1±2.3	None stated	Not reported	None stated
Atay 2006	Not reported	11/51 vs 5/55	27.1±0.9 vs 26.2±1.1	None stated	26.1±1.91 vs 25.8±1.77	None stated	2.2±0.7 vs 2.4±0.9	None stated
Badawy Sept 2009	Not reported	82/218 vs 94/220	27.1±3.2 vs 29.3±2.9	None stated	28.1±3.2 vs 27.1±3.1	None stated	Not reported	None stated
Bayar 2006	8/40 vs 7/40	9/40 vs 7/40	32.2±3.9 vs 30.6±4.0	None stated	Not reported	None stated	5 (1-10) vs 3 (3-11)	None stated
Begum 2009;	12/32 vs 6/32	13/32 vs 6/32	25.47±3.98 vs 26.09±3.62	None stated	22.72±2.77 vs 23.63±3.23	None stated	2.66±1.11 vs 2.58±1.10	None stated
Davar 2011	Not reported	4/50 vs 1/50	28.54±3.13 vs 29.55±3.47	None stated	28.98±3.83 vs 29.21±2.92	None stated	3.81 vs 3.76	None stated
Dehbashi 2009	10/50 vs 6/50	13/50 vs 7/50	23.62±2.92 vs 24.32±3.43	None stated	27.45±4.61 vs 27.09±3.61	None stated	2.00±1.34 vs 2.30±1.85	None stated
Foroozan-fard 2011	18/60 vs 16/60	22/60 vs 16/60	25.8±3.75 vs 25.33±4.14	Aged 20 - 35 years	24.12±2.33 vs 24.87±2.00	None stated	2.76±2.27 vs 2.60±2.07	Infertility at least for 1 year
Legro 2014	103/374 vs 73/376	117/374 vs 81/376	29±5 vs 28±4	Aged 18 - 40 years	35±10 vs 35±9	None stated	Not reported	None stated
Nazik 2012	Not reported	7/31 vs 8/33	25.55±4.45 vs 27.80±6.18	None stated	24.66±3.57 vs 24.90±4.80	None stated	3.40±3.04 vs 4.40±3.58	None stated

Table 1. Subgroup characteristics for aromatase inhibitors versus other ovulation induction agents (Continued)

Ray 2012	20/69 vs 13/78	20/69 vs 14/78	28 (19-35) vs 29 (20-35)	None stated	28.8 (23.2-34.6) vs 28.5 (24.2 - 33.6)	None stated	2.2 vs 2.4	None stated
Roy 2012	39/104 vs 21/108	43/104 vs 28/108	26.1±1.8 vs 26.5±1.3	>35y were excluded	25.8±2.1 vs 25.4±1.56	>28 were excluded	6.4±3.8 vs 5.8±3.1	<1 year infertility
Selim 2012	Not reported	29/102 vs 20/99	26.0±2.7 vs 25.1±3.1	None stated	24.4±4.3 vs 23.8±3.7	None stated	2.9±0.6 vs 2.6±0.7	None stated
Sh-El-Arab Elsedeek 2011	Not reported	20/62 vs 16/62	24.95±3.11 vs 25±3.59	None stated	27.7±3.48 vs 29.18±3.47	>35 were excluded	Not reported	>5 years of infertility
Sohrabvand 2006	10/30 vs 3/30	10/30 vs 5/30	28.24±3.11 vs 29.55±3.47	None stated	29.98±4.83 vs 30.21±3.92	None stated	3.78 vs 3.81	None stated

APPENDICES

Appendix I. MDSG search strategy

Menstrual Disorders and Subfertility Group (MDSG) specialised register search for SFR1820 04.07.12

Keywords CONTAINS "Polycystic Ovary Syndrome" or "PCOS" or "*Ovulation Induction" or "ovulation stimulation" or "ovarian hyperstimulation" or "superovulation" or Title CONTAINS "Polycystic Ovary Syndrome" or "PCOS" or "*Ovulation Induction" or "ovulation stimulation" or "ovarian hyperstimulation" or "superovulation"

AND

Keywords CONTAINS "aromatase inhibition" or "aromatase inhibitor" or "aromatase P450" or "Anastrozole" or "letrozole" or "letrozole" or "Exemestane" or "arimidex" or Title CONTAINS "aromatase inhibition" or "aromatase inhibitor" or "aromatase P450" or "Anastrozole" or "letrozole" or "letrozole" or "Exemestane" or "arimidex"

Appendix 2. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2012>

Search Strategy:

- 1 exp Polycystic Ovary Syndrome/ (654)
- 2 Polycystic Ovar\$.tw. (950)
- 3 PCOS.tw. (648)
- 4 PCOD.tw. (23)
- 5 stein leventh\$.tw. (3)
- 6 (ovar\$ adj2 sclerocystic).tw. (0)
- 7 (ovar\$ adj2 degeneration).tw. (1)
- 8 PCO.tw. (309)
- 9 exp ovulation induction/ or exp superovulation/ (913)
- 10 (ovulat\$ adj2 induc\$).tw. (570)
- 11 superovulation.tw. (118)
- 12 (ovari\$ adj2 hyperstimulat\$).tw. (545)
- 13 (ovari\$ adj2 stimulat\$).tw. (725)
- 14 or/1-13 (2886)
- 15 exp aromatase inhibitors/ or exp aminoglutethimide/ or exp fadrozole/ (382)
- 16 aromatase inhibitor\$.tw. (413)
- 17 aminoglutethimide.tw. (153)
- 18 Anastrozole.tw. (294)
- 19 Arimidex.tw. (142)
- 20 Letrozole.tw. (349)
- 21 Femara.tw. (27)
- 22 Exemestane.tw. (161)
- 23 Aromasin.tw. (16)
- 24 Vorozole.tw. (16)
- 25 Rivizor.tw. (3)
- 26 Formestane.tw. (33)
- 27 Lentaron.tw. (7)
- 28 Fadrozole.tw. (28)
- 29 Afema.tw. (0)
- 30 or/15-29 (1094)
- 31 14 and 30 (79)

This search was updated on 24 October 2013.

This search was again updated on 9 September 2014.

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

- 1 exp Polycystic Ovary Syndrome/ (9215)
- 2 Polycystic Ovar\$.tw. (9130)
- 3 PCOS.tw. (5069)
- 4 PCOD.tw. (251)
- 5 stein leventh\$.tw. (581)
- 6 (ovar\$ adj2 sclerocystic).tw. (82)
- 7 (ovar\$ adj2 degeneration).tw. (95)

8 PCO.tw. (3483)
 9 exp ovulation induction/ or exp superovulation/ (9645)
 10 (ovulat\$ adj2 induc\$.tw. (6375)
 11 superovulation.tw. (1611)
 12 (ovari\$ adj2 hyperstimulat\$.tw. (3473)
 13 (ovari\$ adj2 stimulat\$.tw. (4369)
 14 or/1-13 (30073)
 15 exp aromatase inhibitors/ or exp aminoglutethimide/ or exp fadrozole/ (5470)
 16 aromatase inhibitor\$.tw. (4418)
 17 aminoglutethimide.tw. (1347)
 18 Anastrozole.tw. (1141)
 19 Arimidex.tw. (233)
 20 Letrozole.tw. (1404)
 21 Femara.tw. (76)
 22 Exemestane.tw. (683)
 23 Aromasin.tw. (27)
 24 Vorozole.tw. (107)
 25 Rivizor.tw. (5)
 26 Formestane.tw. (121)
 27 Lentaron.tw. (14)
 28 Fadrozole.tw. (287)
 29 Afema.tw. (4)
 30 or/15-29 (7854)
 31 14 and 30 (311)
 32 randomized controlled trial.pt. (335020)
 33 controlled clinical trial.pt. (84917)
 34 randomized.ab. (250120)
 35 placebo.tw. (142679)
 36 clinical trials as topic.sh. (161941)
 37 randomly.ab. (183109)
 38 trial.ti. (107599)
 39 (crossover or cross-over or cross over).tw. (54410)
 40 or/32-39 (820536)
 41 exp animals/ not humans.sh. (3771273)
 42 40 not 41 (756998)
 43 31 and 42 (90)
 This search was updated on 24 October 2013.
 This search was again updated on 9 September 2014.

Appendix 4. EMBASE search strategy

Database: Embase <1980 to 2012 Week 26>

Search Strategy:

1 exp ovary polycystic disease/ (14819)
 2 Polycystic Ovar\$.tw. (11706)
 3 PCOS.tw. (6951)
 4 PCOD.tw. (306)
 5 stein leventh\$.tw. (538)
 6 (ovar\$ adj2 sclerocystic).tw. (81)
 7 (ovar\$ adj2 degeneration).tw. (97)
 8 PCO.tw. (2819)

9 exp ovulation induction/ (10176)
 10 (ovulat\$ adj2 induc\$).tw. (7214)
 11 (ovari\$ adj2 hyperstimulat\$).tw. (4638)
 12 superovulation.tw. (1691)
 13 (ovari\$ adj2 stimulat\$).tw. (5910)
 14 or/1-13 (36936)
 15 exp aromatase inhibitor/ (17443)
 16 aromatase inhibitor\$.tw. (5958)
 17 aminogluthethimide.tw. (1394)
 18 Anastrozole.tw. (1668)
 19 Arimidex.tw. (1489)
 20 Letrozole.tw. (2124)
 21 Femara.tw. (881)
 22 Exemestane.tw. (1041)
 23 Aromasin.tw. (423)
 24 Vorozole.tw. (128)
 25 Rivizor.tw. (27)
 26 Formestane.tw. (159)
 27 Lentaron.tw. (129)
 28 Fadrozole.tw. (312)
 29 Afema.tw. (25)
 30 or/15-29 (18269)
 31 14 and 30 (696)
 32 Clinical Trial/ (870009)
 33 Randomized Controlled Trial/ (327258)
 34 exp randomization/ (59096)
 35 Single Blind Procedure/ (16267)
 36 Double Blind Procedure/ (110342)
 37 Crossover Procedure/ (34696)
 38 Placebo/ (203094)
 39 Randomized controlled trial\$.tw. (77731)
 40 Rct.tw. (9804)
 41 random allocation.tw. (1170)
 42 randomly allocated.tw. (17495)
 43 allocated randomly.tw. (1825)
 44 (allocated adj2 random).tw. (709)
 45 Single blind\$.tw. (12431)
 46 Double blind\$.tw. (129721)
 47 ((treble or triple) adj blind\$).tw. (277)
 48 placebo\$.tw. (177837)
 49 prospective study/ (211224)
 50 or/32-49 (1267084)
 51 case study/ (16626)
 52 case report.tw. (229076)
 53 abstract report/ or letter/ (841093)
 54 or/51-53 (1082122)
 55 50 not 54 (1231853)
 56 31 and 55 (281)
 57 (2010\$ or 2011\$ or 2012\$).em. (2809950)
 58 56 and 57 (94)
 This search was updated on 24 October 2013.
 This search was again updated on 9 September 2014.

Appendix 5. PSYCINFO search strategy

Database: PsycINFO <1806 to June Week 4 2012>

Search Strategy:

1 exp Endocrine Sexual Disorders/ (825)

2 Polycystic Ovar\$.tw. (221)

3 PCOS.tw. (128)

4 PCOD.tw. (5)

5 or/1-4 (979)

6 aromatase inhibitor\$.tw. (143)

7 Anastrozole.tw. (16)

8 Arimidex.tw. (2)

9 Letrozole.tw. (32)

10 Femara.tw. (0)

11 Exemestane.tw. (10)

12 or/6-11 (162)

13 5 and 12 (3)

This search was updated on 24 October 2013.

This search was again updated on 9 September 2014.

WHAT'S NEW

Last assessed as up-to-date: 18 September 2014.

Date	Event	Description
24 September 2014	Amended	This review has been amended. A new search was conducted on 18.9.14 and new ongoing studies added

HISTORY

Protocol first published: Issue 12, 2012

Review first published: Issue 2, 2014

Date	Event	Description
17 July 2014	Amended	Addition of new data made available for Legro 2014. New secondary outcome has been added: Miscarriage rate per pregnancy
26 February 2014	Amended	Correction of search date in Abstract and Methods sections

CONTRIBUTIONS OF AUTHORS

SF wrote the protocol and drafted the full review. WN, JK and CF acted as clinical experts and commented on the protocol and full review.

DECLARATIONS OF INTEREST

No declarations of interest.

SOURCES OF SUPPORT

Internal sources

- MDSG, New Zealand.
editorial support

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A new secondary outcome has been added as an amendment: Miscarriage rate per pregnancy

INDEX TERMS

Medical Subject Headings (MeSH)

Aromatase Inhibitors [*therapeutic use]; Birth Rate; Clomiphene [therapeutic use]; Coitus; Fertility Agents, Female [therapeutic use]; Infertility, Female [*drug therapy; etiology]; Nitriles [*therapeutic use]; Ovary [surgery]; Ovulation Induction [methods]; Polycystic Ovary Syndrome [*complications]; Pregnancy Outcome; Randomized Controlled Trials as Topic; Triazoles [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy