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Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome (Review)

Franik S, Le QK, Kremer JAM, Kiesel L, Farquhar C

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TABLE OF CONTENTS

[Intervention Review]

Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome

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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 5% to 20% of women worldwide and often leads to anovulatory infertility. Aromatase inhibitors (AIs) are a class of drugs that were introduced for ovulation induction in 2001. Since about 2001 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), a selective oestrogen receptor modulator (SERM).

Objectives

To evaluate the effectiveness and safety of AIs (letrozole) (with or without adjuncts) compared to SERMs (with or without adjuncts) for infertile women with anovulatory PCOS for ovulation induction followed by timed intercourse or intrauterine insemination.

Search methods

We searched the following sources, from their inception to 4 November 2021, to identify relevant randomised controlled trials (RCTs): the Cochrane Gynaecology and Fertility Group Specialised Register, CENTRAL, MEDLINE, Embase and PsycINFO. We also checked reference lists of relevant trials, searched the trial registers and contacted experts in the field for any additional trials. We did not restrict the searches by language or publication status.

Selection criteria

We included all RCTs of AIs 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 risks of bias using RoB 1. We pooled trials where appropriate using a fixed-effect model to calculate 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 rate and OHSS rate. Secondary outcomes were clinical pregnancy, miscarriage and multiple pregnancy rates. We assessed the certainty of the evidence for each comparison using GRADE methods.

Main results

This is a substantive update of a previous review; of six previously included trials, we excluded four from this update and moved two to 'awaiting classification' due to concerns about validity of trial data. We included five additional trials for this update that now includes a total of 41 RCTs (6522 women). The AI, letrozole, was used in all trials.

Letrozole compared to SERMs with or without adjuncts followed by timed intercourse

Live birth rates were higher with letrozole (with or without adjuncts) compared to SERMs followed by timed intercourse (OR 1.72, 95% CI 1.40 to 2.11; I^2 = 0%; number needed to treat for an additional beneficial outcome (NNTB) = 10; 11 trials, 2060 participants; high-certainty evidence). This suggests that in women with a 20% chance of live birth using SERMs, the live birth rate in women using letrozole with or without adjuncts would be 27% to 35%. There is high-certainty evidence that OHSS rates are similar with letrozole or SERMs (0.5% in both arms: risk difference (RD) −0.00, 95% CI −0.01 to 0.01; I^2 = 0%; 10 trials, 1848 participants; high-certainty evidence). There is evidence for a higher pregnancy rate in favour of letrozole (OR 1.69, 95% CI 1.45 to 1.98; I^2 = 0%; NNTB = 10; 23 trials, 3321 participants; high-certainty evidence). This suggests that in women with a 24% chance of clinical pregnancy using SERMs, the clinical pregnancy rate in women using letrozole with or without adjuncts would be 32% to 39%. There is little or no difference between treatment groups in the rate of miscarriage per pregnancy (25% with SERMs versus 24% with letrozole: OR 0.94, 95% CI 0.66 to 1.32; I^2 = 0%; 15 trials, 736 participants; high-certainty evidence) and multiple pregnancy rate (2.2% with SERMs versus 1.6% with letrozole: OR 0.74, 95% CI 0.42 to 1.32; I^2 = 0%; 14 trials, 2247 participants; high-certainty evidence). However, a funnel plot showed mild asymmetry, indicating that some trials in favour of SERMs might be missing.

Letrozole compared to laparoscopic ovarian drilling (LOD)

One trial reported very low-certainty evidence that live birth rates may be higher with letrozole compared to LOD (OR 2.07, 95% CI 0.99 to 4.32; 1 trial, 141 participants; very low-certainty evidence). This suggests that in women with a 22% chance of live birth using LOD with or without adjuncts, the live birth rate in women using letrozole with or without adjuncts would be 24% to 47%. No trial reported OHSS rates. Due to the low-certainty evidence we are uncertain if letrozole improves pregnancy rates compared to LOD (OR 1.47, 95% CI 0.95 to 2.28; I^2 = 0%; 3 trials, 367 participants; low-certainty evidence). This suggests that in women with a 29% chance of clinical pregnancy using LOD with or without adjuncts, the clinical pregnancy rate in women using letrozole with or without adjuncts would be 28% to 45%. There seems to be no evidence of a difference in miscarriage rates per pregnancy comparing letrozole to LOD (OR 0.65, 95% CI 0.22 to 1.92; I^2 = 0%; 3 trials, 122 participants; low-certainty evidence). This also applies to multiple pregnancies (OR 3.00, 95% CI 0.12 to 74.90; 1 trial, 141 participants; very low-certainty evidence).

Authors' conclusions

Letrozole appears to improve live birth rates and pregnancy rates in infertile women with anovulatory PCOS, compared to SERMs, when used for ovulation induction, followed by intercourse. There is high-certainty evidence that OHSS rates are similar with letrozole or SERMs. There was high-certainty evidence of no difference in miscarriage rate and multiple pregnancy rate. We are uncertain if letrozole increases live birth rates compared to LOD. In this update, we added good quality trials and removed trials with concerns over data validity, thereby upgrading the certainty of the evidence base.

PLAIN LANGUAGE SUMMARY

Aromatase inhibitors for infertility treatment in women with polycystic ovary syndrome

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

Background: PCOS is the most common cause of infrequent or absent menstrual periods, and affects about 5% to 20% of women worldwide. It often causes anovulatory infertility (infertility related to inability to ovulate). Aromatase inhibitors (AIs) are used to make ovulation happen. Since about 2001 clinical trials have reached differing conclusions as to whether the AI, letrozole, is at least as effective for treating infertility as the most commonly used treatment, clomiphene citrate.

Trial characteristics: The review includes clinical trials where participants were randomly assigned to the intervention (letrozole) or to the comparison group (i.e. clomiphene citrate). These trials are called randomised controlled trials. Our review includes 41 randomised controlled trials with 6522 women. In all trials, the aromatase inhibitor used was letrozole. Comparators included clomiphene citrate, which was used in 26 of the randomised controlled trials, and laparoscopic ovarian drilling (a surgical technique used to trigger ovulation), which was used in four randomised controlled trials. Several trials included other treatments.

Key results: Letrozole appears to improve live birth rates and pregnancy rates compared to clomiphene citrate when used to cause ovulation, followed by timed intercourse. There appeared to be no difference for miscarriage rate or multiple pregnancy rate. Ovarian hyperstimulation syndrome, a serious adverse event of hormonal stimulation, was a very rare event and in most trials it did not occur. The certainty of the evidence for all these outcomes was high and seems to be reliable.

There appeared to be very low-certainty evidence for higher live birth rates with letrozole compared to laparoscopic ovarian drilling, although there was only one relevant trial. The result for clinical pregnancy rate was uncertain. We are uncertain if letrozole decreases miscarriage and multiple pregnancy rates compared to laparoscopic ovarian drilling. No trials reported on ovarian hyperstimulation syndrome. The evidence is current to November 2021.

Certainty of the evidence: The overall certainty of the evidence ranged from very low to high. We downgraded evidence when we had small trials with few women or when methods were unclear.

Summary of findings 1. Letrozole with or without adjuncts compared to SERMs with or without adjuncts followed by timed intercourse for infertile women with polycystic ovary syndrome

Letrozole with or without adjuncts compared to SERMs with or without adjuncts followed by timed intercourse for infertile women with polycystic ovary syndrome

Patient or population: infertile women with polycystic ovary syndrome
Setting: (fertility) clinics or outpatient settings
Intervention: letrozole with or without adjuncts followed by timed intercourse
Comparison: SERMs (clomiphene citrate) with or without adjuncts followed by timed intercourse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with SERMs with or without adjuncts	Risk with letrozole with or without adjuncts				
Live birth rate	204 per 1000	307 per 1000 (265 to 352)	OR 1.72 (1.40 to 2.11)	2060 (11 RCTs)	⊕⊕⊕⊕ High	
Ovarian hyperstimulation syndrome rate	7 per 1000	5 per 1000 (5 to 5)	RD −0.00 (−0.01 to 0.01)	1848 (10 RCTs)	⊕⊕⊕⊕ High	
Clinical pregnancy rate	242 per 1000	350 per 1000 (316 to 387)	OR 1.69 (1.45 to 1.98)	3321 (23 RCTs)	⊕⊕⊕⊕ High	
Miscarriage rate per pregnancy	252 per 1000	240 per 1000 (182 to 307)	OR 0.94 (0.66 to 1.32)	736 (15 RCTs)	⊕⊕⊕⊕ High	
Multiple pregnancy rate	22 per 1000	16 per 1000 (9 to 28)	OR 0.74 (0.42 to 1.32)	2247 (14 RCTs)	⊕⊕⊕⊕ High	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RD:** risk difference; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 2. Letrozole compared to laparoscopic ovarian drilling for infertile women with polycystic ovary syndrome

Letrozole compared to laparoscopic ovarian drilling compared to placebo for infertile women with polycystic ovary syndrome

Patient or population: infertile women with polycystic ovary syndrome
Setting: (fertility) clinics or outpatient settings
Intervention: letrozole with or without adjuncts followed by timed intercourse
Comparison: laparoscopic ovarian drilling (LOD) followed by timed intercourse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with LOD	Risk with letrozole				
Live birth rate	229 per 1000	380 per 1000 (227 to 561)	OR 2.07 (0.99 to 4.32)	141 (1 RCT)	⊕⊝⊝⊝ Very Low[a,b,c]	
Ovarian hyperstimulation syndrome rate	No trials reported on this outcome					
Clinical pregnancy rate	290 per 1000	375 per 1000 (279 to 482)	OR 1.47 (0.95 to 2.28)	376 (3 RCTs)	⊕⊕⊝⊝ Low[a,b]	
Miscarriage rate per pregnancy	151 per 1000	104 per 1000 (38 to 254)	OR 0.65 (0.22 to 1.92)	122 (3 RCTs)	⊕⊕⊝⊝ Low[a,b]	
Multiple pregnancy rate	0 per 1000	0 per 1000 (0 to 0)	OR 3.00 (0.12 to 74.90)	141 (1 RCT)	⊕⊝⊝⊝ Very Low[a,b,c]	

***The risk in the intervention group** (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; **OR:** odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Insufficient data to allow judgement of risk of bias in some trials - downgraded one level for serious risk of bias.
[b]There is insufficient data to determine if there is a difference as opposed to no evidence of a difference - downgraded one level for imprecision.
[c]Analysis is based on only one trial - downgraded one additional level for imprecision.

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 5% to 20% of women worldwide in their fertile years (Abu 2012; Lizneva 2016). Many of these women are infertile, but for most of them it just takes longer to become pregnant naturally and only a small percentage need 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 hormone, luteinising hormone (LH) and of the male hormones (androgens) which interfere with the normal function of the ovaries (Azziz 2006).

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

- Oligoovulation (infrequent ovulation) or anovulation (absence of ovulation), or both
- 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 more than 10 mL. Antral follicles are defined as measuring between 2 mm and 9 mm in diameter.

Other definitions of PCOS include the National Institutes of Health Criteria (NIH), defined in 1990. They included only the presence of clinical and/or biochemical hyperandrogenism and oligo/amenorrhoea anovulation (Zawadski 1992). The Androgen Excess Society (AES) defined PCOS as hyperandrogenism with ovarian dysfunction or polycystic ovaries (Azziz 2006). Based on the definition, the phenotype of women identified with PCOS can be very different, as could be the morbidity and hence the success of treatment (Lizneva 2016).

Description of the intervention

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

Clomiphene citrate (CC) is a selective oestrogen receptor modulator (SERM), and is the most common medication used for treating the condition. It was first introduced in 1960 for treatment of World Health Organization (WHO) type II anovulation (a type of infertility where hormone levels stay normal) in infertile women, and has been the first-line treatment ever since. CC is given orally and is relatively safe and inexpensive, but there are also adverse effects associated with it, 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). Since about 2001, 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 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 the endometrium and cervix compared with CCs (Baruah 2009; Jirge 2010; Samani 2009). Despite evidence of effectiveness and safety in well-designed large randomised controlled trials (RCTs), letrozole is still used off-label for ovulation induction, since it has not been approved by the US Food and Drug Administration (FDA) for this indication (Amer 2017; Legro 2014). A 2005 study (Biljan 2005), including 150 babies, raised some concerns about the teratogenicity of letrozole, but there were major methodological flaws in this study, as the intervention group was not well controlled. Two other large trials, including 911 and 470 infants respectively, compared the use of letrozole to CC in spontaneously-conceiving women. Both reported no higher levels of minor or major congenital malformations or cardiac abnormalities in newborns after use of letrozole for ovulation induction (Forman 2007; Tulandi 2006).

Due to the short half-life elimination time of letrozole, it should be completely cleared out of the system before implantation takes place. Some clinicians recommend testing the blood levels of beta-human chorionic gonadotropin (ß-hCG) prior to treatment with letrozole to exclude pregnancy (Casper 2011). CC and AIs are usually both given for 5 days, starting on day 3 of the cycle. The dose for CC ranges from 50 mg to 150 mg a day, and for letrozole from 2.5 mg to 7.5 mg a day (Lee 2011).

Since many women 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 concludes that the use of metformin and other insulin-sensitising agents as an adjunct is limited, and might be favourable only in women who are resistant to CC alone (Brown 2016).

Human menopausal gonadotropins (hMGs) were introduced into clinical practice in 1961 for ovulation induction. They exert a central role in ovulation induction in CC-resistant infertile normogonadotropic anovulatory women (Lunenfeld 2004). However, women with PCOS are at particular risk for complications such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Ovarian hyperstimulation syndrome is a rare complication that can occur in women taking medication to stimulate egg growth and ovulation induction. The pathophysiology is not completely understood, but high levels of vascular endothelial growth factor (VEGF), secreted from many stimulated follicles under the prolonged effect of hCG, lead to a capillary leak and a fluid shift into the third space. This can result in ascites and hypovolaemia with subsequent circulatory, respiratory and renal problems (Soares 2008).

A low-dose step-up protocol was introduced to reach the follicle stimulating hormone (FSH) threshold gradually in order to minimise the risks of OHSS and multiple pregnancies (White 1996). The use of FSH for ovulation induction in women with PCOS appears to be safe and effective (Homburg 2011).

For all the above-mentioned drugs for ovulation induction, follicular growth should be monitored during a stimulation cycle

to reassure effectiveness and also to minimise the occurrence of adverse events, such as multiple pregnancy (Von Hofe 2015).

Finally, another possible option for ovulation induction in cases of CC resistance is laparoscopic ovarian diathermy (or drilling, LOD), during which the damaging of localised areas in the ovarian cortex and stroma seems to have similar success rates compared with gonadotropin therapy (Farquhar 2002). It is not fully understood how the partial destruction of the ovary results in follicle development and ovulation induction (Farquhar 2012), however, long-term outcomes of a study with 8 to 12 years of follow-up indicate that LOD is safe and effective (Nahuis 2011).

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 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 mono-ovulation (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 AIs has fluctuated over the last decade, and new data based on recent RCTs have become available, an update of the existing Cochrane Review was necessary to provide up-to-date information for daily practice.

This review evaluates the effectiveness and safety of AIs compared to other agents for ovulation induction or laparoscopic ovarian drilling, to provide evidence about whether or not AIs should be used in infertile women with PCOS who are trying to conceive.

OBJECTIVES

To evaluate the effectiveness and safety of AIs (letrozole) (with or without adjuncts) compared to SERMs (with or without adjuncts) for infertile women with anovulatory PCOS for ovulation induction followed by timed intercourse or intrauterine insemination.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) for inclusion in the review. We excluded cross-over trials unless phase one data were available separately.

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

Exclusion criteria

We excluded RCTs of women with hyperprolactinaemia or Cushing's syndrome, or both. We also excluded trials covering women with WHO type I anovulation (hypogonadotropic hypogonadal anovulation). Women in this group have amenorrhoea, low or low-normal serum FSH concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of GnRH or pituitary unresponsiveness to GnRH. We excluded trials using methods other than ovulation induction followed by intercourse or intrauterine insemination, for example, in vitro fertilisation (IVF).

Types of interventions

We considered for inclusion AIs (letrozole) for ovulation induction, alone or in conjunction with medical adjuncts, e.g. metformin or FSH compared to SERMs with or without adjuncts followed by sexual intercourse or intrauterine insemination in women with anovulatory infertility.

Types of outcome measures

Primary outcomes

Effectiveness

- Live birth rate, defined as delivery of a live foetus after 20 completed weeks of gestational age

Adverse events

- OHSS rate, as defined by the trial authors

Secondary outcomes

- Clinical pregnancy rate, defined as viable intrauterine pregnancy confirmed by ultrasound
- Miscarriage rate per woman, defined as the involuntary loss of a clinical pregnancy before 20 weeks of gestation, including partial loss of a multiple pregnancy
- Miscarriage rate per pregnancy, defined as the involuntary loss of a clinical pregnancy before 20 weeks of gestation, including partial loss of a multiple pregnancy
- Multiple pregnancy rate, 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 investigating the use of AIs for ovulation induction in anovulatory women with PCOS in consultation with the Cochrane Gynaecology and Fertility (CGF) Information Specialist. We used both indexed and free-text terms, and applied no language or date restrictions.

Electronic searches

We searched the following databases.

- The Cochrane Gynaecology and Fertility (CGF) Specialised Register, ProCite platform, searched from inception to 4 November 2021 (Appendix 1).
- CENTRAL, via the Cochrane Register of Studies Online (CRSO), Web platform, searched from inception to 4 November 2021 (Appendix 2).
- MEDLINE, Ovid platform, searched from 1946 to 4 November 2021 (Appendix 3).
- Embase, Ovid platform, searched from 1980 to 4 November 2021 (Appendix 4).
- PsycINFO, Ovid platform, searched from 1806 to 4 November 2021 (Appendix 5).

We combined the MEDLINE search with the Cochrane highly-sensitive search strategy for identifying randomised trials which appears in the *Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook)* (Version 6.2 chapter 4, 4.4.7) (Lefebvre 2021). We combined the Embase search with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/what-we-do/methodology/search-filters).

Searching other resources

We checked the references of relevant systematic reviews and RCTs obtained by the search, and contacted experts in the field and manufacturers of AIs, to pick up any additional, relevant trials.

We also searched the following up to November 2021 for grey literature of additional trials that had not been indexed in major databases.

- International trial registers
  - ClinicalTrials database, a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home)
  - World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx)
- Google Scholar

Data collection and analysis

We conducted data collection and analysis in accordance with the *Cochrane Handbook* (Higgins 2021).

Selection of studies

For this update of the review, two review authors (SF and QL) independently selected the trials to be included, in accordance with the aforementioned criteria. We excluded trials from the review if they made comparisons other than those specified above. Studies from non-English language journals were translated if necessary. If a trial was published more than once, we only included the most complete and up-to-date data. We contacted authors of primary studies if papers did not contain enough information to enable an accurate assessment of eligibility for inclusion. We provide a list of excluded studies, showing the reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

For this update of the review, two review authors (SF and QL) independently extracted the data, resolving any disagreements by recourse to a third party. We used a data extraction form designed and piloted by the review authors. All data collected for our analyses were dichotomous. If studies had multiple publications, we included only the main trial report. The review authors contacted trial investigators to resolve any data queries, as required.

Assessment of risk of bias in included studies

We assessed the included trials for risks of bias, using the Cochrane RoB 1 tool (Higgins 2017). We evaluated the following seven domains of possible bias.

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

We judged the different types of bias using the criteria from the *Cochrane Handbook* (Higgins 2017). Two review authors (SF and SE) checked these domains of bias independently and rated them as being at high, low or unclear risk of bias. The assessments were compared and any disagreements resolved by consensus or by discussion with a third review author (CF). The conclusions are presented in the risk of bias table and were incorporated into the interpretation of the 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 trial as odds ratios (ORs) with 95% confidence intervals (CIs). For the very rare outcome, OHSS, we have used a risk difference (RD) analysis to allow CIs for the difference in percentage points. A RD approach was chosen over OR due to zero events in one or more trial arms. Based on the specified outcomes, there were no continuous data measures.

Unit of analysis issues

The primary analysis was per woman randomised. We also analysed the secondary outcome of miscarriage rate per pregnancy. We contacted authors of trials that used cycles as the denominator rather than women, for additional information; if we could not obtain it, we did not include the trial in the analysis. If there were multiple cycles, the unit of analysis remained as the woman randomised. We used only the first phase of cross-over trials in the analysis, as successful treatment prevents a cross-over. We treated multiple live births as one event.

Dealing with missing data

If data were missing from included studies, we contacted the investigators 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 had not occurred. For other outcomes, we analysed only the available data. We subjected any imputation to sensitivity analysis. We analysed the data on an intention-to-treat (ITT) basis, as far as possible.

Assessment of heterogeneity

We tested the results of the included trials for heterogeneity by measuring the scatter in the data points on the graph and the overlap in their CIs. We used the I^2 statistic, which describes the percentage of total variation across the trials that is due to heterogeneity rather than to chance (Higgins 2021). The values of the I^2 statistic lie between 0% (no heterogeneity) and 100% (extreme heterogeneity). We take values above 50% to indicate moderate heterogeneity and we explored them within sensitivity and subgroup analyses.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible trials and by being alert to 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, we produced a funnel plot to test for reporting bias.

Data synthesis

We used a fixed-effect model to combine the data from the primary studies if they were sufficiently similar. We conducted statistical analysis with Review Manager 5 (Review Manager 2020), in accordance with the guidelines for statistical analysis developed by Cochrane (Higgins 2021).

Our comparisons were:

- letrozole compared to placebo;
- letrozole compared to SERMs with or without adjuncts followed by timed intercourse;
- letrozole compared to SERMs with or without adjuncts followed by intrauterine insemination;
- letrozole compared to LOD with or without adjuncts;
- letrozole compared to FSH;
- letrozole compared to anastrozole;
- letrozole compared to berberine;
- comparison of different administration protocols of letrozole;
- dosage studies of letrozole.

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

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis for primary outcomes only, to evaluate the evidence for a trial population with an average body mass index (BMI) > 25 compared to women with an average BMI < 25 within their trial group. We conducted a further subgroup analysis comparing women with no previous treatment for ovulation induction to women that were CC-resistant. We intended to perform subgroup analyses on other parameters, such as the age of the woman, the duration of infertility and the duration and drug dosages, but this was not possible due to the lack of data.

Sensitivity analysis

We conducted a sensitivity analysis for the primary outcomes to evaluate whether the conclusions are robust to arbitrary decisions made about the eligibility and analysis of trials. This analysis includes consideration of whether the review conclusions would have differed if:

- eligibility was restricted to trials without high or unclear risk of bias;
- we had used a random-effects model;
- we had implemented alternative imputation strategies;
- the summary effect measure had been the risk ratio (RR) instead of the OR.

Summary of findings and assessment of the certainty of the evidence

We generated summary of findings tables using GRADE (Schünemann 2013) and GRADEpro GDT software (GRADEpro GDT), to evaluate the overall certainty of the body of evidence for: aromatase inhibitors (letrozole) with or without adjuncts compared to SERMs, with or without adjuncts (summary of findings table 1); and aromatase inhibitors (letrozole) compared to LOD (summary of findings table 2). GRADE criteria includes: trial limitations (risk of bias), consistency of effect, imprecision, indirectness and publication bias. Judgements about evidence certainty (high, moderate, low or very low) were justified, documented and incorporated into the reporting of results for each outcome. Two review authors independently evaluated the overall certainty of the evidence for the main outcomes of the review (live birth rate, OHSS rate, clinical pregnancy rate, miscarriage rate per pregnancy, multiple pregnancy rate). There are no summary of findings tables for the remaining comparisons of the review, because we considered them less clinically important. The results of these comparisons are discussed within the text of the review.

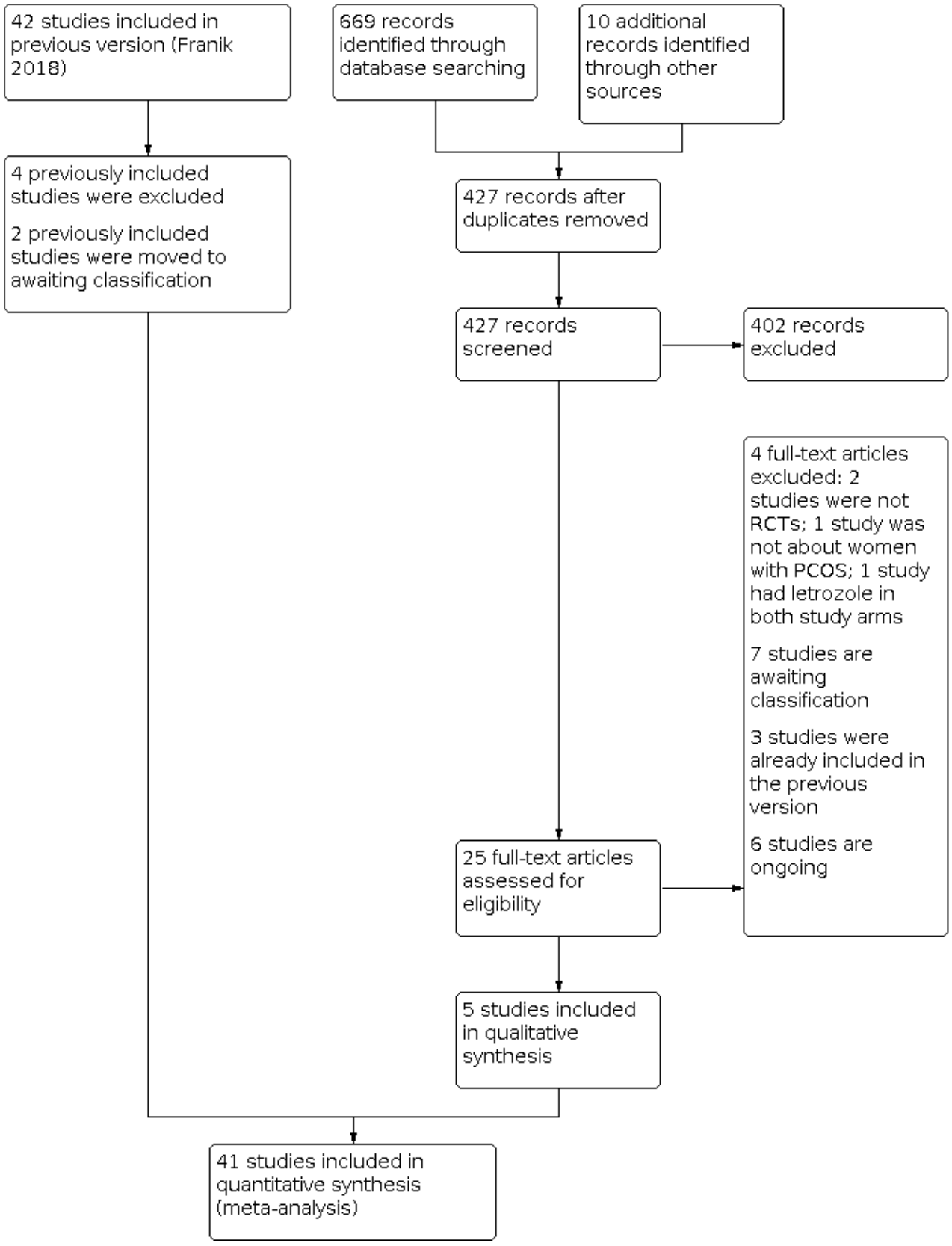
RESULTS

Description of studies

Results of the search

The previous version of this review included 42 trials. The searches for the 2021 review update resulted in the retrieval of 25 full-text papers (Figure 1). We included five new trials (Characteristics of included studies). We excluded four new trials (Characteristics of excluded studies). Seven new trials are awaiting classification (Characteristics of studies awaiting classification); we have contacted their authors and still await a response. Six new trials are ongoing (Characteristics of ongoing studies). We have moved four trials from included to excluded (Abu Hashim 2010; Badawy 2008; Badawy 2009a; Badawy 2009b), and two trials from included to awaiting classification due to concerns about validity of the trial data (Abu Hashim 2010a; Abdellah 2011). The review update contains 41 included trials (Figure 1).

Figure 1. Study flow diagram for update 2021



Included studies

Study design and setting

We include 41 parallel-designed RCTs in this 2021 updated review.

The trials were done in different parts of the world.

- China (Chen 2016; Liu 2015; Liu 2017; Shi 2019; Wu 2016)
- Egypt (El-Gharib 2015; El-Khayat 2016; Elgafor 2013; Hassan 2017; Hendawy 2011; Ibrahim 2017; Moussa 2016; Selim 2012)
- India (Begum 2009; Ganesh 2009; Kamath 2010; Kar 2012; Ray 2012; Roy 2012; Sh-El-Arab Elsedeek 2011)
- Iraq (Al-Omari 2004; Sharief 2015)
- Iran (Behnoud 2019; Davar 2011; Dehbashi 2009; Foroozanfard 2011; Ghahiri 2016; Ghomian 2015; Najafi 2020 Ramezanzadeh 2011; Seyedoshohadaei 2016; Sohrabvand 2006; Zarei 2015; Zeinalzadeh 2010)
- Mexico (Salazar-Ortiz 2016)
- Pakistan (Ashfaq 2018)
- Turkey (Atay 2006; Bayar 2006; Nazik 2012)
- UK (Amer 2017)
- USA (Legro 2014)

The following different settings recruited women into the trials.

- Not stated (Atay 2006; Ray 2012; Roy 2012; Selim 2012)
- Subfertility clinic (Amer 2017; Begum 2009; Davar 2011; Dehbashi 2009; Foroozanfard 2011; Ghahiri 2016; Ganesh 2009; Kar 2012; Nazik 2012; Ramezanzadeh 2011; Sh-El-Arab Elsedeek 2011; Seyedoshohadaei 2016; Sohrabvand 2006; Zeinalzadeh 2010)
- Outpatient clinic (Bayar 2006; El-Gharib 2015; Ibrahim 2017; Shi 2019)
- Department of obstetrics and gynaecology (Al-Omari 2004; Ashfaq 2018; Chen 2016; Elgafor 2013; Legro 2014)
- Division of reproductive endocrinology (Kamath 2010)
- Maternity and child hospital (Seyedoshohadaei 2016; Zarei 2015)
- University hospital (Behnoud 2019; El-Khayat 2016; Ghomian 2015; Hassan 2017; Hendawy 2011; Liu 2015; Liu 2017; Moussa 2016; Najafi 2020; Wu 2016)
- Women's health institute (Salazar-Ortiz 2016)

Participants

The trials included 6522 women who were infertile due to anovulatory PCOS. The ages of the women ranged from 18 to 40 years.

Interventions

- 2/41 trials compared letrozole to placebo (Kamath 2010; Zarei 2015).
- 28/41 trials compared letrozole to SERMs with or without adjuncts followed by intercourse (Amer 2017; Ashfaq 2018; Atay 2006; Bayar 2006; Begum 2009; Behnoud 2019; Chen 2016; Davar 2011; Dehbashi 2009; El-Gharib 2015; El-Khayat 2016; Foroozanfard 2011; Ghahiri 2016; Hendawy 2011; Legro 2014; Liu 2017; Moussa 2016; Najafi 2020; Nazik 2012; Ray 2012; Roy 2012; Salazar-Ortiz 2016; Selim 2012; Seyedoshohadaei 2016; Sharief 2015; Sh-El-Arab Elsedeek 2011; Shi 2019; Sohrabvand 2006).
- 3/41 trials compared letrozole to SERMs with or without adjuncts followed by intrauterine insemination (Ganesh 2009; Kar 2012; Zeinalzadeh 2010).
- 3/41 trials compared letrozole to laparoscopic ovarian drilling (Elgafor 2013; Ibrahim 2017; Liu 2015).
- 1/41 trials compared letrozole to FSH (Hassan 2017).
- 1/41 trials compared letrozole to anastrozole (Al-Omari 2004).
- 1/41 trials compared letrozole to berberine (Wu 2016).
- 1/41 trials compared different administration protocols of letrozole (Ghomian 2015).
- 1/41 trials compared different doses of letrozole (Ramezanzadeh 2011).

See Characteristics of included studies.

Outcomes

- 14/41 trials reported live birth rate (Amer 2017; Bayar 2006; Begum 2009; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Liu 2015; Liu 2017; Kamath 2010; Ray 2012; Roy 2012; Seyedoshohadaei 2016; Shi 2019; Wu 2016).
- 17/41 trials reported OHSS rate (Bayar 2006; Begum 2009; Chen 2016; El-Khayat 2016; Foroozanfard 2011; Ganesh 2009; Ghahiri 2016; Hassan 2017; Kamath 2010; Legro 2014; Nazik 2012; Ramezanzadeh 2011; Roy 2012; Selim 2012; Shi 2019; Zarei 2015; Zeinalzadeh 2010).
- 37/41 trials reported clinical pregnancy rate (Al-Omari 2004; Amer 2017; Atay 2006; Bayar 2006; Begum 2009; Chen 2016; Davar 2011; Dehbashi 2009; El-Gharib 2015; El-Khayat 2016; Elgafor 2013; Foroozanfard 2011; Ganesh 2009; Ghahiri 2016; Ghomian 2015; Hassan 2017; Ibrahim 2017; Kamath 2010; Kar 2012; Legro 2014; Liu 2015; Liu 2017; Moussa 2016; Nazik 2012; Ramezanzadeh 2011; Ray 2012; Roy 2012; Salazar-Ortiz 2016; Selim 2012; Sh-El-Arab Elsedeek 2011; Seyedoshohadaei 2016; Sharief 2015; Shi 2019; Sohrabvand 2006; Wu 2016; Zarei 2015; Zeinalzadeh 2010).
- 25/41 trials reported miscarriage rate per woman and per pregnancy (Bayar 2006; Begum 2009; Chen 2016; Davar 2011; Dehbashi 2009; El-Khayat 2016; Elgafor 2013; Foroozanfard 2011; Ganesh 2009; Ghahiri 2016; Hassan 2017; Ibrahim 2017; Kamath 2010; Kar 2012; Liu 2015; Liu 2017; Nazik 2012; Ramezanzadeh 2011; Ray 2012; Roy 2012; Seyedoshohadaei 2016; Shi 2019; Sohrabvand 2006; Wu 2016; Zarei 2015).
- 25/41 trials reported multiple pregnancy rate (Al-Omari 2004; Amer 2017; Atay 2006; Bayar 2006; Begum 2009; Chen 2016; Dehbashi 2009; El-Khayat 2016; Foroozanfard 2011; Ganesh 2009; Hassan 2017; Hendawy 2011 Kamath 2010; Kar 2012; Legro 2014; Liu 2015; Nazik 2012; NCT00610077; Ramezanzadeh 2011; Roy 2012; Selim 2012; Sharief 2015; Shi 2019; Wu 2016; Zeinalzadeh 2010).

See Characteristics of included studies.

Excluded studies

We excluded 38 trials from the review. Eight of these were identified for the 2021 update (Abu Hashim 2010; Al-Obaidi 2018; Badawy 2008; Badawy 2009a; Badawy 2009b; Huang 2019; NCT03135301; Wang 2019). The primary reasons for exclusion of the trials were inclusion criteria, interventions, concerns about the validity of the trial data (study retraction/expression of concern) and no randomisation (see Characteristics of excluded studies).

Studies awaiting classification

Fourteen studies are awaiting classification (Abdellah 2011; Abu Hashim 2010a; Aygen 2007; Ghoneim 2020; Jindal 2019; Kamel 2019; Lorzadeh 2011; NCT02551367; NCT02703649; NCT03664050; Rezk 2018; Safdarian 2012; Saha 2020; Shirin 2009).

Ongoing studies

Seven studies are ongoing (ChiCTR2100042082; CTRI/2018/04/013343; Cutler 2018; Huang 2020; IRCT2016030926962N2; NCT03009838; Priest 2019).

Risk of bias in included studies

See Characteristics of included studies; Figure 2; Figure 3.

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

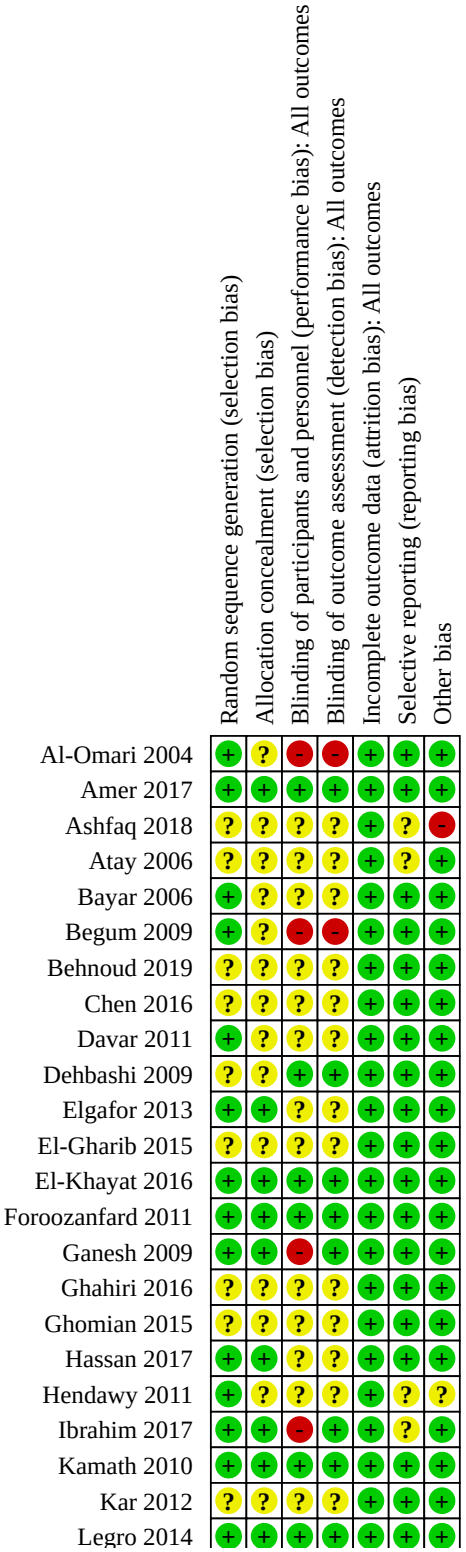


Figure 2. (Continued)

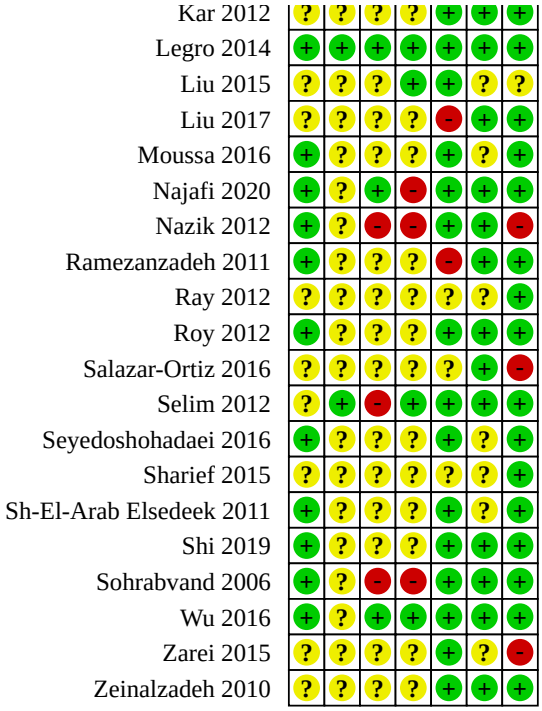
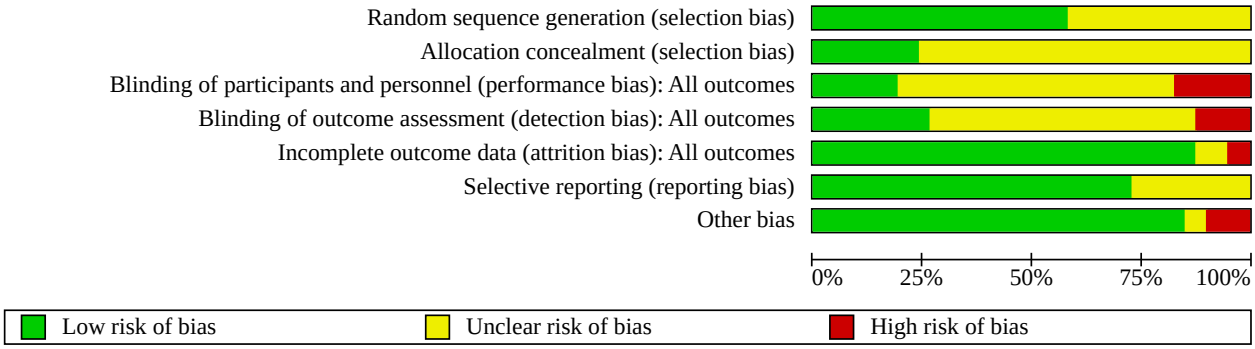


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Twenty-four trials were at low risk of selection bias related to random sequence generation. They used computer randomisation, a random-number table or lottery. The remaining 17 trials did not fully describe their method of randomisation and the contacted authors did not respond, so we rated them at unclear risk of this bias (Figure 2).

Ten trials 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, or the randomisation schedule was produced by an interactive voice response system vendor. The other 31 trials did not describe allocation concealment sufficiently and the authors did not respond to our emails, so we rated them at unclear risk of bias (Figure 2).

Blinding

Eight out of 41 trials described the blinding of participants and personnel, and were thus rated at low risk of performance bias. Twenty-six trials did not mention blinding of participants of personnel and the authors did not respond to our emails, so we rated them at unclear risk of bias. Seven trials stated that there was no blinding of participants or personnel or both, and were at high risk of bias (Figure 2).

Eleven of 41 trials reported that the outcome assessors were blinded and were therefore at low risk of bias. Twenty-five trials did

not mention blinding of outcome assessors and the authors did not respond to our email contact, so were rated at unclear risk of bias. Five trials were at high risk of detection bias, because they reported that the outcome assessors were not blinded (Figure 2).

Incomplete outcome data

Thirty-six of 41 trials included all or nearly all women they had randomised (more than 90%) and were therefore at low risk of attrition bias. Three trials were at unclear risk of attrition bias. One trial had peculiar group numbers and none of the other biases were addressed, so we tried without success to contact the authors (Ray 2012). Another two trials did not report how many women were originally randomised (Sharief 2015; Salazar-Ortiz 2016). Two more trials were at high risk of attrition bias: one trial 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). The second trial excluded 28 of 268 women from analysis; 13 were lost to follow-up, three were excluded, and 12 had complications (Liu 2017; Figure 2).

Selective reporting

Thirty of the 41 included trials reported the outcomes they had stated in the Methods section, and we therefore judged them to be at low risk of bias. In 11 of the 41 trials only a few outcomes were presented and the contacted authors did not respond, so we rated them at unclear risk of reporting bias (Figure 2).

Other potential sources of bias

In one trial there were substantial baseline differences in age and duration of infertility between the two groups and we deemed the risk of bias to be high (Nazik 2012). In a second trial, the methods were not well described and the clinical trial registration number led to a different trial (Zarei 2015). In a third trial, the methods were also not well described in general and the sample size was very small (Salazar-Ortiz 2016). In a fourth trial the power calculation implied a very strong effect in favour of letrozole compared to CC (Ashfaq 2018). We judged two trials to be at unclear risk of other bias (Hendawy 2011; Liu 2015). We found no potential sources of within-study bias in the other trials (Figure 2).

Effects of interventions

See: **Summary of findings 1** Letrozole with or without adjuncts compared to SERMs with or without adjuncts followed by timed intercourse for infertile women with polycystic ovary syndrome; **Summary of findings 2** Letrozole compared to laparoscopic ovarian drilling for infertile women with polycystic ovary syndrome

1. Letrozole compared to placebo

Primary outcomes

1.1 Live birth rate

Two trials including 167 participants compared an AI (letrozole) with placebo (Kamath 2010; Zarei 2015). Only one trial reported live birth rate, and there was insufficient evidence to suggest a difference in live birth rate (odds ratio (OR) 3.17, 95% confidence interval (CI) 0.12 to 83.17; 1 trial, 36 participants; Analysis 1.1).

1.2 OHSS rate

A risk difference (RD) analysis for OHSS rate showed insufficient evidence of a difference in frequency of this adverse event (RD 0.00, 95% CI −0.05 to 0.05; I^2 = 0%; 2 trials, 167 participants; Analysis 1.2).

Secondary outcomes

1.3 Clinical pregnancy rate

The clinical pregnancy rate was higher using letrozole compared to placebo (OR 2.88, 95% CI 1.08 to 7.66; I^2 = 0%; 2 trials, 167 participants; Analysis 1.3).

1.4 Miscarriage rate per woman and per pregnancy

Due to a wide CI in our analysis for miscarriage rate, compared to placebo, we are uncertain if letrozole decreases miscarriage rate per woman (OR 1.60, 95% CI 0.26 to 9.89; 2 trials, 167 participants; Analysis 1.4) or per pregnancy (OR 0.55, 95% CI 0.07 to 4.56; 1 trial, 20 participants; Analysis 1.5).

1.5 Multiple pregnancy rate

Multiple pregnancy rate was not estimable because there were no cases reported. Sensitivity and subgroup analyses were not possible because there were too few trials.

2. Letrozole with or without adjuncts compared to SERMs with or without adjuncts followed by timed intercourse

23 trials including 3321 women compared letrozole to SERMs, with or without adjuncts (Amer 2017; Atay 2006; Bayar 2006; Begum 2009; Chen 2016; Davar 2011; Dehbashi 2009; El-Gharib 2015; El-Khayat 2016; Foroozanfard 2011; Ghahiri 2016; Legro 2014; Liu 2017; Moussa 2016; Nazik 2012; Ray 2012; Roy 2012; Salazar-Ortiz 2016; Selim 2012; Seyedoshohadaei 2016; Sharief 2015; Sh-El-Arab Elsedeek 2011; Sohrabvand 2006).

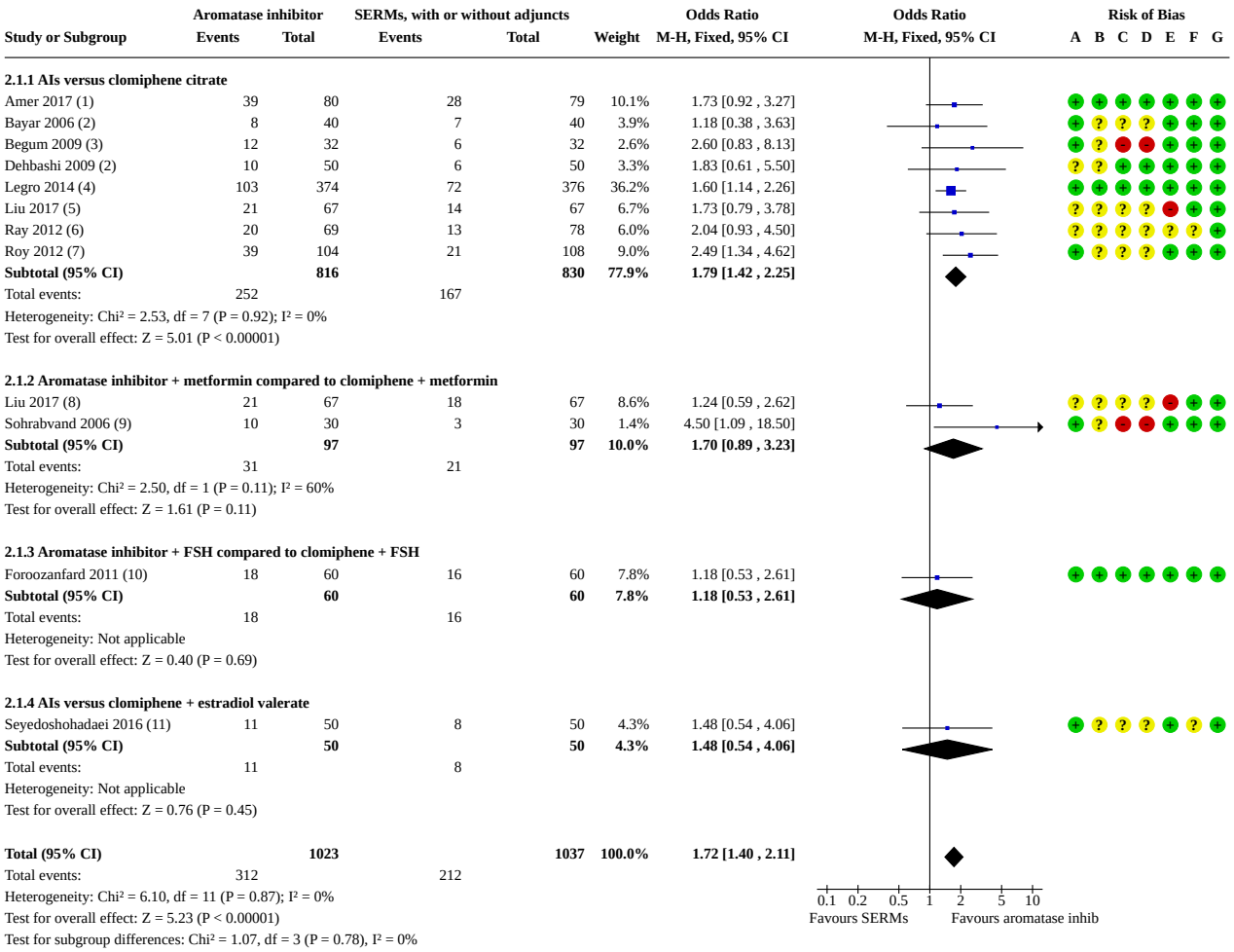
- Letrozole (2.5 mg to 7.5 mg/day) versus SERMs such as CC (50 mg to 150 mg/day), either alone or in combination with metformin (1000 mg to 1500 mg daily); 75 IU hMG to 150 IU hMG in one or both arms; estradiol valerate 4 mg/day.

Primary outcomes

2.1 Live birth rate

Eleven trials including 2060 women compared letrozole to SERMs, with or without adjuncts in one or both arms, and reported live birth rate (Amer 2017; Bayar 2006; Begum 2009; Dehbashi 2009; Foroozanfard 2011; Legro 2014; Liu 2017; Ray 2012; Roy 2012; Seyedoshohadaei 2016; Sohrabvand 2006). Letrozole resulted in an increased live birth rate compared to SERMs for ovulation induction (OR 1.72, 95% CI 1.40 to 2.11; I^2 = 0%; number needed to treat for an additional beneficial outcome (NNTB) = 10; 11 trials, 2060 participants; high-certainty evidence; Figure 4; Analysis 2.1). This suggests that in women with a 20% chance of live birth using SERMs with or without adjuncts, the live birth rate in women using letrozole with or without adjuncts would be 27% to 35%.

Figure 4. Forest plot of comparison: 2 Aromatase inhibitors compared to selective oestrogen receptor modulators (SERMs), outcome: 2.1 Live birth rate.



Footnotes

(1) Previous subfertility treatment unknown; starting dose 2.5 mg letrozole vs 50 mg clomiphene citrate/day
(2) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene 100 mg/day
(3) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(4) Cumulative live birth rate; treatment naïve patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(5) Previous treatment for subfertility unknown; clomiphene 50 - 150 mg versus letrozole 5 mg
(6) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene 100 mg/day
(7) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 - 5 mg/day versus clomiphene 50 - 100 mg/day
(8) Previous treatment for subfertility unknown; clomiphene 50 - 150 mg versus letrozole 5 mg; both groups received 1000 - 1500 mg metformin daily
(9) Clomiphene-resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day
(10) Clomiphene-resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG
(11) Clomiphene-resistant women; letrozole 5mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

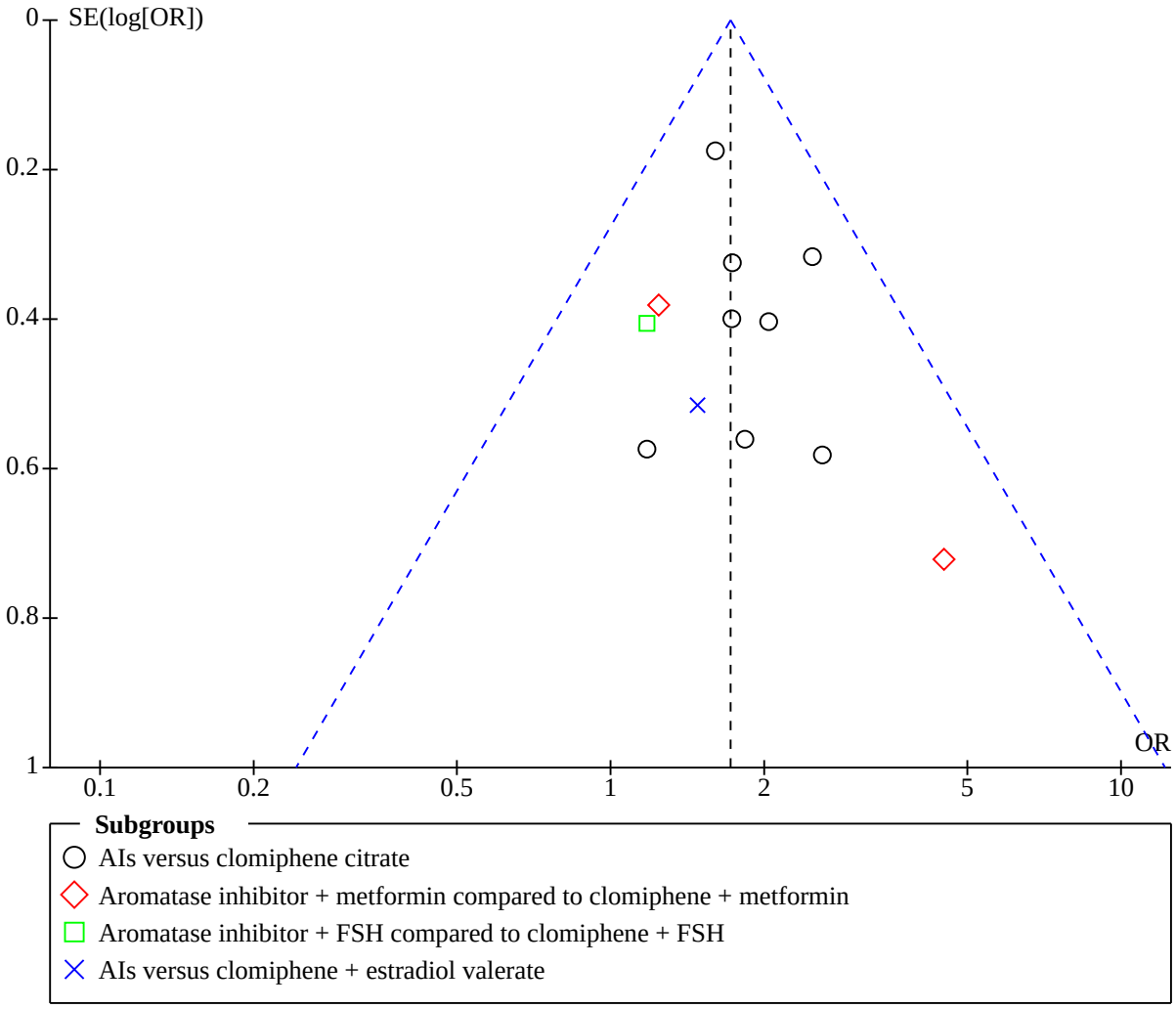
Eight of the 11 trials compared letrozole alone with CC alone (OR 1.79, 95% CI 1.42 to 2.25; I^2 = 0%; 1646 participants)

Subgroup analysis showed insufficient evidence to suggest a difference by mean BMI above or below 25 (P = 0.87). Another subgroup analysis showed insufficient evidence to suggest a difference in women that were CC-resistant versus women who had no previous treatment for ovulation induction (P = 0.80) (analysis not shown).

Sensitivity analysis excluding one trial with high risk of detection bias showed no substantive influence on the treatment effect

(Begum 2009). A sensitivity analysis comparing trials with unclear and low risk for allocation bias also showed insufficient evidence for a difference in treatment effect between the two subgroups (P = 0.36). In our other sensitivity analyses, findings for live birth were not influenced by the use of a random-effects model, alternative imputation strategies, or RR rather than OR. A funnel plot for live birth rate was symmetrical, indicating that our findings might not be influenced by publication bias (Figure 5).

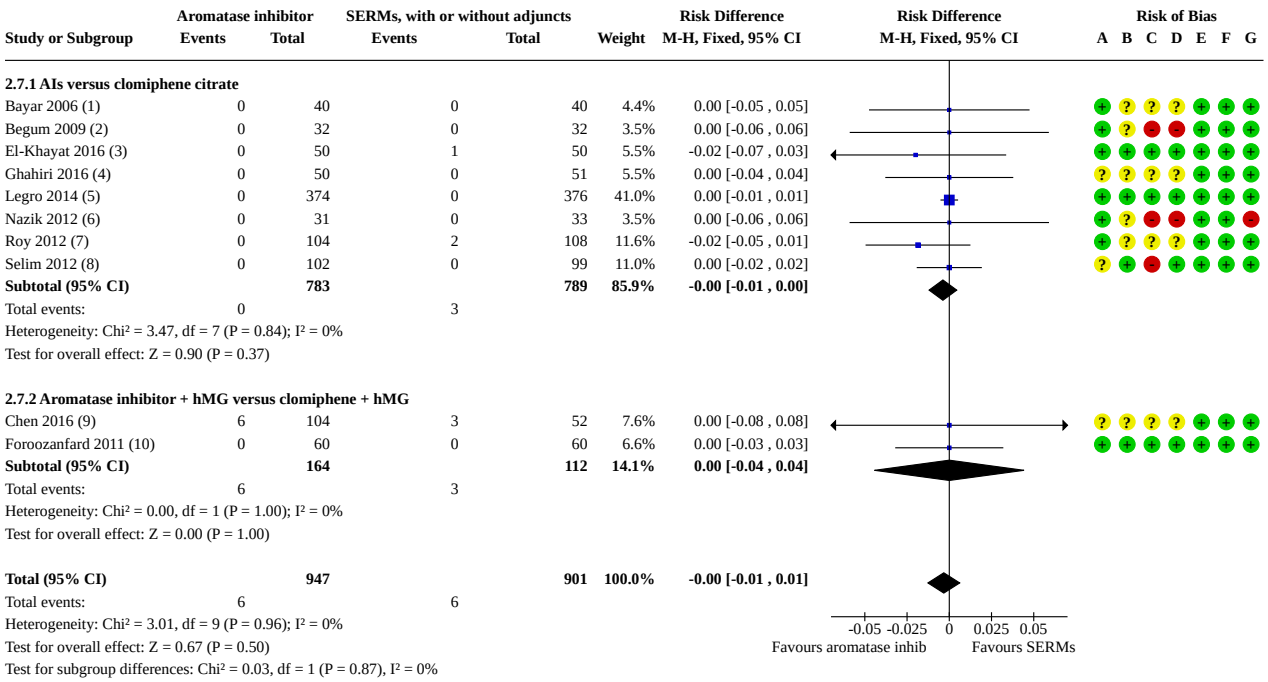
Figure 5. Funnel plot of comparison: 2 AIs compared to SERMs with or without adjuncts, followed by timed intercourse, outcome: 2.1 Live birth rate.



2.2 OHSS rate

Ten trials including 1848 women compared letrozole to SERMs, with or without adjuncts in one or both arms, and reported the occurrence of OHSS (Bayar 2006; Begum 2009; Chen 2016; El-Khayat 2016; Foroozanfard 2011; Ghahiri 2016; Legro 2014; Nazik 2012; Roy 2012; Selim 2012). Our RD analysis showed that there is high-certainty evidence of a similar frequency of this adverse event in both groups (RD −0.00, 95% CI −0.01 to 0.01; I^2 = 0%; 10 trials, 1848 participants; high-certainty evidence; Figure 6; Analysis 2.7). This suggests that the risk of OHSS was 0.5% in both groups. No OHSS occurred in women that were treated with letrozole alone. A subgroup analysis showed insufficient evidence to suggest a difference by BMI mean (P = 0.79) (analysis not shown). No differences in results were observed in our prespecified sensitivity analyses. A funnel plot for OHSS was insufficient for detection of a potential publication bias because there were no events in most of the trials (analysis not shown).

Figure 6. Forest plot of comparison: 2 Aromatase inhibitors compared to selective oestrogen receptor modulators SERMs, outcome: 2.6 Ovarian hyperstimulation syndrome rate.



Footnotes

(1) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(2) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(3) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(4) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(5) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(6) No previous ovulation induction; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(7) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(8) Unknown if primary fertility treatment or CC-resistant; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(9) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(10) Clomiphene resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Secondary outcomes

2.3 Clinical pregnancy rate

Clinical pregnancy rate was reported in 23 trials, including 3321 women (Amer 2017; Atay 2006; Bayar 2006; Begum 2009; Chen 2016; Davar 2011; Dehbashi 2009; El-Gharib 2015; El-Khayat 2016; Foroozanfard 2011; Ghahiri 2016; Legro 2014; Liu 2017; Moussa 2016; Nazik 2012; Ray 2012; Roy 2012; Salazar-Ortiz 2016; Selim 2012; Seyedoshohadaei 2016; Sharief 2015; Sh-El-Arab Elsedeek 2011; Sohrabvand 2006). Use of letrozole resulted in a higher clinical pregnancy rate compared to SERMs, with or without adjuncts in one or both arms (OR 1.69, 95% CI 1.45 to 1.98; I^2 = 0%; NNTB = 10; 23 trials, 3321 participants; high-certainty evidence; Analysis 2.9). This suggests that in women with a 24% chance of clinical pregnancy using SERMs with or without adjuncts, the clinical pregnancy rate in women using letrozole with or without adjuncts would be 32% to 39%. No differences in results were observed in our prespecified sensitivity analyses. A funnel plot for clinical pregnancy rate was symmetrical, indicating that our findings might not be influenced by publication bias (analysis not shown).

2.4 Miscarriage rate per woman and per pregnancy

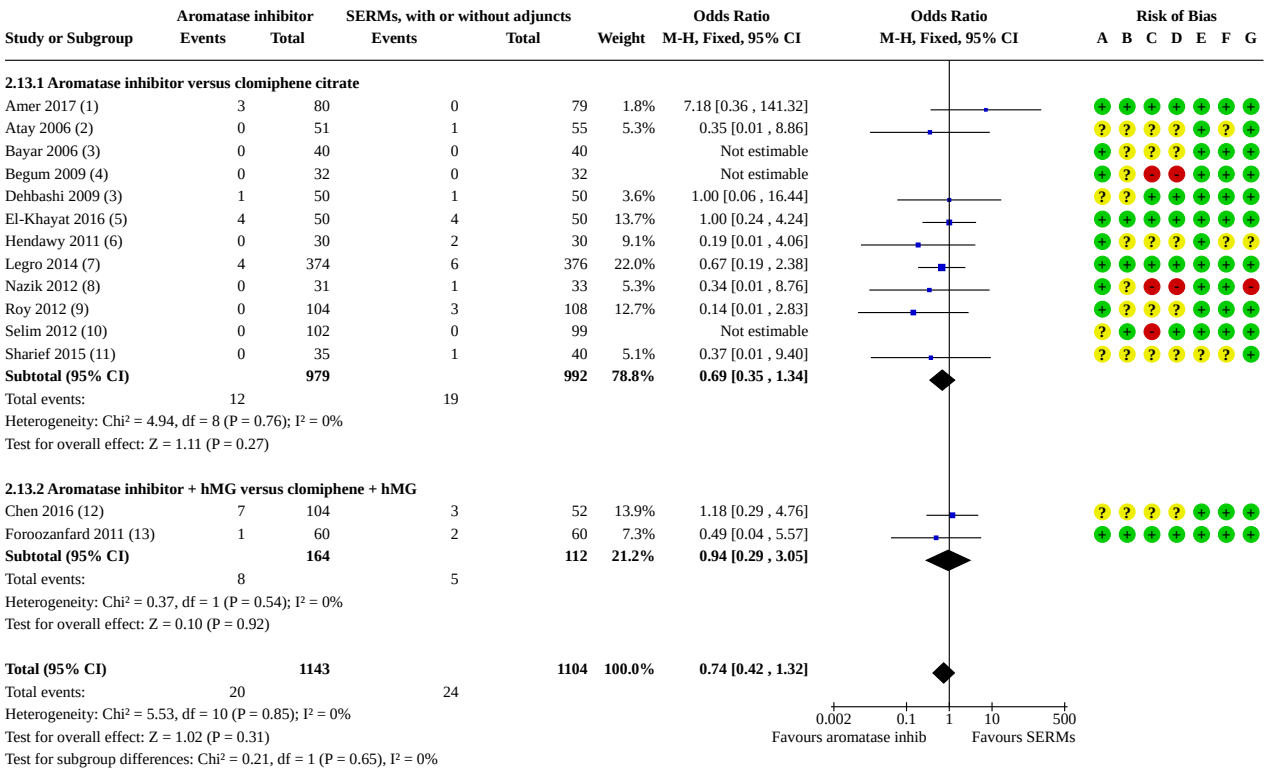
Miscarriage rate was reported in 15 trials, including 2422 women (Bayar 2006; Begum 2009; Chen 2016; Davar 2011; Dehbashi 2009; El-Khayat 2016; Foroozanfard 2011; Ghahiri 2016; Legro 2014; Liu 2017; Nazik 2012; Ray 2012; Roy 2012; Seyedoshohadaei 2016; Sohrabvand 2006). The analysis of miscarriage rate per woman showed little evidence for a difference in favour of SERMs with or without adjuncts in one or both arms (OR 1.37, 95% CI 1.01 to 1.87; I^2 = 0%; 15 trials, 2422 participants; high-certainty evidence; Analysis 2.11). However, the results of the analysis of miscarriage rate per pregnancy showed little or no difference between the groups (OR 0.94, 95% CI 0.66 to 1.32; I^2 = 0%; 15 trials, 736 participants; high-

certainty evidence; Analysis 2.12). This suggests that in women with a 25% risk of miscarriage per pregnancy using SERMs with or without adjuncts, the miscarriage rate in women using letrozole with or without adjuncts would be 18% to 30%.

2.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in 14 trials, including 2247 women (Amer 2017; Atay 2006; Bayar 2006; Begum 2009; Chen 2016; Dehbashi 2009; El-Khayat 2016; Foroozanfard 2011; Hendawy 2011; Legro 2014; Nazik 2012; Roy 2012; Selim 2012; Sharief 2015). The analysis of multiple pregnancy rate per woman showed high-certainty evidence of no difference in multiple pregnancy rate for letrozole compared to SERMs (OR 0.74, 95% CI 0.42 to 1.32; I^2 = 0%; 14 trials, 2247 participants; high-certainty evidence; Figure 7; Analysis 2.13). This suggests that in women with a 2.2% chance of multiple pregnancy using SERMs with or without adjuncts, the multiple pregnancy rate in women using letrozole with or without adjuncts would be 1.6% to 2.8%.

Figure 7. Forest plot of comparison: 2 Aromatase inhibitors compared to selective oestrogen receptor modulators SERMs, outcome: 2.5 Multiple pregnancy rate.



Footnotes

(1) Previous subfertility treatment unknown; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(2) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(3) No previous ovulation induction; letrozole 5 mg/day versus clomiphene 100 mg/day
(4) CC-resistant women; letrozole 7.5 mg/day versus clomiphene 150 mg/day
(5) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(6) Treatment naive women; starting dose letrozole 2.5 mg/day vs clomiphene 50mg/day
(7) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(8) No previous ovulation induction; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(9) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 – 5 mg/day versus clomiphene 50 – 100 mg/day
(10) Unknown if primary fertility treatment or CC-resistant; letrozole 5 mg/day versus clomiphene 100 mg/day
(11) Primary subfertility treatment unknown; letrozole 2.5 – 5 mg/day vs clomiphene 100 – 200 mg/day
(12) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(13) Clomiphene-resistant women; letrozole 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Publication bias

We produced a funnel plot for both primary outcomes and for the outcome of clinical pregnancy rate. A funnel plot for live birth rate was symmetrical, indicating that our findings might not be influenced by publication bias (Figure 5). A funnel plot for OHSS was insufficient for detection of a potential publication bias because there were no events in most of the trials (analysis not shown). The funnel plot for the secondary outcome clinical pregnancy rate showed some asymmetries, with a gap on the left side. This indicates that there were possibly some trials with effects in favour of SERMs which were not reported, and therefore the results of our meta-analysis might have overestimated the effect of letrozole on pregnancy rate.

3. Letrozole compared to SERMs with or without adjuncts followed by intrauterine insemination

Three trials including 1597 women compared the use of letrozole with or without adjuncts to SERMs followed by intrauterine insemination (Ganesh 2009; Kar 2012; Zeinalzadeh 2010).

- Letrozole (2.5 mg to 5 mg daily, cycle days 3 to 7 or 2 to 6) versus SERMs such as CC (50 mg to 150 mg daily, cycle days 3 to 7 or 2 to 6) with or without adjuncts or recombinant follicle-stimulating hormone (rFSH) only (rFSH 75 IU to 100 IU from day 2 until the day of hCG administration).

Primary outcomes

3.1 Live birth rate

No trials comparing letrozole to SERMs reported live birth rate.

3.2 OHSS rate

Two trials reported OHSS rate comparing use of letrozole to SERMs (Ganesh 2009; Zeinalzadeh 2010). Our RD analysis showed insufficient 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; I^2 = 0%; 2 trials, 1494 participants; Analysis 3.1). Sensitivity and subgroup analyses were not possible because there were too few trials.

Secondary outcomes

3.3 Clinical pregnancy rate

Clinical pregnancy rate was reported in three trials comparing letrozole to SERMs (Ganesh 2009; Kar 2012; Zeinalzadeh 2010). The analysis showed evidence in favour of letrozole compared to SERMs for ovulation induction followed by intrauterine insemination (OR 1.71, 95% CI 1.30 to 2.25; I^2 = 0%; 3 trials, 1597 participants; Analysis 3.2).

3.4 Miscarriage rate per woman and per pregnancy

Miscarriage rate was reported in two trials comparing letrozole to SERMs (Ganesh 2009; Kar 2012). There was insufficient evidence of a difference between the two groups for miscarriage rate per woman (OR 1.22, 95% CI 0.62 to 2.40; I^2 = 30%; 2 trials, 1490 participants; Analysis 3.3) or per pregnancy (OR 0.76, 95% CI 0.37 to 1.57; I^2 = 0%; 2 trials, 260 participants; Analysis 3.4).

3.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in three trials comparing letrozole to SERMs, with or without adjuncts (Ganesh 2009; Kar 2012; Zeinalzadeh 2010). There was insufficient evidence of a difference between the two groups (OR 1.03, 95% CI 0.49 to 2.13; I^2 = 0%; 3 trials, 1597 participants; Analysis 3.5).

4. Letrozole compared to LOD

Three trials including 367 women compared letrozole with or without metformin to LOD (Elgafor 2013; Ibrahim 2017; Liu 2015).

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

Primary outcomes

4.1 Live birth rate

Live birth rate was reported in one trial including 141 women, comparing letrozole to LOD (Liu 2015). There was very low-certainty evidence of a higher live birth rate in favour of letrozole compared to LOD (OR 2.07, 95% CI 0.99 to 4.32; 1 trial, 141 participants; Analysis 4.1). This suggests that in women with a 22% chance of live birth using LOD with or without adjuncts, the live birth rate in women using letrozole with or without adjuncts would be 24% to 47%. Subgroup and sensitivity analyses were not possible because there was only one trial.

4.2 OHSS rate

No trials comparing letrozole to LOD reported OHSS rate.

Secondary outcomes

4.3 Clinical pregnancy rate

Clinical pregnancy rate was reported in three trials including 367 women, comparing letrozole with or without metformin to LOD (Elgafor 2013; Ibrahim 2017; Liu 2015). There was low-certainty evidence of no difference between the two groups (OR 1.47, 95% CI 0.95 to 2.28; I^2 = 0%; 3 trials, 367 participants; Analysis 4.2). This suggests that in women with a 29% chance of clinical pregnancy using LOD with or without adjuncts, the clinical pregnancy rate in women using letrozole with or without adjuncts would be 28% to 45%.

4.4 Miscarriage rate per woman and per pregnancy

Miscarriage rate was reported in three trials including 367 women, comparing letrozole with or without metformin to LOD (Elgafor 2013; Ibrahim 2017; Liu 2015). There was low-certainty evidence of no difference between the two groups for miscarriage rate per woman (OR 0.87, 95% CI 0.31 to 2.44; I^2 = 0%; 3 trials, 367 participants; Analysis 4.3) and per pregnancy (OR 0.65, 95% CI 0.22 to 1.38; I^2 = 0%; 3 trials, 122 participants; Analysis 4.4). This suggests that in women with a 16% risk of miscarriage per pregnancy using LOD with or without adjuncts, the risk of miscarriage in women using letrozole with or without adjuncts would be 4% to 21%.

4.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in one trial including 141 women, comparing letrozole to LOD (Liu 2015). There was low-certainty evidence of no difference between the two groups for multiple pregnancy rate per woman (OR 3.00, 95% CI 0.12 to 74.90; I^2 = 0%; 1 trial, 141 participants; Analysis 4.5). The risk of multiple pregnancy was below 1% in both treatment groups.

5. Letrozole compared to FSH

Two trials including 236 women compared use of letrozole to FSH (Hassan 2017; Shi 2019).

- Letrozole 2.5 mg twice daily for 5 days versus urinary FSH (uFSH) 75 IU a day for 7 days (Hassan 2017) or human menopausal gonadotropin (hMG) 75 IU a day for 5 days (Shi 2019), both groups starting on the third day of menstruation.

Primary outcomes

5.1 Live birth rate

Live birth rate was reported in one trial comparing letrozole to hMG (Shi 2019). There was insufficient evidence of a difference between the two groups (OR 1.00, 95% CI 0.34 to 2.93; 1 trial, 96 participants; Analysis 5.1).

5.2 OHSS rate

OHSS was reported in two trials comparing letrozole to gonadotropins (Hassan 2017; Shi 2019). A RD analysis showed insufficient evidence of a difference between the two treatment groups (RD -0.03, 95% CI −0.08 to 0.01; 2 trials, 236 participants; Analysis 5.2).

Secondary outcomes

5.3 Clinical pregnancy rate

Clinical pregnancy rate was reported in two trials comparing letrozole to gonadotropins (Hassan 2017; Shi 2019). There was insufficient evidence of a difference between the two groups (OR 0.81, 95% CI 0.46 to 1.43; 2 trials, 236 participants; Analysis 5.3).

5.4 Miscarriage rate per woman and per pregnancy

Miscarriage rate was reported in two trials comparing letrozole to gonadotropins (Hassan 2017; Shi 2019). There was insufficient evidence of a difference between the two groups for miscarriage rate per woman (OR 0.61, 95% CI 0.19 to 1.92; 2 trials, 236 participants; Analysis 5.4) or per pregnancy (OR 0.74, 95% CI 0.11 to 4.90; 1 trial, 140 participants; Analysis 5.5).

5.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in two trials comparing letrozole to FSH (Hassan 2017; Shi 2019). There was insufficient evidence to suggest a difference between the two treatment groups (OR 0.22, 95% CI 0.04 to 1.32; 2 trials, 236 participants; Analysis 5.6).

6. Letrozole compared to anastrozole

One trial including 40 women compared letrozole to the AI, anastrozole (Al-Omari 2004).

- Letrozole 2.5 mg/day versus anastrozole 1 mg/day for 5 days, both starting on cycle day 3.

Primary outcomes

6.1 Live birth rate

No trials comparing letrozole to anastrozole reported live birth rate.

6.2 OHSS rate

No trials comparing letrozole to anastrozole reported OHSS rate.

Secondary outcomes

6.3 Clinical pregnancy rate

Clinical pregnancy rate was reported in one trial comparing letrozole to anastrozole (Al-Omari 2004). There was insufficient evidence of a difference between the two groups (OR 1.88, 95% CI 0.40 to 8.88; 40 participants; 1 trial; Analysis 6.1).

6.4 Miscarriage rate per woman and per pregnancy

No trials comparing letrozole to anastozole reported miscarriage rate per woman or per pregnancy.

6.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in one trial comparing letrozole to anastrozole (Al-Omari 2004). This trial did not report any cases of multiple pregnancies and an OR was therefore not estimable (Al-Omari 2004; Analysis 6.2).

7. Letrozole compared to berberine followed by timed intercourse

One trial including 644 women compared letrozole to berberine (Wu 2016).

- Letrozole 2.5 mg/day starting on cycle day 3 versus berberine 1.5 g for 6 months

Primary outcomes

7.1 Live birth rate

Live birth rate was reported in one trial comparing letrozole to berberine (Wu 2016). Letrozole resulted in an increased live birth rate compared to berberine (OR 1.94, 95% CI 1.33 to 2.84; 1 trial, 644 participants; Analysis 7.1).

7.2 OHSS rate

No trials comparing letrozole to berberine reported OHSS rate.

Secondary outcomes

7.3 Clinical pregnancy rate

Clinical pregnancy rate was reported in one trial comparing letrozole to berberine (Wu 2016). Letrozole resulted in an increased pregnancy rate compared to berberine (OR 2.15, 95% CI 1.48 to 3.13; 1 trial, 644 participants; Analysis 7.2).

7.4 Miscarriage rate per woman and per pregnancy

Miscarriage rate was reported in one trial comparing letrozole to berberine (Wu 2016). There was insufficient evidence of a difference between the two groups for miscarriage rate per women randomised (OR 1.60, 95% CI 0.26 to 9.89; 1 trial, 644 participants; Analysis 7.3) and for miscarriage rate per pregnancy (OR 4.53, 95% CI 0.24 to 84.46; 1 trial, 644 participants; Analysis 7.4).

7.5 Multiple pregnancy rate

Multiple pregnancy rate was reported in one trial comparing letrozole to anastrozole (Al-Omari 2004). This trial did not report any cases of multiple pregnancies and an OR was therefore not estimable (Al-Omari 2004; Analysis 6.2).

8. Different administration protocols of letrozole

Letrozole day 3-7 administration versus day 5-9 administration

One trial including 70 women compared starting letrozole on day 3 with day 5 administration protocol (Ghomian 2015).

Primary outcomes

8.1 Live birth rate

This trial did not report live birth rate.

8.2 OHSS rate

This trial did not report OHSS rate.

Secondary outcomes

8.3 Clinical pregnancy rate

The analysis showed insufficient evidence of a difference between the two groups in clinical pregnancy rate (OR 1.38, 95% CI 0.28 to 6.66; 1 trial, 70 participants; Analysis 8.1).

8.4 Miscarriage rate

This trial did not report miscarriage rate.

8.5 Multiple pregnancy rate

This trial did not report multiple pregnancy rate.

9. Dosage studies of letrozole

One trial compared a 5 mg/day administration of letrozole to a 7.5 mg/day administration protocol (Ramezanzadeh 2011).

Primary outcomes

9.1 Live birth rate

This trial did not report live birth rate.

9.2 OHSS rate

A RD analysis on OHSS rate showed insufficient evidence to suggest a difference in occurrence of OHSS between the two treatment groups (RD 0.00, 95% CI −0.05 to 0.05; 1 trial, 80 participants; Analysis 9.1).

Secondary outcomes

9.3 Clinical pregnancy rate

The results show insufficient evidence of a difference between the groups in clinical pregnancy rate (OR 1.00, 95% CI 0.32 to 3.17; 1 trial, 80 participants; Analysis 9.2).

9.4 Miscarriage rate per woman and per pregnancy

The results show insufficient evidence of a difference between the groups in miscarriage rate per woman (OR 0.33, 95% CI 0.01 to 8.22; 1 trial, 80 participants; Analysis 9.3), or miscarriage rate per pregnancy (OR 0.29, 95% CI 0.01 to 8.39; 1 trial, 80 participants; Analysis 9.4).

9.5 Multiple pregnancy rate

The results show insufficient evidence of a difference between the groups in multiple pregnancy rate (OR 1.00, 95% CI 0.06 to 16.56; 1 trial, 80 participants; Analysis 9.5).

DISCUSSION

Summary of main results

Letrozole compared to placebo

Two trials compared letrozole to placebo. There is a lack of evidence with only two small studies with small numbers of participants.

Letrozole compared to SERMs with or without adjuncts followed by timed intercourse

The results of our analysis of 23 trials comparing letrozole to SERMs followed by timed intercourse suggest that letrozole improves the live birth rate and pregnancy rate compared to SERMs (Summary of findings 1).

A funnel plot for live birth rate was symmetrical, indicating that our findings might not be influenced by publication bias (Figure 5).

Letrozole resulted in 10% more pregnancies, consequently the miscarriage rate expressed per woman was also higher. However, the miscarriage rate expressed per pregnancy was comparable between letrozole and SERMs. A RD analysis suggested that letrozole and CC are equally safe in terms of ovarian hyperstimulation and miscarriage rates (Summary of findings 1).

The funnel plot for clinical pregnancy rate was symmetrical, suggesting that our findings might not be influenced by publication bias. A funnel plot investigating the impact of possible allocation bias on clinical pregnancy rate showed some asymmetry, suggesting that the results might be influenced by allocation bias in favour of letrozole.

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

Six of our 23 trials in this analysis included women resistant to CC (Begum 2009; Davar 2011; El-Gharib 2015; Foroozanfard 2011; Seyedoshohadaei 2016; Sohrabvand 2006); the other 17 trials included women not resistant to CC (Bayar 2006; Dehbashi 2009; Legro 2014; Nazik 2012; Salazar-Ortiz 2016; Sh-El-Arab Elsedeek 2011), or it was not mentioned (Amer 2017; Atay 2006; Chen 2016; El-Khayat 2016; Ghahiri 2016; Liu 2017; Moussa 2016; Selim 2012; Sharief 2015; Ray 2012; Roy 2012).

Data based on 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 SERMs (Reproductive Medicine Network 2013).

Letrozole compared to SERMs with or without adjuncts followed by intrauterine insemination

Three trials compared letrozole to SERMs for ovulation induction followed by intrauterine insemination (Ganesh 2009; Kar 2012; Zeinalzadeh 2010). None reported live birth. Two reported OHSS: only three cases occurred and there was insufficient evidence of a difference despite a trial population of 1494 women. Clinical pregnancy rates were increased in women treated with letrozole, compared to SERMs and FSH. There was insufficient evidence of a difference in rates of miscarriage or multiple pregnancy.

Letrozole compared to LOD

Three trials compared letrozole to LOD in CC-resistant women (Summary of findings 2). There was very low-certainty evidence of higher live birth rates with letrozole compared to LOD. However, we note that trials reporting live birth tended to report higher clinical pregnancy rates in the letrozole group than trials that failed to report live birth, with insufficient evidence of a difference in miscarriage rates per pregnancy. This suggests that findings might be less favourable to letrozole if all trials reported live birth. OHSS was not reported. There was low-certainty evidence of no difference in rates of pregnancy, miscarriage or multiple pregnancy rate.

Letrozole compared to FSH

Two trials, including 236 women, compared use of letrozole to FSH (Hassan 2017; Shi 2019). Live birth rate was not reported and there were no events of OHSS. There was insufficient evidence of a difference for clinical pregnancy, miscarriage or multiple pregnancy rates.

Letrozole compared to anastrozole

Letrozole was compared to anastrozole in one trial including 40 women (Al-Omari 2004). Live birth rate, OHSS rate and miscarriage rate were not reported. There was insufficient evidence of a difference for rates of clinical pregnancy and multiple pregnancies.

Letrozole compared to berberine

The results of one trial comparing letrozole to berberine followed by timed intercourse suggest that letrozole improves the live birth rate and pregnancy rate compared to berberine (Wu 2016). The OHSS rate was not reported. There was insufficient evidence of a difference for rates of miscarriage and multiple pregnancies.

Different administration protocols of letrozole

Letrozole day 3-7 administration versus day 5-9 administration protocol

A single trial including 70 women compared a day 3 to 5 versus day 5 to 9 administration protocol. Only pregnancy rate was reported and there was insufficient evidence for a difference.

Dosage studies of letrozole

We intended to analyse different doses of letrozole in the range from 2.5 mg/day to 5 mg/day, but we found only one trial including 80 women comparing a dosage of 5 mg/day to 7.5 mg/day. There was insufficient evidence of a difference in effectiveness as only seven pregnancies were reported in each group. There was also insufficient evidence of a difference in adverse events, but the size of the trial population might have been too small because only one or no cases were reported in each group for OHSS, miscarriage and multiple pregnancy rate.

Overall completeness and applicability of evidence

For our main comparison of letrozole compared to SERMs with or without adjuncts followed by timed intercourse, we found sufficient trials for our analysis of live birth and OHSS rates to answer our research question. For all other comparisons except for the comparison of letrozole versus placebo, more trials could improve the certainty of evidence.

Most of the trials included were conducted in Egypt or the Middle East. There are, however, two large trials from the USA and Europe confirming the results (Amer 2017; Legro 2014).

Certainty of the evidence

We included 41 trials with 6522 women in the review. We rated the overall certainty of the evidence as high for all outcomes for our main comparison: letrozole versus SERMs, with or without adjuncts followed by timed intercourse (Summary of findings 1). Based on the large numbers of participants (number of trials ranging from 10 to 23 depending on the outcome) and the addition of trials at low risk of bias, it is unlikely that additional trials are going to alter the effect estimates of our main comparison.

The other comparisons included only one to five trials. We downgraded much of the evidence for risks of bias and imprecision (Summary of findings 2). We rated the certainty of the evidence for live birth and multiple pregnancy rates as very low, and as low for clinical pregnancy and miscarriage rates.

Potential biases in the review process

We conducted a comprehensive search with the help of an experienced Information Specialist, and ran extensive manual searches in order to identify all relevant trials and in an effort to minimise the risk of publication bias. We generated a funnel plot for the outcomes of live birth and pregnancy rates in the comparison of letrozole versus SERMs, which was symmetrical and therefore indicated there is no publication bias.

We followed Cochrane guidelines to select trials, extract data and assess the certainty and potential risks of different types of biases in all our included trials, in order to minimise the chance of error and bias by the review authors.

We requested further information from trial author teams; we did not receive a response from five of them.

Agreements and disagreements with other studies or reviews

Our meta-analysis shows evidence for increased live birth rates in favour of letrozole when compared to CC in women with PCOS. This differs from a previous review, which did not detect a difference (Misso 2012). This is most likely due to the limited number of trials included in the previous review. They included six RCTs, comparing the pregnancy rate between letrozole and CC, including 889 women in total (odds ratio (OR) 1.53, 95% CI 0.91 to 2.58). Another recent meta-analysis is in accordance with our findings of increased live birth rate (risk ratio (RR) 1.55, 95% CI 1.26 to 1.90; I^2 = 0%; 5 trials, 1289 participants) and pregnancy rate (RR 1.38, 95% CI 1.05 to 1.83; I^2 = 61%; 7 trials, 1833 participants), as well as no difference for miscarriage and multiple pregnancy rates (Roque 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Letrozole appears to improve live birth and pregnancy rates in infertile women with anovulatory PCOS, compared to SERMs, when used for ovulation induction, followed by intercourse. There is high-certainty evidence that OHSS rates are similar with letrozole or SERMs. There was high-certainty evidence of no difference in

miscarriage rate and multiple pregnancy rate. We are uncertain if letrozole increases live birth rates compared to LOD. In this update, we added good quality trials and removed trials with concerns over data validity, thereby upgrading the certainty of the evidence base.

Implications for research

For letrozole compared to placebo, additional trials are not necessary, since there is evidence in favour of letrozole compared to CC, which was proven to be more effective compared to placebo for live birth and pregnancy rates (Bayar 2006; Dehbashi 2009; Nazik 2012; Sh-El-Arab Elsedeek 2011). Further RCTs could also be conducted, investigating a 5- or 10-day administration protocol and day 3 to 5 or day 5 to 9 administration of letrozole.

Overall, it is very important for fertility trials to report on the standardised core outcome set for fertility trials as suggested by Duffy 2020.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Omari 2004

Study characteristics	
Methods	Randomised double-blind clinical trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** non-fertile clomiphene-resistant women with PCOS **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. Participants had to end clomiphene treatment at least 2 months before enrolment. **Number of centres:** quote: "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." (Email) **Number of women randomised:** 22 in the letrozole group and 18 in the anastrozole group **Number of women analysed:** 22 in the letrozole group and 18 in the anastrozole group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A letrozole: 28.4 ± 5.18, group B anastrozole: 25.56 ± 6.26

Al-Omari 2004 *(Continued)*

	BMI (kg/m²): group A letrozole: 29.95 ± 3.73, group B anastrozole: 27.90 ± 5.29 **Duration of infertility (y):** group A letrozole: 3.95 ± 2.70, group B anastrozole: 4.50 ± 3.61 **Country:** Iraq
Interventions	**Group A:** letrozole 2.5 mg/day orally given for 5 days during cycle days 3-7 **Group B:** anastrozole 1 mg/day orally given for 5 days during cycle days 3-7 Treatment was continued for 3 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 2 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:** quote: "Ethical approval was obtained from the Iraqi Board for medical specialization/Scientific committee" (email contact) **Informed consent:** quote: "written consent was obtained from all patients" (email contact) **Source of funding:** quote: "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 reported We had email contact with Dr Al-Omari, but there was no further information available about the outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Actually, we just put all envelopes in a box, mixing them then the patient herself selected one." (email with Dr Al-Omari)
Allocation concealment (selection bias)	Unclear risk	Quote: "My associate informed me that for randomisation we distributed blank envelops containing the medications at our Gyn.clinic on twice weekly basis." (email 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 plausible 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	None

Amer 2017

Study characteristics	
Methods	Randomised double-blind controlled clinical trial **Duration and location of the trial:** quote: "This study was conducted at the Fertility Unit, Derby Teaching Hospitals NHS Foundation Trust between April 2007 and June 2014."
Participants	**Inclusion criteria:** quote: "eligible participants were women aged 18–39 years with BMI ≤ 35 kg/m2, anovulatory infertility, and a diagnosis of PCOS based on Rotterdam consensus (two of three criteria: oligo-/anovulation, hyperandrogaenemia and sonographic appearance of polycystic ovaries) (Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Diagnosis of oligo-/anovulation was based on a menstrual pattern of oligo-/amenorrhoea (cycle > 35 days) and/or a low mid-luteal serum progesterone concentration. Hyperandrogenaemia was diagnosed either clinically (acne/hirsutism) or biochemically (testosterone ≥ 2.5 nmoL/L or free androgen index [FAI] ≥ 5). Ultrasound criteria included ≥ 12 follicles (2 – 9 mm) and/or an ovarian volume of > 10 ml (Jonard et al., 2003). All participants had proven patency of at least one fallopian tube and normal semen analysis of their male partners (WHO, 1999)." **Exclusion criteria:** quote: "We excluded patients who have received OI within 6 months and those with uncontrolled thyroid disease or hyperprolactinaemia. Patients with marked hyperandrogaenemia were screened for adult onset congenital adrenal hyperplasia (by measuring serum 17- α -hydroxyl-progesterone concentration) and Cushing syndrome (by measuring urinary free cortisol)." **Number of women randomised:** 159 women were randomised in total; 79 to CC, 80 to letrozole **Number of women analysed:** all women randomised were also analysed in the ITT analysis. **Number of withdrawals/exclusions/loss to follow-up and reasons:** 3 women in the CC group discontinued treatment due to failing to attend; also 3 women discontinued treatment in the letrozole arm (1 due to social reasons, 1 failed to attend, 1 withdrew consent). **Number of centres:** this was a single-centre, 2-arm double-blind RCT **Age (y):** letrozole: 28.3 (4.4) versus CC: 28.1 (4.2) **BMI (kg/m^2):** letrozole: 27.5 (23.4-32.2) versus CC: 27.7 (23.0-31.0) **Duration of infertility (y):** 1.5 (1.0-2.0) for both groups **Country:** UK
Interventions	**Group A:** letrozole was prescribed (by the senior investigator, SA) orally daily for 5 days starting on Days 2 – 4 of a menstrual period or a progestogen-induced bleed (medroxy-progesterone acetate 10 mg twice daily for 5 days). The starting dose was 1 tablet/day (letrozole 2.5 mg) and if ovulation was not achieved, the dose would be doubled in the second cycle. **Group B:** CC was prescribed daily for 5 days starting on days 2–4 of a menstrual period or a progestogen-induced bleed (medroxy-progesterone acetate 10 mg twice daily for 5 days). The starting dose was 1 tablet/day (50 mg) and if ovulation was not achieved, the dose would be doubled in the second cycle. Participants who failed to ovulate on the maximum dose (2 tablets) or to conceive after 6 ovulatory cycles were crossed over to the other drug (after a 6-week washout period) following the same procedures as with the first drug.
Outcomes	**Primary outcomes:** clinical pregnancy (diagnosed by ultrasonographic visualisation of a gestational sac) rate per participant on primary treatment (before the cross-over). **Secondary outcomes:** ovulation, live birth, pregnancy by ovulating participant, pregnancy by strata, mono-ovulation, endometrial development (thickness and grades), pregnancy outcome and pregnancy complications.

Amer 2017 *(Continued)*

	Other outcomes included pregnancy and live birth rates on secondary and overall (primary and secondary) treatments.
Notes	**Ethical approval:** the trial was approved by West Midlands Research Ethics Committee (Reference: 07/MRE07/5) and by the Medicines and Healthcare Products Regulatory Agency (MHRA). **Informed consent:** all participants gave written informed consent and the trial was monitored by the sponsor. **Source of funding:** sponsored by the University of Nottingham **Power calculation:** quote: "to detect a clinically significant difference of 20% between the previously reported pregnancy rate of CC (~35%) and letrozole with a two-sided 5% significance level and power of 80%, a sample size of 212 participants (106 per arm) was required (Dickey and Holtkamp, 1996; Kousta et al., 1997; Imani et al., 2002)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent pharmacist randomly allocated participants to letrozole or CC, in 1:1 ratio according to a randomisation list created by the trial statistician using NQuery Advisor v6.0 software. Randomization was stratified by patients' BMI (non-obese < 30 kg/m^2 and obese 30 – 35 kg/m^2) using mixed block sizes."
Allocation concealment (selection bias)	Low risk	Quote: "An independent pharmacist randomly allocated participants to letrozole or CC, in 1:1 ratio."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, patients, outcome assessors and the statistician were blinded to the allocation of participants."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators, patients, outcome assessors and the statistician were blinded to the allocation of participants."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Intention-to-treat (ITT) analysis included all randomised subjects, regardless of whether or not they received the study drug. Per protocol (PP) analysis included all randomised subjects who received the study drug and were not lost to follow-up. Participants who were lost to follow-up were assumed neither to be pregnant nor to have given LB in the ITT analysis."
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Ashfaq 2018

Study characteristics

Methods	Randomised controlled clinical trial **Duration and location of the trial:** conducted in the Department of Obstetrics & Gynecology Unit-I, Services Hospital, Lahore from January to December 2014

Ashfaq 2018 *(Continued)*

Participants	**Inclusion criteria:** age > 18 years but < 30 years; diagnosed PCOS assessed by presence of any two of the following finding (peripherally arranged 2-9 follicles of 8 mm to 10 mm), increase LH and FCH ratio > 2; History of oligomenorrhea i.e. < 6 cycles/year; serum testosterone > 0.65 ng/mL **Exclusion criteria:** endocrine disorders like thyroid disorders assessed by TSH (0.5 IU/L to 5IU/L), T3 (4.3 pmol/L to 8.6 pmol/L) and T4 (9 Pmol/L to 22 Pmol/L), hyperprolactinemia assessed by serum prolectin levels (> 400 miu/L); other causes of anovulatory infertility (kalmann's syndrome, stress, exercise, anorexia nervosa) **Number of centres:** single-centre trial **Number of women randomised:** 40 in the letrozole group and 40 in the CC group **Number of women analysed:** 40 in the letrozole group and 40 in the CC group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** mean age overall group: 23.78 ± 2.41 years **Mean BMI (kg/m^2):** BMI 23.58 ± 2.89 kg/m^2 **Mean duration of infertility (y):** 2.45 ± 0.62 years **Country:** Pakistan
Interventions	**Group A:** 40 women given letrozole, 5 mg for 5 days of menstrual cycle **Group B:** 40 women given CC, 100 mg for 5 days of menstrual cycle
Outcomes	**Primary outcomes:** ovulation rate **Secondary outcomes:** none
Notes	**Ethical approval:** not stated **Informed consent:** quote: "Informed consent was taken to include their data in study." **Source of funding:** not stated **Power calculation:** quote: "Eighty cases (40 in each group) is calculated using 95% confidence interval. 80% power of test with an expected percentage of efficacies of letrozole group is 63.3% and 29.4% in clomiphene citrate group. Non-probability, purposive sampling technique was used."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported in detail, quote "patients were divided in two groups randomly by lottery method".
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

Ashfaq 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were also analysed
Selective reporting (reporting bias)	Unclear risk	Protocol of the trial was not available
Other bias	High risk	The power calculation implies a very strong effect in favour of letrozole compared to CC and exactly reflects the results of the trial.

Atay 2006

Study characteristics	
Methods	Randomised controlled clinical trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** women with primary infertility and PCOS with no other known cause of infertility were enrolled in the trial. All participants had a history of oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2 mm to 10 mm in diameter and hyperechogenic stroma. **Exclusion criteria:** none declared **Number of centres:** setting unknown, tried to contact authors via email **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/m^2):** group A letrozole: 26.1 ± 1.9, group B CC: 25.8 ± 1.8 **Duration of infertility (y):** group A letrozole: 2.2 ± 0.7, group B CC: 2.4 ± 0.9 **Country:** Turkey
Interventions	**Group A:** letrozole, 2.5 mg/day orally given for 5 days starting on cycle day 3 **Group B:** CC, 100 mg/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 trial protocol was approved by the institutional ethics committee **Informed consent:** yes, informed consent was obtained from all trial participants **Source of funding:** not stated **Conflicts of interest:** quote: “Conflicts of interest: No conflicts of interest were declared in relation to this article” **Power calculation:** not stated We contacted Dr V Atay via email about the trial setting, about how randomisation and allocation were done, blinding and if data are available on OHSS, miscarriage rate and live birth rate, but no response.

Atay 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how it was done
Allocation concealment (selection bias)	Unclear risk	Unclear how it was done
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)	Unclear risk	Protocol of the trial was not available
Other bias	Low risk	None

Bayar 2006

Study characteristics

Methods	Randomised controlled trial **Duration and location of the trial:** quote: "During the study period of 2004 through 2005, 80 patients with PCOS who attended the outpatient clinics of the Infertility and Reproductive Medicine Unit of the Zonguldak Karaelmas University Hospital (Zonguldak, Turkey) participated in this study.“
Participants	**Inclusion criteria:** women with anovulatory PCOS diagnosed 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:** 1, 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 letrozole and 40 in group B CC **Number of women analysed:** 38 in group A letrozole 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 CC: 30.6 ± 4.0 **BMI (kg/m²):** not stated **Duration of infertility (y):** group A letrozole: 5 (1-10), group B CC: 3 (3-11)

Bayar 2006 *(Continued)*

	Country: Turkey
Interventions	**Group A:** letrozole, 5 mg/day orally given for 5 days during cycle days 3-7 **Group B:** CC, 100 mg/day orally given for 5 days during cycle days 3-7
Outcomes	**Outcomes:** ovulation rate by cycle, pregnancy rate by cycle, delivery rate by cycle, miscarriage rate (abortion), multiple pregnancy rate, endometrial thickness on the day of hCG (mm), N 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 trial 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 participants (30 in each group) was targeted to be able to detect a difference of at least one follicle or of 200 pmol/L between the 2 groups, with alfa (type I error) set at 0.05 and 80% power. We contacted Dr Bayar by email 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 participants.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind but it is not clear who was actually blinded and how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double-blind but it is not clear who was actually blinded and how this was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants lost to follow-up, 4 and 2 respectively
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Begum 2009

Study characteristics

Methods	Randomised non-blinded controlled trial

Begum 2009 *(Continued)*

	Duration and location of the trial: quote: "The study was conducted in a private infertility care setting as a randomized controlled trial between August 2004 and December 2005.“
Participants	**Inclusion criteria:** infertile women with PCOS diagnosed by the Rotterdam criteria 2003 who failed to ovulate by taking 100 mg of CC/day for 5 days in 2 consecutive cycles **Exclusion criteria:** women 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 trial. **Number of centres:** 1, private infertility care setting **Number of women randomised:** 32 in each group **Number of women analysed:** 32 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A letrozole: 25.5 ± 4.0, group B CC: 26.1 ± 3.6 **BMI (kg/m^2):** group A letrozole: 22.7 ± 2.8, group B CC: 23.6 ± 3.2 **Duration of infertility (y):** group A letrozole: 2.7 ± 1.1, group B CC: 2.6 ± 1.1 **Country:** India
Interventions	**Group A:** letrozole, 7.5 mg/day orally given for 5 days from cycle days 3-7 **Group B:** CC, 150 mg/day orally given for 5 days from cycle days 3-7
Outcomes	**Primary outcomes:** ovulation and pregnancy rate **Secondary outcomes:** follicular development by day 16 (mm), serum E2 on day of hCG (pg/mL), endometrial development by day 16 (mm), serum progesterone on day 21 (ng/mL), multiple pregnancies, OHSS cases. Live birth rate was provided by email contact.
Notes	**Ethical approval:** yes, the trial protocol was approved by the institutional review board (IRB) of Dhaka medical college. **Informed consent:** yes, participants were counselled and informed consent was obtained before recruitment. **Source of funding:** the trial was self-funded. **Power calculation:** a trial 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. Authors were contacted by email, and additional information was provided.

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 opaque envelope. By calculating sample size they made 64 pieces of paper, 32 for letrozole and 32 for CC.
Allocation concealment (selection bias)	Unclear risk	Quote: "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." (by email contact with Prof Rashida)

Begum 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "There was no blinding" (by email contact with Prof Rashida)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "There was no blinding" (email 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	None

Behnoud 2019

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** quote: "The present randomized clinical trial was conducted in Ali ibn Abitaleb hospital, Zahedan University of Medical Sciences, during 2016-2017."
Participants	**Inclusion criteria:** the statistical population consisted of 80 patients aged 18-40 years old with PCOS referring to the Infertility Clinic of Hospital and were diagnosed as infertile in the context of PCOS. The inclusion criteria were: normalisation of thyroid function tests and prolactin, having at least one healthy fallopian tube and normal uterine cavity, normalisation of the patient's semen analysis, and a 1-year history of infertility with respect to regular sexual intercourse (2 to 3 times per week) without contraception. **Exclusion criteria:** thyroid dysfunction and high prolactin, tubal dysfunction, uterus factor, impaired semen analysis of the patient's partner and using medications such as metformin, previous history of using clomiphene or letrozole and underlying medical problems such as renal and pulmonary diseases, diabetes, and antiphospholipid syndrome. **Number of centres:** single-centre trial **Number of women randomised:** 40 in each group **Number of women analysed:** 40 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Mean age (y):** CC and letrozole groups 29.85 ± 6.39 and 29.92 ± 6.97 years, respectively. **Mean BMI (kg/m^2):** CC and letrozole groups 24.82 ± 3.38 kg/m2 and 25.55 ± 3.49 kg/m2, respectively. **Duration of infertility (y):** quote: "The mean and standard deviation of the duration of infertility in the clomiphene-receiving group was 5.62 ± 3.95 years, varying at least from 2 to 15 years, compared to the mean and standard deviation of the duration of infertility in the letrozole group which was 4.07 ± 4.77 years, varying from at least 1 to maximum 15 years." **Country:** Iran

Behnoud 2019 *(Continued)*

Interventions	**Group A:** CC group, patients received 100 mg of clomiphene daily (2 x 50 mg tablets daily based on infertility literature) during the third to seventh days of the menstrual cycle for 5 days. **Group B:** letrozole group, 5 mg (equivalent to 2 x 2.5 mg tablets based on infertility literature) were received daily for 5 days from the third to seventh days of the menstrual cycle.
Outcomes	**Primary outcomes:** ovulation rate based on ultrasound monitoring; pregnancy rate based on serum BHCG 12 days after ovulation
Notes	**Ethical approval:** yes, quote: "The ethical code (IR.ZAUMS.REC.1395.47) was obtained from the Ethics Committee of the University and the trial was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20180602039952N2)." **Informed consent:** yes, participants were counselled and informed consent was obtained before recruitment. **Source of funding:** the trial was self-funded. **Power calculation:** a trial 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. Authors were contacted by email, and additional information was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After obtaining informed consent, easy and accessible sampling and blocked randomisation, patients were divided into two groups of 40 and were treated with letrozole or CC."
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	All participants randomised were also analysed.
Selective reporting (reporting bias)	Low risk	No trial protocol was found, but all outcomes reported were also analysed.
Other bias	Low risk	None

Chen 2016

Study characteristics

Methods	Randomised controlled trial

Chen 2016 *(Continued)*

	Duration and location of the trial: quote: "All patients were admitted in our hospital between January 2013 and January 2015, who were not pregnant without contraception for over one year.“
Participants	**Inclusion criteria:** quote: "all the cases were PCOS infertility patients in line with the PCOS diagnostic criteria of the 2003 Rotterdam Conference, i.e. at least two of the following three were met: 1) ovulation abnormality (sporadic ovulation or no ovulation) occurred after continuous monitoring for two or more natural cycles; 2) the results of B ultrasound showed polycystic ovary; 3) patients had hyperandrogenism or showed clinical manifestations of androgen excess. Through salpingography or hydrotubation under transvaginal B ultrasound and other examinations, all cases were confirmed to have tubal patency on at least one side. The semen of male was normal." **Exclusion criteria:** quote:"Those with androgen excess caused by other diseases such as adrenal hyperplasia Cushing’s syndrome and androgen-secreting tumours were excluded. Exclusion criteria: 1) Infertility patients caused by non-PCOS ovulatory disorder or other factors; 2) patients with history of ovarian surgery or complication with endometriosis or pelvic adhesion; 3) patients complicated with liver, kidney or thyroid dysfunction; 4) patients who did not receive treatment after enrolment according to the established regimen or gave up in the midst of treatment." **Number of women randomised:** 156 patients, 52 in each group **Number of women analysed:** 156 patients, 52 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** none reported **Number of centres:** single-centre trial **Age (y):** letrozole group 26.4 ± 4.2; CC group 27.1 ± 4.7; letrozole + hMG group 27.7 ± 5.2 years **BMI (kg/m^2):** letrozole group 22.4 ± 4.5; CC group 23.4 ± 1.5; letrozole + hMG group 22.6 ± 2.6 years **Duration of infertility (y):** letrozole group 3.4 ± 1.1; CC group 3.2 ± 0.7; letrozole + hMG group 3.3 ± 1.3 years **Country:** China
Interventions	**Group A (letrozole):** the participants orally took 2.5 mg/d-1 to 5.0 mg/d-1 letrozole (trade name: Fu Rui, Jiangsu Hengrui Medicine Co, Ltd.) on the 3rd - 5th days of menstrual cycle for 5 consecutive days. **Group B** (**CC group):** the participants were orally administered with 50 mg/d-1 to 100 mg/d-1 CC (trade name: Fertilan, Codal Synto Pharmaceutical Co, Ltd.) on the 3rd - 5th days of menstrual cycle for 5 consecutive days. **Group C(letrozole + hMG group):** the participants orally took 2.5 mg/d-1 to 5.0 mg/d-1 letrozole on the 3rd - 5th days of menstrual cycle for 5 consecutive days. Starting from the day of oral administration of CC, 75 IU hMG (trade name: Lebaode, Livzon Group Livzon Pharmaceutical Co. Ltd.) was intramuscularly injected every other day for 5 consecutive days.
Outcomes	**Primary outcomes:** clinical pregnancy, defined as a foetal heart beat visible via transvaginal ultrasound on 30th day after ovulation **Secondary outcomes:** OHSS, miscarriage (abortion), multiple pregnancy
Notes	**Ethical approval:** this trial has been approved by the ethics committee of our hospital. **Informed consent:** written consent has been obtained from all patients. **Source of funding:** quote: “None” **Power calculation:** no power calculation was reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

Chen 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: “the patients were randomly divided into an LE group, a CC group and an LE + hMG group”
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	All participants randomised were also analysed.
Selective reporting (reporting bias)	Low risk	No trial protocol was found, but all outcomes reported were also analysed.
Other bias	Low risk	None

Davar 2011

Study characteristics	
Methods	Single-blind randomised clinical trial **Duration and location of the trial:** quote: "In this single blind randomized trial, 148 ovarian cycles were studied in 100 clomiphene- resistance patients with PCOS who were chosen among 250 PCOS patients attending the Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran during the years 2007-2008.“
Participants	**Inclusion criteria:** women who received 150 mg CC daily for 3 cycles and failed to become pregnant, and were diagnosed with anovulatory PCOS based on Rotterdam 2003. **Exclusion criteria:** quote: “We excluded patients with liver and kidney dysfunction, cardiovascular disease, diabetics, and those who use metformin or drugs affecting insulin secretion and CC in recent 2 cycles.” **Number of centres:** 1, research and clinical centre for infertility, Shahid Sadoughi University of Medical Sciences, Yazd **Number of women randomised:** 100 women, 50 in group A metformin-letrozole, 50 in group B metformin-CC **Number of women analysed:** 48 in group A metformin-letrozole, 50 in group B metformin-CC **Number of withdrawals/exclusions/loss to follow-up and reasons:** 2, experienced side effects with metformin before letrozole was started **Age (y):** group A metformin-letrozole: 28.5 ± 3.1, group B metformin-CC: 29.6 ± 3.5 **BMI (kg/m^2):** group A metformin-letrozole: 29.0 ± 3.8, group B metformin-CC: 29.2 ± 2.9 **Duration of infertility (y):** group A metformin-letrozole: 3.8, group B metformin-CC: 3.8

Davar 2011 *(Continued)*

	Country: Iran
Interventions	**Group A:** metformin 1500 mg daily for 6-8 weeks, followed by 5 mg letrozole daily orally given for 5 days during cycle days 3-7 if pregnancy did not occur **Group B:** metformin 1500 mg daily for 6-8 weeks, followed by 100 mg CC daily orally given for 5 days during cycle days 3-7 if pregnancy did not occur
Outcomes	E2 (pg/mL) on day of hCG administration, number of follicles > 18 mm in diameter, endometrial thickness on day of hCG administration (mm), clinical pregnancy rate, miscarriage rate (abortion)
Notes	**Ethical approval:** yes, the trial was approved by ethical board of Shahid Sagoughi University of Medical Sciences, Yazd. **Informed consent:** no, at least nothing written about it – authors contacted **Source of funding:** quote: “the study was fully supported and funded by Shahid Sadoughi University of Medical Sciences, Yazd, Iran” **Power calculation:** quote: "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%" We contacted Dr Davar by email to get additional information, but we did not get a response.

Risk of bias

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 participants 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	None

Dehbashi 2009

Study characteristics	
Methods	Double-blind randomised trial

Dehbashi 2009 *(Continued)*

	Duration and location of the trial: quote: "During the period of February 2004 through November 2006, 100 patients with PCOS who attended the outpatient infertility clinics at Shiraz University of Medical Sciences participated in the present study.“
Participants	**Inclusion criteria:** infertility for at least 1 year, diagnosis of PCOS by the Rotterdam criteria 2003, having patent tubes on hysterosalpingogram, and normal semen analysis of the husband **Exclusion criteria:** participants must not have received any other medication for ovulation induction before enrolment into the trial. **Number of centres:** 1, outpatient infertility clinics at Shiraz University of Medical Sciences **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: 23.6 ± 2.9, group B CC: 24.3 ± 3.4 **BMI (kg/m^2):** group A letrozole: 27.5 ± 4.6, group B CC: 27.1 ± 3.6 **Duration of infertility (y):** group A letrozole: 2.0 ± 1.3, group B CC: 2.3 ± 1.9 **Country:** Iran
Interventions	**Group A:** letrozole, 5 mg/day orally given for 5 days during cycle days 3-7 **Group B:** CC, 100 mg/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 (abortion), multiple pregnancy rate, live birth rate
Notes	**Ethical approval:** yes, quote: “The study was approved by the Institutional Ethics Committee of the University.” **Informed consent:** yes, quote: “An informed written consent was obtained from each patient” **Source of funding:** not stated **Conflicts of interest:** quote: "Conflicts of interest: None declared" **Power calculation:** not stated Authors contacted about randomisation, allocation, and information about OHSS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated how it was done
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 participants.
Blinding of outcome assessment (detection bias)	Low risk	Only the pharmacist knew the name of the medication that had been taken by the participants.

Dehbashi 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants excluded or lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Elgafor 2013

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** CC-resistant women with infertility due to PCOS, diagnosed according to the Rotterdam 2003 criteria. CC resistance was defined as failure to achieve adequate follicular maturation after 3 consecutive induction cycles with CC at 150 mg/day for 5 days. **Exclusion criteria:** exclusion criteria include women with other causes of infertility such as male factor or tubal factor, those with endocrine disorders such as thyroid dysfunction and hyperprolactinaemia, women who received hormonal treatment or ovulation induction drugs 3 months before the trial **Number of centres:** 1, Zagazig University Hospital, Egypt **Number of women randomised:** 146 women, 73 in each group **Number of women analysed:** 146 women, 73 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A metformin + letrozole: 24.7 ± 1.8, group B LOD: 25.1 ± 2.1 **BMI (kg/m^2):** group A metformin + letrozole: 31.5 ± 3.3, group B LOD: 32.4 ± 4.4 **Duration of infertility (y):** group A metformin + letrozole: 3.4 ± 0.9, group B LOD: 3.9 ± 1.1 **Country:** Egypt
Interventions	**Group A:** metformin 850 mg to 1700 mg daily for 6-8 weeks, followed by 5 mg letrozole daily orally given for 5 days during cycle days 3-7 if pregnancy did not occur **Group B:** LOD, laparoscopy was performed using 3-puncture technique.
Outcomes	Cycle regularity, ovulation rate, clinical pregnancy rate, miscarriage rate
Notes	**Ethical approval:** yes, quote: “Ethics Committee of Zagazig University approved the study" **Informed consent:** yes, quote: “written informed consent was obtained from each patient at the start of the study” **Source of funding:** not stated **Conflicts of interest:** quote: "conflicts of interest: none" **Power calculation:** not stated

Elgafor 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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 participants 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	None

El-Gharib 2015

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** quote: "This prospective intervention study was performed during the period from January 2010 till August 2012 at the outpatient clinic of Tanta University Hospital.“
Participants	**Inclusion criteria:** the most important inclusion criteria were fulfilment of at least 2 of Rotterdam criteria of PCOS, negative history of medical problems that can affect fertility such as diabetes mellitus, thyroid dysfunction, hyperprolactinaemia, congenital adrenal hyperplasia, normal hysterosalpingography and BMI between 20 and 30. **Exclusion criteria:** history of medical problems which affect fertility, history of recent hormonal therapy, having pelvic infections and/or having abnormal laboratory findings other than PCOS findings. Women whose husbands had defective semen were also excluded. **Number of women randomised:** 60 participants, 30 in each group **Number of women analysed:** 60 participants analysed **Number of withdrawals/exclusions/loss to follow-up and reasons:** no participants were lost to follow-up. **Number of centres:** 1, single-centre trial **Age (y):** letrozole 26.2 ± 0.9; tamoxifen 26.9 ± 1.1

El-Gharib 2015 *(Continued)*

	BMI (kg/m²): letrozole 27.7 ± 4.1; tamoxifen 28.4 ± 3.8 **Duration of infertility (y):** letrozole 3.2 ± 2.7; tamoxifen 3.0 ± 2.1 **Country:** Egypt
Interventions	**Group A:** letrozole (Femara; Novartis) 2.5 mg/day given from day 5-9 of the menstrual cycle, for 3 successive cycles **Group B:** tamoxifen 20 mg/day given from day 5-9 of the menstrual cycle, for 3 successive cycles
Outcomes	Pregnancy rate, follicular growth, endometrial thickness, cumulative ovulation
Notes	**Ethical approval:** the trial was approved by the institutional ethics committee of Tanta Faculty of Medicine. **Informed consent:** all women subjected to history taking, physical examination, counselling and signing a written consent **Source of funding:** not reported **Power calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of randomisation were not sufficiently described: quote: "arranged at random, by sealed envelopes"
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	60 participants were randomised and analysed.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

El-Khayat 2016

Study characteristics

Methods	Randomised double-blind controlled trial

El-Khayat 2016 *(Continued)*

	Duration and location of the trial: quote: "A prospective double-blind randomized controlled trial was conducted at the Teaching University Hospital of Cairo University, Cairo, Egypt, between August 1, 2013, and December 31, 2014."
Participants	**Inclusion criteria:** quote: "eligible women were younger than 40 years, had primary or secondary infertility associated with PCOS, and had not ovulated in response to three cycles of 150 mg CC every day for 5 days from day 3 of the menstrual cycle. PCOS diagnoses were based on the revised 2003 Rotterdam consensus criteria. The presence of at least two of the following characteristics was considered diagnostic of PCOS: oligo ovulation or anovulation; hyperandrogenism; and polycystic ovaries detected using vaginal ultrasonography." **Exclusion criteria:** quote: "exclusion criteria were other factors of infertility, diabetes mellitus, hypertension, liver or kidney malfunction, heart disease, urinary symptoms, persistent hyperprolactinaemia, thyroid dysfunction, gonadotropin induction, and previous ovarian drilling. Male factor infertility was defined as a sperm count of less than 15 × 10^6/mL, a total motility of less than 40%, or normal morphology of less than 4%. Tubal factor infertility was confirmed by hysterosalpingography." **Number of women randomised:** 100 women were randomised. **Number of women analysed:** 100 women were analysed, 50 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** none **Number of centres:** single centre **Age (y):** CC 26.6 ± 2.9; letrozole 25.8 ± 3.6 **BMI (kg/m²):** CC 26.6 ± 2.7; letrozole 26.5 ± 2.8 **Duration of infertility (y):** CC 3.1 ± 1.4; letrozole 2.7 ± 1.6 **Country:** Egypt
Interventions	**Group A:** (control group) received 100 mg CC, given as 2 x 50 mg tablets daily for 5 days from the third day of the menstrual cycle. **Group B:** 5 mg letrozole, given as 2 x 2.5 mg tablets daily for 5 days from the third day of the menstrual cycle. Participants in both groups also received metformin and pioglitazone, which was taken daily as 1 tablet containing 850 mg metformin and 15 mg pioglitazone, for 10 days starting from the first day of the menstrual cycle.
Outcomes	**Primary outcomemeasure**: cumulative ovulation rate (proportion of cycles in which ovulation occurred in the whole follow-up period). **Other outcome measures**: number of follicles ≥ 18 mm in size, endometrial thickness and serum estradiol levels on the day of hCG administration, serum progesterone level on day 21, and rate of clinical pregnancy (at least 1 intrauterine gestational sac detected)
Notes	**Ethical approval:** approved by the research ethics committee of the teaching University Hospital of Cairo University **Informed consent:** all participants signed a written informed consent form. **Source of funding:** Cairo University **Power calculation:** previous data indicated that the ovulation rate in group A would be 62%. If the ovulation rate for the letrozole, metformin, and pioglitazone (experimental) group was 87% (previous unpublished data from the trial unit), a total of 47 women would have to be recruited to each group to ensure a sufficiently powered trial. Assuming an attrition of 10%, the total number of patients to be recruited was 50 per group. ITT analyses were planned.

El-Khayat 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Enrolled women were randomly allocated using computer-generated random number tables (block size four)"
Allocation concealment (selection bias)	Low risk	Quote: "Opaque sealed envelopes containing group allocations were prepared at a separate location every 24 hours. These envelopes were sent to an assigned nurse, who opened them before commencing ovulation induction"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, the staff who conducted follow-up, and data analysts were masked to the allocation to avoid bias"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, the staff who conducted follow-up, and data analysts were masked to the allocation to avoid bias"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	None

Foroozanfard 2011

Study characteristics	
Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "This clinical trial was performed on 120 infertile women with PCOS who attended in the outpatient infertility clinic in Kashan, Iran during 2008."
Participants	**Inclusion criteria:** quote: "Our inclusion criteria were age 20-35 years, infertility for at least one year and resistance to Clomiphene (at least 3 cycles Clomiphene usage, 150 mg/day with no ovulatory response)" **Exclusion criteria:** exclusion criteria were BMI > 27, endocrine disorders such as hypothyroidism, hyperprolactinaemia, infertility due to male factors, uterine factors and adhesive diseases due to pelvic surgery. **Number of centres:** 1, 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 letrozole + hMG: 25.8 ± 3.8, group B CC + hMG: 25.3 ± 4.1 **BMI (kg/m^2):** group A letrozole + hMG: 24.1 ± 2.3, group B CC + hMG: 24.9 ± 2.0

Foroozanfard 2011 *(Continued)*

	Duration of infertility (y): group A letrozole + hMG: 2.8 ± 2.3, group B CC + hMG: 2.6 ± 2.1 **Country:** Iran
Interventions	**Group A:** letrozole, 5 mg/day orally given for 5 days from cycle days 3-7 + 150 IU hMG intramuscularly during cycle days 5-8 **Group B:** CC, 100 mg/day orally given for 5 days from cycle days 3-7 + 150 IU hMG intramuscularly during cycle days 5-8
Outcomes	Live birth rate, OHSS rate, pregnancy rate, miscarriage rate, multiple birth rate, number of dominant follicles, endometrial thickness (mm), ectopic pregnancies
Notes	**Ethical approval:** yes, quote: ”approval was obtained from the Institute Research Board to perform this study.“ **Informed consent:** yes, quote: “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, quote: “Authors acknowledge the research deputy of Kashan University of Medical Sciences for providing the financial support.” **Power calculation:** not stated Authors contacted by email, all information provided

Risk of bias

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	By sequentially-numbered opaque sealed envelopes (email with authors)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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." (email 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	None

Ganesh 2009

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** not stated
Participants	**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. Specific inclusion criteria for the trial were normal TSH and prolactin levels and normozoospermic male partners as per WHO guidelines. **Exclusion criteria:** women with pre-existing ovarian cyst on day 3 and previous history of ovarian drilling were excluded. **Number of centres:** 1, a tertiary infertility care unit, Institute of Reproductive Medicine, Kolkata, India **Number of women randomised:** 1378 **Number of women analysed:** 1378 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A letrozole: 30.3 ± 4.9, group B CC: 30.4 ± 5.2, group C rFSH: 30.8 ± 4.6 **BMI (kg/m^2):** group A letrozole: 24.5 ± 3.8, group B CC: 24.8 ± 4.1, group C rFSH: 24.1 ± 3.4 **Duration of infertility (y):** not reported **Country:** India
Interventions	**Group A:** letrozole, 5 mg/day orally given for 5 days from cycle days 3-7 **Group B:** CC, 100 mg/day orally given for 5 days from cycle days 3-7 + 75 or 100 IU rFSH during cycle days 3 and 8. **Group C:** rFSH 75IU/100IU from day 2 until the day of hCG administration
Outcomes	**Primary outcomes:** ovulation rate, cancellation rate, miscarriage rate and pregnancy rate **Secondary outcomes**: OHSS rate and multiple pregnancy rate.
Notes	**Ethical approval:** yes, approval was obtained from the institutional Research Ethics Board. **Informed consent:** yes, quote: “Written informed consent was taken from all women included in this study.” **Source of funding:** quote: "This study was not funded by any funding agency.” **Power calculation:** not stated Authors contacted by email, all information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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 by email from the author)

Ganesh 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "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	Quote: "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	Quote: "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	None

Ghahiri 2016

Study characteristics	
Methods	Randomised controlled clinical trial **Duration of the trial:** quote: "This was a randomized prospective clinical trial, including consecutive women with primary or secondary infertility due to PCOS from Jan 2009 to Sept 2011."
Participants	**Inclusion criteria:** the major criteria for diagnosis of PCOS were oligo- and/or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries, in accord with the revised 2003 Rotterdam criteria of PCOS. Thyroid function, prolactin level, and husband's sperm analysis were checked for normal values. **Exclusion criteria:** women with other causes of infertility, infertility < 1 year, and those who had previous treatment(s) for infertility were not included in the trial. **Number of women randomised:** 103; 51 to group A (CC), 52 to group B (letrozole) **Number of women analysed:** 50 participants in group A, 51 in group B **Number of withdrawals/exclusions/loss to follow-up and reasons:** 2 participants, 1 from each group lost to follow-up due to no show **Number of centres:** single-centre trial **Age (y): n**o mean age reported for the treatment groups **BMI (kg/m^2):** group A 27.1 ± 4.9; group B 28.2 ± 5.2 **Duration of infertility (y):** no means reported **Country:** Iran
Interventions	**Group A:** CC 100 mg for 5 days starting from day 3 of their menstrual cycle **Group B:** letrozole 5 mg for 5 days from day 3 of their menstrual cycle

Ghahiri 2016 *(Continued)*

	Both groups were advised to have intercourse on days 11, 13, and 15 of their menstrual cycles.
Outcomes	Pregnancy rate, miscarriage rate, multiple pregnancies, ectopic pregnancies, OHSS rate
Notes	**Ethical approval:** the protocol was approved by the ethical investigation committee of the institution **Informed consent:** informed consent was obtained from all the participants after full informative session. **Source of funding:** not reported **Power calculation:** quote: "based on our statistical data, the fair needed number for performing this study was 50 per group (the sample size was calculated by considering z, p, and d as 1.96, 0.15, and 0.1, respectively)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	All candidates were randomised based on envelope method into either CC group (group A, n = 51) or letrozole group (group B, n = 50)
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	2 of 103 participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	None

Ghomian 2015

Study characteristics	
Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "The study was performed from March to November 2010 at the Mashhad IVF center, a university based infertility center.“
Participants	**Inclusion criteria:** based on Rotterdam criteria, 70 women with PCOS were enrolled in this randomised clinical trial. The diagnosis of PCOS was made when 2 of the following 3 criteria existed: oligomenorrhoea or amenorrhoea, clinical hyperandrogenism, and polycystic ovaries on ultrasonography. The inclusion criteria were as follows: i. previous diagnosis of PCOS according to Rotterdam criteria, ii. age between 20 and 30 years, iii. no previous history of ovarian surgery, and iv. lack of ovulation with CC in

Ghomian 2015 *(Continued)*

	at least 3 previous cycles (lack of follicle ≥ 18 mm on ultrasound scan). The woman's age, her partner's age, duration of infertility, type of infertility (primary and secondary), history of previous intrauterine insemination (IUI) cycles, pattern of ovary (PCO and non-PCO), pattern of menstruation (regular, oligomenorrhoea and amenorrhoea), BMI and basal LH/FSH ratio were recorded for each participant. **Exclusion criteria:** the exclusion criteria were as follows: i. no other infertility factors, ii. exposure to cytotoxic drugs and iii. pelvic radiation therapy. **Number of women randomised:** 70 **Number of women analysed:** 69 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 1 patient discontinued treatment in group B **Number of centres:** single-centre trial **Age (y):** group A: 25.3 ± 4.4, group B: 25.6 ± 3.5 **BMI (kg/m²):** group A: 27.0 ± 3.8, group B: 26.4 ± 4.8 **Duration of infertility (y):** number of previous treatment cycles (CC): group A: 1.1 ± 0.4, group B: 1.3 ± 0.5 **Country:** Mashhad, Iran
Interventions	**Group A:** group A (n = 35) receiving 5 mg letrozole (Letrofem; Iran Hormone, Iran) on cycle days 3-7 **Group B:** group B (n = 35) receiving the same amount on cycle days 5-9
Outcomes	The cycle characteristics, the ovulation and pregnancy rate
Notes	**Ethical approval:** this trial was approved by Ethical Committee of Mashhad University of Medical Sciences. **Informed consent:** a written informed consent was taken from all women participating in this trial. **Source of funding:** not reported **Power calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
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)	Low risk	1 participant was excluded from analysis due to discontinuation of treatment

Ghomian 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	None

Hassan 2017

Study characteristics	
Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "This was a balanced, randomized (allocation ratio 1:1), parallel group trial conducted in Cairo and Beni-Suef University Hospitals from May 2013 to January 2015."
Participants	**Inclusion criteria:** women included in the trial had CC-resistant PCOS, and were aged 20–40 years. PCOS was diagnosed according to the Rotterdam 2003 criteria. CC resistance was defined as failure of ovulation despite receiving 150 mg of CC for 5 days during successive menstrual cycles for 3 months. **Exclusion criteria:** other causes of infertility, BMI> 35 kg/m^2, hyperprolactinaemia, allergy to FSH, and previous use of FSH or letrozole therapies. **Number of women randomised:** 140, 70 to each group **Number of women analysed:** 140, 70 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 3 women in the letrozole group and 2 women in the uFSH group were lost to follow-up; ITT analysis was adopted in which these participants were considered anovulatory in the 3 cycles. **Number of centres:** 2-centre trial **Age (y):** letrozole group 28.7 ± 6.2, uFSH group 30.0 ± 5.6 **BMI (kg/m^2):** letrozole group 27.6 ± 4.1, uFSH group 27.2 ± 3.8 **Duration of infertility (y):** letrozole group 4.9 ± 2.1, uFSH group 5.2 ± 2.2 **Country:** Cairo University and Beni-Suef University Hospitals, Egypt
Interventions	**Group A:** quote: "group 1 received letrozole (Femara VR, Novartis, Basel, Switzerland) 2.5 mg twice daily for five days starting from the third day of menstruation or progesterone withdrawal bleeding." **Group B:** quote: "group 2 received uFSH (Fostimon VR IBSA, Geneva, Switzerland). To minimize the risk of multiple pregnancy and OHSS, we used a low-dose FSH setup regimen. The starting daily dose of uFSH was 75 IU for seven days starting from the third day of menstruation or progesterone withdrawal bleeding. If the follicular diameter did not exceed 9 mm, the daily dose was increased by 37.5 IU every seven days. The cycle was cancelled if no follicles exceeded 9 mm by four weeks after starting FSH."
Outcomes	Cumulative clinical pregnancy, defined as the presence of an intrauterine gestational sac 5 weeks after timed intercourse Secondary outcomes were ovulation, miscarriage and possible drug side effects, i.e. OHSS, headache, dizziness, hot flushes, nausea, vomiting or constipation
Notes	**Ethical approval:** the trial was approved by the research ethics committees of both institutions. **Informed consent:** written informed consent was obtained

Hassan 2017 *(Continued)*

Source of funding: quote: "The study was self-funded"

Power calculation: quote: "The required sample size was estimated using PS Power and Sample Size Calculations software, version 3.0.11 for Microsoft Windows. We needed to study 64 women receiving letrozole and 64 women receiving uFSH for three cycles to be able to reject the null hypothesis that the pregnancy rates for letrozole and uFSH in CC-resistant women were equal, with a probability (power) of 0.9."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent individual generated the allocation sequence using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation was concealed using sequentially-numbered opaque sealed envelopes
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	All participants randomised were also analysed
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	None

Hendawy 2011

Study characteristics

Methods	Randomised controlled clinical trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** quote: "infertile patients (defined as one year of unprotected coitus without conception in patients who have never conceived before) with PCOS, aged younger than 35 years, and attending the infertility out- patient clinic at Ain Shams University Hospital and/or a local private outpatient setting. Diagnosis of PCOS was based on the Rotterdam criteria (2003 ESHRE/ASRM consensus), whereby patients diagnosed with PCOS require the presence of two of three criteria, i.e., oligomenorrhoea and/or anovulation, clinical and/ or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound. All patients had a history of failed induction of ovulation with appropriately timed intercourse at least 4–6 times." **Exclusion criteria:** women with infertility due to uterine and tubal pathologies or male factor **Number of women randomised:** 60 women with primary infertility **Number of women analysed:** 54 women were analysed, 28 in group 1 (letrozole) and 26 in group 2 (CC)

Hendawy 2011 *(Continued)*

	Number of withdrawals/exclusions/loss to follow-up and reasons: during folliculometry, 2 participants in Group 1 and 4 participants in Group 2 showed no follicular response and were excluded from the trial. **Number of centres:** 2-centre trial **Age (y):** group 1 included 30 women aged 21–34 (mean ± SD, 27.2 ± 5.18) years, group 2 included 30 women aged 20–33 **BMI (kg/m²):** group 1 included 30 women with a BMI of 24–31 (26.2 ± 1.8). Group 2 included 30 women with a BMI of 23–32 (29.1 ± 2.3) **Duration of infertility (y):** mean duration of infertility not reported **Country:** Egypt
Interventions	**Group A:** group 1 included 30 women who were given letrozole (Femara, Novartis, Basel, Switzerland) orally at a dose of 2.5 mg once daily on days 3-7 of the menstrual cycle. **Group B:** group 2 included 30 women who were given CC (Clomid, Sano Aventis, France) 50 mg orally twice daily on days 3–7 of the menstrual cycle.
Outcomes	Pregnancy rate, multiple pregnancy rate, number of follicles on hCG administration day, endometrial thickness
Notes	**Ethical approval:** the trial was approved by the medical ethics committee of Ain Shams University Hospital. **Informed consent:** obtained from all participants **Source of funding:** not reported **Power calculation:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated programme
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind randomised, but not reported how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind randomised, but not reported how blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/60 participants were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No trial protocol was found

Hendawy 2011 *(Continued)*

Other bias	Unclear risk	None

Ibrahim 2017

Study characteristics	
Methods	Randomised controlled trial **Duration of the trial:** quote: "The study was conducted during the period from 1st August 2015 to 30th March 2016.“
Participants	**Inclusion criteria:** quote: "age >20 and <35 years old, patients were diagnosed to have PCOS criteria of diagnosis of PCO. Normal HSG and their partners had normal semen analysis according to WHO criteria (WHO, 2010) and CC-resistant. If patients fail to respond to 150 mg/day for 5 days for 3 consecutive cycles, they are considered as CC-resistant." **Exclusion criteria:** quote: "Age less than 20 yr or more than 35 yr, non-PCOS, and those Patients with poor ovarian reserve i.e. hyperprolactinaemia, hypo and hyperthyroidism, diabetic patients and Cushing's syndrome were excluded, non-classical congenital adrenal hyperplasia, current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, antidiabetic or antiobesity drugs, or other hormonal drugs, any subject was affected by either neoplastic, metabolic, hepatic, or cardiovascular disorder or other concurrent medical illness (i.e. diabetes, renal disease, or malabsorptive disorders) were excluded, pelvic diseases, previous pelvic surgery, suspected peritoneal factor infertility, tubal infertility and male factor infertility were excluded with a hysterosalpingogram and with semen analysis, respectively." **Number of women randomised:** 80 women, 40 within each group **Number of women analysed:** 80 women, 40 within each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** none **Number of centres:** single-centre trial **Age (y):** LOD group 28.8 ± 3.1 versus letrozole group 29.7 ± 3.7 **BMI (kg/m^2):** LOD group 29.1 ± 1.6, letrozole group 29.2 ± 1.7 **Duration of infertility (y):** no mean ± SD reported **Country:** Egypt
Interventions	**Group A:** quote: "In group A, laparoscopy was performed under intravenous general anaesthesia with the patient in a supine position. A 5 mm incision was made in the navel, through which a long sheath punctured into the abdominal cavity, and the inflatable pneumoperitoneum was placed. Another two 5-mm incisions were made on the right and left lower abdomen and the surgical instruments were inserted into the abdominal cavity. The patient was adjusted into a position with the head high up, the pelvic organs were exposed and a comprehensive exploration of the pelvic organs was made, focusing on the structure and position of the adjacent organs of the bilateral ovaries. Once immobilized, each ovary was cauterized at 4–6 points, using a monopolar electrosurgical needle, according to the size of each ovary. Following cauterization, a bilateral tubal hydrotubation with methylene blue was performed. During the procedure. The pelvis was irrigated using physiological saline. Ringer's solution plus dexamethasone was added into the abdominal cavity to avoid adhesion. The total duration of the procedure, as well as any intra-operative or post-operative complications, was noted." **Group B:** quote: "In group B, 2.5 mg twice daily LE oral tablets were administered on the 3rd day of menses and then every day for 5 days.

Ibrahim 2017 *(Continued)*

	Treatment was repeated for up to six cycles if the patient failed to ovulate, the patients were followed-up for 6 months after the treatment in both groups."
Outcomes	Pregnancy rate, abortion rate, ovulation, regular cycles, ovarian volume, antral follicle count
Notes	**Ethical approval:** trial was approved by Minia University Ethical Committee **Informed consent:** quote: “Informed consent was obtained from all participating women after the nature and purpose of the study had been explained to them and were fully understood” **Source of funding:** quote: “We have not received any funding from any corporate body or pharmaceutical company. “ **Power calculation:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was achieved via the use of a randomisation number allocated prior to dosing, once eligibility had been determined, and a randomisation schedule was produced by an interactive voice response system vendor."
Allocation concealment (selection bias)	Low risk	Quote: "randomisation schedule was produced by an interactive voice response system vendor"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Once the patients had been allocated to one of the two groups, the treatment was revealed to the investigator; however, the doctor responsible for performing the transvaginal ultrasound follow up assessment was blinded to the treatment groups."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were also analysed.
Selective reporting (reporting bias)	Unclear risk	We found no reporting of outcomes in a trial protocol or Methods section
Other bias	Low risk	None

Kamath 2010

Study characteristics

Methods	Randomised double-blind placebo-controlled trial **Duration and location of the trial:** quote: "This trial was conducted in a university teaching hospital between 2007 and 2009.“
Participants	**Inclusion criteria:** women with PCOS and clomiphene resistance who were being treated with ovulation induction. Additionally, women had to have a normal hormone profile and a male partner with

Kamath 2010 *(Continued)*

	normal semen parameters by WHO criteria. Normal hormone profile was defined as a FSH level of < 12 IU/L, serum prolactin level of < 25 ng/mL, and a TSH value between 0.3 µIU/mL and 4.5 µIU/mL. **Exclusion criteria:** women with other endocrine disorders such as Cushing syndrome, and congenital adrenal hyperplasia **Number of centres:** 1, Reproductive Medicine Unit, Christian Medical College, Vellore, Tamil Nadu, India **Number of women randomised:** 18 in each group **Number of women analysed:** 17 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 2 lost to follow-up before treatment started **Age (y):** group A letrozole: 25.6 ± 3.6, group B placebo: 25.7 ± 3.7 **BMI (kg/m^2):** group A letrozole: 26.1 ± 3.7, group B placebo: 24.7 ± 4.2 **Duration of infertility (y):** group A letrozole: 5.2 ± 3.2, group B placebo: 3.6 ± 2.2 **Country:** India
Interventions	**Group A:** letrozole, orally given 2.5 mg/day for 5 days from cycle days 2-6 **Group B:** placebo, also given for 5 days from cycle days 2-6
Outcomes	**Primary Outcome:** ovulation rate **Secondary Outcomes:** live birth rate, OHSS rate, pregnancy rate, miscarriage rate, multiple pregnancy rate, endometrial thickness (mm), day 21 serum progesterone (nmoL/L), number of participants with mature follicle (%)
Notes	**Ethical approval:** yes, the protocol of the trial was approved by the institutional review board **Informed consent:** yes, written informed consent was obtained from each participant **Source of funding:** not stated **Conflicts of interest:** quote: "The Authors have nothing to disclose" **Power calculation:** quote: "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 were done in detail. All information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly distributed using a computer-generated randomisation sequence in blocks of 6, into 2 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)	Low risk	The randomisation code was maintained by the pharmacy department, which revealed the group assignments at the end of the trial.

Kamath 2010 *(Continued)*

All outcomes		
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	1 woman 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	None

Kar 2012

Study characteristics	
Methods	Randomised controlled trial **Duration of the trial:** quote "The prospective randomized trial was conducted between July 2010 and July 2011.“
Participants	**Inclusion criteria:** quote: "PCOS was diagnosed according to Rotterdam criteria. All women were treatment-naive i.e. had not undergone any significant treatment for infertility/ovulation induction earlier." **Exclusion criteria:** quote: "Patients with hyperprolactinaemia, thyroid disorder, male factor, suspected tubal factor, endometriosis, unexplained infertility were not included in the study." **Number of centres:** quote: "This study was conducted at a private hospital with a large gynaecological practice." **Number of women randomised:** 103 women, 52 in the letrozole group and 51 in the CC group. **Number of women analysed:** 103 women, 52 in the letrozole group and 51 in the CC group. **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A letrozole: 26.3 ± 2.4, group B CC: 26.3 ± 2.5 **BMI (kg/m²):** group A letrozole: 25.9 ±3.6, group B placebo: 26.0 ± 3.3 **Duration of infertility (y):** group A letrozole: 3.1 ± 1.9, group B CC: 3.1 ± 2.2 **Country:** India
Interventions	**Group A:** letrozole, 5 mg/day orally given for 5 days from cycle days 2-6 **Group B:** CC, 100 mg/day orally given for 5 days from cycle days 2-6
Outcomes	**Primary outcomes:** ovulation rate, endometrial thickness, mono vs. multi-follicular rate, and days to ovulation. **Secondary outcomes:** pregnancy and miscarriage rate
Notes	**Ethical approval:** yes, quote: "Study protocol was approved by the institutional ethics committee." **Informed consent:** not stated.

Kar 2012 *(Continued)*

Source of funding: quote: "Nil"

Power calculation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised 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	None

Legro 2014

Study characteristics

Methods	Randomised double-blind multicentre trial **Duration of the trial:** quote: "Enrollment began in February 2009 and was completed in January 2012."
Participants	**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 > 14 million/mL **Exclusion criteria:** quote: "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." **Number of centres:** multicentre trial **Number of women randomised:** 750, 374 in the letrozole group and 376 in the CC group **Number of women analysed:** 750, 374 in the letrozole group and 376 in the CC group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A letrozole: 29 ± 5, group B CC: 28 ± 4 **BMI (kg/m^2):** group A letrozole: 35 ± 10, group B CC: 35 ± 9 **Duration of infertility (y):** not reported

Legro 2014 *(Continued)*

	Country: USA
Interventions	**Group A:** letrozole, orally given 2.5 mg/day for 5 days during cycle days 3-7 **Group B:** CC, orally given 100 mg/day for 5 days during cycle days 3-7
Outcomes	Live birth, ovulation rate, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate
Notes	**Ethical approval:** quote: "The institutional review board at each centre approved the protocol, and all participants (women and their male partners) gave written informed consent." **Informed consent:** quote: "The institutional review board at each centre approved the protocol, and all participants (women and their male partners) gave written informed consent." **Source of funding:** quote: "The study is funded through a cooperative agreement by the Eunice Kennedy ShriverNational Institutes of Child Health and Human Development (NICHD)" **Power calculation:** a sample size of 300 subjects in each arm of the randomisation 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^2 test with a 2-sided significance level of 0.05

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Almac statisticians will generate the randomisation scheme for the study."
Allocation concealment (selection bias)	Low risk	Third-party allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order to maintain the double-blind, CC and letrozole will be over encapsulated and packaged in identically appearing numbered study kits (using AlmacClinical Services, Durham NC) which will then be directly shipped to each clinical site."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In order to maintain the double-blind, CC and letrozole will be over encapsulated and packaged in identically appearing numbered study kits (using AlmacClinical Services, Durham NC) which will then be directly shipped to each clinical site. The randomisation 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	None

Liu 2015

Study characteristics

Liu 2015 *(Continued)*

Methods	Randomised controlled clinical trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** quote: "the women were diagnosed with PCOS based on the Revised 2003 Consensus Diagnostic Criteria for PCOS. Clomiphene resistance, i.e. failure to ovulate following 100 mg CC for 5 days for at least three cycles; patent fallopian tubes, confirmed by hysterosalpingography or hysteroscopic diagnosis; normal semen analysis parameters of the patients' spouses according to the modified criteria of the World Health Organization (14); normal serum prolactin, thyroid stimulating hormone and 17-OH progesterone; no systemic disease; no gonadotropin or other hormonal drug treatment during the preceding 3 months; normal blood count and blood chemistry, including glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, urea nitrogen, creatinine, glucose and urine analysis. The semen of the patients' spouses was tested to strengthen the comparability between the two groups. During the period of treatment, all patients were requested to follow a normal diet and rest regime and to avoid intense physical activities in any form and mental stress and fatigue." **Exclusion criteria:** infertility induced by reasons other than PCOS; uterine cavity lesions or ovarian cyst; > 40 years old; BMI > 26 kg/m^2; contraindications to general anaesthesia; history of pelvic surgery; other endocrine diseases; or a history of liver or kidney disease **Number of women randomised:** 141 women were randomly assigned, 71 to group A (letrozole) and 70 to group B (LOD) **Number of women analysed:** all women randomised were also analysed **Number of withdrawals/exclusions/loss to follow-up and reasons:** none **Number of centres:** single-centre trial **Age (y):** letrozole group 29.5 ± 3.3, LOD group 28.1 ±3.6 **BMI (kg/m^2):** letrozole group 22.5 ± 1.5, LOD group 22.4 ± 2.1 **Duration of infertility (y):** letrozole group 3.4 ± 0.4, LOD group 3.2 ± 0.7 **Country:** China
Interventions	**Group A:** quote: "In group A, 2.5 mg LE oral tablets (Adooq Bioscience, Nanjing, China) were administered on the fifth day of menses and then every day for 5 days. Treatment was repeated for up to six cycles if the patient failed to conceive." **Group B:** quote: "In group B, laparoscopy was performed under intravenous general anaesthesia (Diprivan; AstraZeneca S.p.A., Rome, Italy) with the patient in a supine position. A 5-mm incision was made in the navel, through which a long sheath punctured into the abdominal cavity, and the inflatable pneumoperitoneum (Guangxi University, Yuannan, China) was placed. Another two 5-mm incisions were made on the right and left lower abdomen and the surgical instruments were inserted into the abdominal cavity. The patient was adjusted into a position with the head high up, the pelvic organs were exposed and a comprehensive exploration of the pelvic organs was made, focusing on the structure and position of the adjacent organs of the bilateral ovaries. Once immobilized, each ovary was cauterized at 4-6 points, each for 4 sec at 40 W, at a depth of 7-8 mm and a diameter of 3-5 mm, using a monopolar electrosurgical needle (Kirgen Co., Shanghai, China), according to the size of each ovary. Following cauterization, a bilateral tubal hydrotubation with methylene blue was performed. During the procedure, small pieces of the ovaries were obtained for pathological analysis. The pelvis was irrigated using physiological saline. Ringer's solution (ZiQi Bioscience, Shanghai, China) plus dexamethasone was added into the abdominal cavity to avoid adhesion. The total duration of the procedure, as well as any intra-operative or post-operative complications, was noted. The patients were followed-up for 6 months after the procedure."
Outcomes	Live birth rate, OHSS, clinical pregnancy was defined by a foetal heart beat monitored by ultrasound at 6 weeks of gestation.

Liu 2015 *(Continued)*

	Biochemical pregnancy was considered when hCG was > 2.5 mIU/mL in the absence of menstruation. Ovulation rate, endometrial thickness in mm, synchronous cycles, mean follicular diameter, spontaneous abortion rate, multiple pregnancy rate
Notes	**Ethical approval:** this trial was approved by Tongji Hospital Research Ethics Committee (Shanghai, China) **Informed consent:** all participants provided informed consent prior to inclusion in the trial. **Source of funding:** the present trial was supported by the Shanghai Natural Science Foundation (grant no. 12ZR1434200). **Power calculation:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The women were randomly allocated into the either the letrozole or LOD group (groups A and B, respectively)."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Once the patients had been allocated to one of the two groups, the treatment was revealed to the investigator; however, the doctor responsible for performing the transvaginal ultrasound `follow-up` assessment was blinded to the treatment groups."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Once the patients had been allocated to one of the two groups, the treatment was revealed to the investigator; however, the doctor responsible for performing the transvaginal ultrasound `follow-up` assessment was blinded to the treatment groups."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were also analysed
Selective reporting (reporting bias)	Unclear risk	Live birth and spontaneous abortion were reported as outcomes, but not prespecified in the methods
Other bias	Unclear risk	None

Liu 2017

Study characteristics

Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "PCOS patients attending the outpatient department of the hospital between April 2012 and March 2014, who had a desire for childbearing and fulfilled the Rotterdam diagnostic criteria as well, were recruited for this study.“
Participants	**Inclusion criteria:** quote: "PCOS patients attending the outpatient department of the hospital between April 2012 and March 2014, who had a desire for childbearing and fulfilled the Rotterdam diagnostic criteria as well, were recruited for this trial. The inclusion criteria for this study were as follows: (1) patency of at least one side of the fallopian tube and (2) normal spouse’s sperm."

Liu 2017 *(Continued)*

	Exclusion criteria: quote: "The exclusion criteria were as follows: (1) patients with gynaecologic tumours or genital tract malformations, (2) patients with severe systemic disease or acute and chronic urogenital tract infections, (3) patients with other endocrine diseases such as thyroid disease and adrenal disease, (4) body mass index (BMI) > 30, and (5) age over 35 years or below 20 years." **Number of women randomised:** 268 women **Number of women analysed:** unknown if all 268 or only 240 were analysed **Number of withdrawals/exclusions/loss to follow-up and reasons:** 28 women left the trial; 13 in the CC groups, 15 in the letrozole groups; 5 in the CC + metformin and 7 in the letrozole + metformin group left the trial due to complications; 3 participants were excluded (no reasons reported), the rest were lost to follow-up **Number of centres:** single-centre trial **Age (y): g**roup A (CC) 26.8 ± 3.1; group B (CC + metformin) 27.2 ± 2.8; group C (letrozole) 27.0 ± 3.0; group D (letrozole + metformin) 27.2 ± 3.3 **BMI (kg/m²):** group A (CC) 21.1 (19.9, 22.8); group B (CC + metformin) 21.4 (19.8, 23.6); group C (letrozole) 20.8 (19.1, 22.3); group D (letrozole + metformin) 21.6 (19.2, 23.6) **Duration of infertility (y):** group A (CC) 1 (0, 2); group B (CC + metformin) 1 (0, 3); group C (let) 1 (0, 2); group D (let + metformin) 1 (0, 3) **Country:** China
Interventions	**Group A:** oral administration of CC was started in the group CC or CC + metformin from day 3 to day 5 of the menstrual cycle at a daily dose of 50 mg for 5 days; and the daily dose gradually increased to 100 mg or 150 mg at maximum in the next cycle if the undeveloped follicle (< 16 mm) was present in the previous cycle. **Group B:** oral administration of letrozole started in the group letrozole or letrozole + metformin from day 3 to day 5 of the menstrual cycle at a daily dose of 5 mg for 5 days. Additional metformin (1000 mg/d to 1500 mg/d) was orally administered to participants in the groups CC + metformin and letrozole + metformin.
Outcomes	Ovulation rate, pregnancy rate, live birth rate, miscarriage rate, premature delivery, OHSS, multiple pregnancy rate
Notes	**Ethical approval:** the trial was approved by the ethics committee of the West China Second University Hospital, Sichuan University, China (approval No. Medical Research 2012 No. 004), and the trial was registered in the Chinese Clinical Trial Registry Center (registration No. ChiCTR-TRC-11001821). **Informed consent:** obtained from each participant **Source of funding:** self-supported by West China Women's and Children's Hospital SCU **Power calculation:** ovulation rate as the main indicator, the sample size was calculated by introducing maximal and minimal ovulation rate retrieved in literatures into the formula

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer random-number generator but participants numbered and randomly divided into groups according to the order of inclusion
Allocation concealment (selection bias)	Unclear risk	Not reported

Liu 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	28 of 268 women left the trial (> 10%) Unknown if all 268 or only 240 were analysed
Selective reporting (reporting bias)	Low risk	All outcomes expected were reported
Other bias	Low risk	None

Moussa 2016

Study characteristics	
Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "Three hundred and thirty seven infertile women with anovulatory (PCOS) were recruited from the outpatient clinics of both 6th October and Bab Elshaaria University Hospitals from August 2014 and January 2015.“
Participants	**Inclusion criteria:** infertile women with anovulatory (PCOS), age between 20 and 35 years, BMI between 18 kg/m^2 and 30 kg/m^2, normal uterus and patent tubes by hysterosalpingography, normal semen analysis and normal serum prolactin **Exclusion criteria:** women with endocrinal disturbance, active liver disease, local disease as hydro- or pyosalpinx, and history of previous ovarian surgery **Number of women randomised:** 150 women **Number of women analysed:** 150 women were analysed, 50 within each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** none **Number of centres:** 2-centre trial **Age (y):** group A: 27.5 ± 4.1, group B: 27.2 ± 3.9, group C: 27.5 ± 4.1 **BMI (kg/m^2):** group A: 26.9 ± 1.7, group B: 26.8 ± 1.7, group C: 26.7 ± 1.5 **Duration of infertility (y):** group A: 1.9 ± 0.7, group B: 1.9 ± 0.7,and group C: 2.2 ± 0.7 **Country:** Egypt
Interventions	Each of the 3 groups received 2 tablets for 5 days starting from day 3 to day 7 of the cycle **Group A:** 100 mg (50 mg/tablet) CC **Group B:** 5 mg (2.5 mg/tablet) letrozole **Group C:** 40 mg (20 mg/tablet) tamoxifen

Moussa 2016 *(Continued)*

Outcomes	**Primary outcomes**: endometrial thickness and endometrial blood flow (PI and RI) **Secondary outcomes**: development and number of follicles, and the pregnancy rate
Notes	**Ethical approval:** the trial was approved by the ethical committee of Al Azhar University. **Informed consent:** not reported **Source of funding:** authors declare that they have neither conflict of interest nor received financial support. **Power calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were prospectively randomised into three groups each containing fifty patients by computer"
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	All participants randomised were also analysed
Selective reporting (reporting bias)	Unclear risk	We found no trial protocol
Other bias	Low risk	None

Najafi 2020

Study characteristics

Methods	Double-blind, randomised controlled clinical trial **Duration and location of the trial:** quote: "The double-blind randomised clinical trial (RCT) study was conducted from September 22, 2012, to March 20, 2013, at the Islamic Azad University of Medical Sciences, 22 Bahman hospital in Mashhad, Iran."
Participants	**Inclusion criteria:** quote: "Those included were PCO infertile women aged 18-40 years who had absence of ovulation (oligomenorrhea, amenorrhea), symptoms of increase in androgen in the blood (acne, hirsuitism) and the laboratory symptoms of androgen increasing (increase in testosterone (TST) and Dehydroepiandrosterone (DHEA),2 and with body mass index (BMI) less than 35."

Najafi 2020 *(Continued)*

	Exclusion criteria: quote: "Those with other infertility reasons, such as infertility in the partner, infertility duration more than 5 years, women with ovary cyst and internal pathology of the endometrium, active malignancy of the breast and the ovary, and individuals who avoided using aromatase inhibitor and oestrogen receptor modulator were excluded." **Number of women randomised:** 240 women **Number of women analysed:** 220 women were analysed, 110 within each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 10 women in each group were lost to follow-up **Number of centres:** single centre trial **Age (y):** group A: 27.5 ± 4.1, group B: 27.2 ± 3.9, group C: 27.5 ± 4.1 **BMI (kg/m^2):** group A: 26.9 ± 1.7, group B: 26.8 ± 1.7, group C: 26.7 ± 1.5 **Duration of infertility (y):** group A: 1.9 ± 0.7, group B: 1.9 ± 0.7, group C: 2.2 ± 0.7 **Country:** Egypt
Interventions	Quote: "Patients who received Letrozole 5 mg tablets per night were in group A, and those who received CC 50 mg tablets per night were in group B. The medication lasted 3-7 days in both groups."
Outcomes	Number of follicles, endometrial thickness, pregnancy rate by b-hcg on day 16 after injection of hCG. Serum prolactin, DHEA, TSH, testosterone.
Notes	Ethical approval and informed consent: quote: "Approval was obtained from the institutional ethics committee, and written informed consent was taken from the subjects." Source of funding: quote: "none" conflicts of interest: quote: "none"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At first, researchers drew a chart including 240 rows (001-240). Then, we carried out an allocation to the control and sample group using the table random numbers."
Allocation concealment (selection bias)	Unclear risk	Quote: "Names and characteristics of patients were allocated to each group, and only the researchers were aware of this table, and the patients did not know about the drug."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants did not know about the drug"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "researchers were aware of this table"
Incomplete outcome data (attrition bias) All outcomes	Low risk	20/240 women were lost to follow-up, 10 in each group (9%)

Najafi 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	None

Nazik 2012

Study characteristics	
Methods	A partly-randomised controlled clinical trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** infertile women with PCOS, diagnosis based on the 2003 Rotterdam criteria **Exclusion criteria:** women with ovarian or adnexal surgery, hypothyroidism, hyperprolactinaemia, bilateral tubal occlusion diagnosed with hysterosalpingography and unexplained infertility, and those with follicles greater than 10 mm **Number of centres:** 1, 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: 25.6 ± 4.5, group B CC: 27.8 ± 6.2 **BMI (kg/m²):** group A letrozole: 24.7 ± 3.6, group B CC: 24.9 ± 4.8 **Duration of infertility (y):** group A letrozole: 3.4 ± 3.0, group B CC: 4.4 ± 3.6 **Country:** Turkey
Interventions	**Group A:** letrozole, orally given 2.5 mg/day for 5 days during cycle days 3-7 **Group B:** CC, orally given 100 mg/day for 5 days during cycle days 3-7
Outcomes	**Primary outcomes:** ovulation rate and pregnancy rate **Secondary outcomes:** OHSS rate, miscarriage rate, multiple pregnancy rate, number of follicles on day of hCG (≥ 17 mm), E2 (pg/mL) on hCG day, endometrial thickness (mm), other side effects
Notes	**Ethical approval:** yes, quote: “Ethical approval was obtained from the institutional review board of Atatürk University Medical Faculty in order to conduct this study.” **Informed consent:** quote: "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:** quote: "This study was done by researchers without any funding" **Power calculation:** not stated All questions were answered by Dr Hakan Nazik

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Nazik 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: “The patients were randomly allocated using a computer random list into first and second groups”
Allocation concealment (selection bias)	Unclear risk	Quote: “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	Quote: "There was no blinding in our study" (email with Dr Hakan Nazik)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "There was no blinding in our study" (email 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	Participants in group 2 letrozole were significantly younger and had a significantly shorter duration of infertility.

Ramezanzadeh 2011

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** quote: "The study was conducted in the infertility clinic of a tertiary referral centre (Vali-E-asr Hospital–Tehran University of Medical Sciences) as a randomized controlled trial, between March 2009 and February 2010.“
Participants	**Inclusion criteria:** women with PCOS with infertility who underwent ovulation induction and timed intercourse for the first time. PCOS was diagnosed by the Rotterdam 2003 criteria. Participants were < 35 years old with at least 1 year of infertility with no other infertility factor. **Exclusion criteria:** ovarian cysts on cycle day 3 found by transvaginal ultrasound examination. **Number of centres:** 1, an infertility clinic of a tertiary referral centre **Number of women randomised:** 80; group A letrozole 5 mg: 40, group B letrozole 7.5 mg: 40 **Number of women analysed:** group A letrozole 5 mg: 30, group B letrozole 7.5 mg: 37 **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 **Age (y):** group A letrozole 5 mg: 28.3 ± 5.0, group B letrozole 7.5 mg: 28.2 ± 4.5 **BMI (kg/m^2):** group A letrozole 5 mg: 25.9 ± 4.2, group B letrozole 7.5 mg: 26.7 ± 3.6 **Duration of infertility (y):** group A letrozole 5 mg: 3.6 ± 2.3, group B letrozole 7.5 mg: 4.7 ± 3.2 **Country:** Iran
Interventions	**Group A:** letrozole orally given, 5 mg/day for 5 days from cycle days 3-7

Ramezanzadeh 2011 *(Continued)*

	Group B: letrozole orally given, 7.5 mg/day for 5 days from cycle days 3-7
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, OHSS rate
Notes	**Ethical approval:** yes, the hospital research ethics board approved the trial. **Informed consent:** all participants gave informed consent before inclusion in trial. **Source of funding:** not stated **Conflicts of interest:** quote: “Conflict of interest: All of the authors do not have any conflict of interest” **Power calculation:** quote: "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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated using computer-generated random table into 2 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 participants excluded due to ovarian cyst on day 3 sonography. 9 participants lost to follow-up, 6 from group A and 3 from group B, without reasons given
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None

Ray 2012

Study characteristics

Methods	Comparative randomised phase III open-labelled trial **Duration and location of the trial:** quote: "A comparative, prospective, phase III, open labelled trial study was conducted in the Eden Hospital, Medical College Kolkata between January 2008 and December 2009.“
Participants	**Inclusion criteria:** infertile women aged 20-35 with PCOS diagnosis based on the Rotterdam criteria 2003

Ray 2012 *(Continued)*

	Exclusion criteria: women with hyperprolactinaemia, thyroid disorder, male-factor infertility, known or suspicious tubal-factor infertility (endometriosis and pelvic inflammatory disease). Also women with a history of liver and kidney failure, cardiovascular diseases, diabetes, or women who consumed metformin or drugs affecting insulin secretion or CC in the previous 2 months **Number of centres:** 1, Eden Hopsital, Mecial College Kolkata **Number of women randomised:** 147; group A letrozole: 69, group B CC: 78 **Number of women analysed:** group A letrozole: 69, group B CC: 78 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Age (y):** group A letrozole: 28 (19-35), group B CC: 29 (20-35) **BMI (kg/m^2):** group A letrozole: 28.8 (23.2-34.6), group B CC: 28.5 (24.2-33.6) **Duration of infertility (y):** group A letrozole: 2.2, group B CC: 2.4 (SD or range not given) **Country:** India
Interventions	**Group A:** letrozole, 2.5 mg/day given orally for 5 days from cycle day 3-7 **Group B:** CC, 100 mg/day given orally for 5 days from cycle day 3-7
Outcomes	**Primary outcomes:** ovulation rate, average follicular diameter on day 16, number of mature follicles produced by 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 trial protocol was approved by the ethical committee of Medical College Kolkata **Informed consent:** yes, participants were counselled and informed consent was obtained before recruitment **Source of funding:** quote: "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 We contacted Dr Ray by email about randomisation, allocation, blinding, multiple pregnancy rate, and OHSS, but he did not respond.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how randomisation was done
Allocation concealment (selection bias)	Unclear risk	Unclear how allocation was done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported if anyone was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported if anyone was blinded

Ray 2012 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants stated as lost, but 147 participants is an odd number to start with, and 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	None

Roy 2012

Study characteristics	
Methods	Randomised clinical trial **Duration and location of the trial:** quote: "This prospective randomized controlled trial was performed at a tertiary care hospital from January 2005 to January 2010."
Participants	**Inclusion criteria:** women aged 20-35 years having infertility for > 1 year, BMI < 28, and with anovulatory PCOS based on the Rotterdam 2003 criteria **Exclusion criteria:** quote: "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." **Number of centres:** 1, a tertiary care hospital in India **Number of women randomised:** 212 women; group A letrozole: 104, group B CC: 108 **Number of women analysed:** letrozole group: 98, CC group: 106 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 8 lost to follow-up **Age (y):** group A letrozole: 26.1 ± 1.8, group B CC: 26.5 ± 1.3 **BMI (kg/m^2):** group A letrozole: 25.8 ± 2.1, group B CC: 25.4 ± 1.6 **Duration of infertility (y):** group A letrozole: 6.4 ± 3.8, group B CC: 5.8 ± 3.1 **Country:** India
Interventions	**Group A:** letrozole, orally given in doses of 2.5 mg/day and 5 mg/day for 5 days during cycle days 3-7 **Group B:** CC, orally given in doses of 50 mg/day and 100 mg/day for 5 days during cycle days 3-7 Treatment was continued for 3 months.
Outcomes	Mean number of follicles, endometrial thickness, ovulatory cycle rate, conception rate, pregnancy outcome, miscarriage rate, multiple pregnancies and OHSS rate
Notes	**Ethical approval:** yes, the necessary ethical approval was taken from Institutional Review Board to conduct this trial. **Informed consent:** yes, the participants were counselled, and informed consent was taken before randomisation.

Roy 2012 *(Continued)*

Source of funding: quote: “Source of support: Nil, Conflict of interest: None declared.”

Power calculation: quote: "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."

We contacted Dr Roy by email to get additional information, but he did not respond.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Online software was used to generate a random-number table (www.randomization.com).
Allocation concealment (selection bias)	Unclear risk	Quote: "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 randomisation code. At the end of allocation, the resident provided us with a randomisation 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 participants
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Salazar-Ortiz 2016

Study characteristics

Methods	Randomised controlled trial **Duration and location of the trial:** prospective trial, randomised, simple, comparative, carried out in patients with infertility for PCOS treated at the Women's Hospital in Mexico City between October 1, 2014 and March 31, 2015.
Participants	**Inclusion criteria:** women with infertility, diagnosed with PCOS using criteria of the 2003 Rotterdam consensus: 1) oligo-ovulation, 2) clinical signs or biochemicals of hyperandrogenism, 3) ovary polycystic to transvaginal ultrasound, with establishment of the diagnosis with two of these three criteria; age between 18 and 39 years, with a infertility period more or less greater than 2 years; FSH concentrations ≤ 12 U/L and serum prolactin within normal limits in the early follicular phase, TSH and T4 in normal parameters; patients examined by ultrasound, laparoscopy and hysteroscopy to rule out anatomical alterations before treatment.

Salazar-Ortiz 2016 *(Continued)*

	Exclusion criteria: coexistence of some other added disease, a residual follicle at the time of the endovaginal ultrasound on day 3 of the menstrual cycle. In patients with previous treatment with CC wait 2 months without treatment before starting the cycle with letrozole, to eliminate any after-treatment effects. **Number of centres:** single centre **Number of women randomised:** not clear how many initially randomised **Number of women analysed:** 24, 12 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** not reported **Age (y):** not reported per group **BMI (kg/m^2):** not reported **Duration of infertility (y):** not reported per group **Country:** Mexico
Interventions	**Group A:** patients administered letrozole, oral, 2.5 mg per day, for 5 days, from the third day of the spontaneous menstrual cycle or induced with progesterone. **Group B**: patients received CC, 100 mg daily for 5 days, starting on the third day of the menstrual cycle.
Outcomes	Clinical pregnancy (confirmed by ultrasound 6 weeks after insemination), endometrial thickness, size of follicles, number of follicles
Notes	**Ethical approval:** yes, the necessary ethical approval was taken from Institutional Review Board to conduct this trial. **Informed consent:** yes, the participants were counselled, and informed consent was taken before randomisation. **Source of funding:** quote: "Source of support: Nil, Conflict of interest: None declared." **Power calculation:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patient groups were determined randomly, with random sampling
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	Unclear risk	No flow chart available, not reported how many initially randomised

Salazar-Ortiz 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Very small sample size, methodology not sufficiently described

Selim 2012

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** diagnosis of PCOS based on Rotterdam criteria provided that anovulation is 1 of the 2 required criteria **Exclusion criteria:** quote: "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 LOD 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 20 x 10^6/mL **Number of centres:** not reported **Number of women randomised:** 220; group A letrozole: 110, group B CC: 110 **Number of women analysed:** group A letrozole: 102, group B CC: 99 **Number of withdrawals/exclusions/loss to follow-up and reasons:** quote: "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)." **Age (y):** group A letrozole: 26.0 ± 2.7, group B CC: 25.1 ± 3.1 **BMI (kg/m²):** group A letrozole: 24.4 ± 4.3, group B CC: 23.8 ± 3.7 **Duration of infertility (y):** group A letrozole: 2.9 ± 0.6, group B CC: 2.6 ± 0.7 **Country:** Saudi Arabia
Interventions	**Group A:** 110 participants treated with 5 mg/day of letrozole (Femara; Novartis, Switzerland) in 2 divided doses from cycle day 3-7 **Group B:** 110 participants treated with 100 mg/day of CC (Clomid; Sanofi Aventis, France) in 2 divided doses from cycle day 3-7
Outcomes	Quote: "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:** quote: "approval was obtained from the Institutional Review Board of Jeddah Clinic Hospital, Jeddah, Saudi Arabia." **Informed consent:** yes, quote: "all participants gave verbal and written informed consent." **Source of funding:** not stated **Conflicts of interest:** quote: "No competing financial interests exist."

Selim 2012 *(Continued)*

Power calculation: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how envelopes were numbered
Allocation concealment (selection bias)	Low risk	Participants were randomly allocated to the letrozole group or CC group by means of a series of blind envelopes numbered from 1 to 220. Each participant 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	Quote: "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 on all participants 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	None

Seyedoshohadaei 2016

Study characteristics

Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "This double blind clinical trial study was conducted on 100 PCOS infertile women who have not responded to initial treatment, referring to the Infertility Center of Sanandaj Besat Hospital from June 2014 to December 2015."
Participants	**Inclusion criteria:** PCOS infertile women who have not responded to initial treatment. PCOS was confirmed by Rotterdam criteria (menstrual disturbances: oligomenorrhoea or amenorrhoea, clinical or biochemical hyperandrogenism and sonographic findings of polycystic ovaries). Women with 2 of the 3 PCOS criteria were included in the trial. **Exclusion criteria:** women with hyperprolactinaemia, thyroid problems and anatomical problem in uterus cavity and fallopian tubes confirmed by hysterosalpangiography, sonohysterography or laparoscopy were excluded from the trial. **Number of women randomised:** 100 women, 50 to each group **Number of women analysed:** 100 women, 50 in each group **Number of withdrawals/exclusions/loss to follow-up and reasons:** none **Number of centres:** single centre

Seyedoshohadaei 2016 *(Continued)*

	Age (y): group A (CC + EV) 30.3 ± 3.1; group B (letrozole) 29.6 ± 5.1 **BMI (kg/m²):** not reported **Duration of infertility (y):** group A (CC + EV) 3.4 ± 2.8; group B (letrozole) 3.9 ± 2.4 **Country:** Iran
Interventions	**Group A:** 100 mg CC (Iran Hormone Pharmaceutical Company) from day 3-7 of menstruation and 4 mg estradiol valerate (Aburaihan Pharmacy Company) after the 8th day of menstruation until 14th day **Group B:** 5 mg letrozole (Iran Hormone Pharmaceutical Company) from day 3-7 of menstruation with placebo from 8th-14th day of menstruation
Outcomes	Pregnancy rate, outcome of pregnancy, live birth, miscarriage rate, endometrial thickness
Notes	**Ethical approval:** quote: "This study was approved by the Ethics Committee of Kurdistan University of Medical Sciences and has been registered in the Iranian Registry of Clinical Trials with registration number IRCT2015052612789N11." **Informed consent:** quote: "Written consent was taken before the intervention." **Source of funding:** quote: "Authors would like to thank Vice Chancellor for Research of Kurdistan University of Medical Sciences to support the study financially. " **Power calculation:** quote: "The sample size was calculated based on previous studies. Considering the mean of endometrial thickness, 5% type I error and 20% type II error, 45 patients were required in each group. To compensate for possible loss and increase the power of the study, 50 patients were studied in each group."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were block-randomised and divided in 2 groups
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "To blind the study, transvaginal sonography was performed by a fellow of infertility, the medication was prescribed by a gynaecologist and the patients in group B received placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "To blind the study, transvaginal sonography was performed by a fellow of infertility, the medication was prescribed by a gynaecologist and the patients in group B received placebo."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were also analysed
Selective reporting (reporting bias)	Unclear risk	No trial protocol was found
Other bias	Low risk	None

Sharief 2015

Study characteristics	
Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "The prospective clinical trial was conducted at Basrah Maternity and Child Hospital, Basrah, Iraq, between January 2012 and April 2013, and comprised women with PCOS and primary infertility.“
Participants	**Inclusion criteria:** quote: "Women with PCOS and primary infertility. The subjects were selected from among those who were attending the infertility centre with primary infertility, which was defined as inability of a couple to obtain pregnancy after 1-2 years of unprotected intercourse. All subjects were diagnosed as having anovulation due to PCOS. PCOS was diagnosed when the ultrasonographic (USG) findings of the ovaries were > 10 follicles 2-8 mm in diameter scattered either around or through an echodense thickened central stroma. In addition, there had to be one or more of the following: oligomenorrhoea, positive progesterone, withdrawal bleeding, hirsutism/acne, obesity, and Luteinizing hormone/Follicle-stimulating hormone (LH/FSH) ratio > 2 or raised circulating androgen, normal thyroid stimulating hormone (TSH). Those included were aged between 18 and 36 years, period of infertility was more than 2 years, serum prolactin level was normal, serum FSH < 12u/L, normal thyroid function, and hirsutism, which was diagnosed when the Ferriman and Gallwey score was > 8.9 Besides, the male partners had to have a normal seminal analysis by World Health Organisation (WHO) criterion." **Exclusion criteria:** all women having had patent tubes by either hysterosalpingogram or laparoscopy, history of pelvic surgery with tubal blockage were excluded from the trial. **Number of women randomised:** not stated how many participants were randomised **Number of women analysed:** 75 women were analysed, 40 in group A, 35 in group B **Number of withdrawals/exclusions/loss to follow-up and reasons:** not stated **Number of centres:** single centre **Age (y):** group A 25.3 ± 2.1 years, group B 26.1 ± 1.3 years **BMI (kg/m^2):** group A 27.8 ± 1.7, group B 28.1 ± 1.9 **Duration of infertility (y):** group A 2.3 ± 0.4, group B 2.4 ± 0.6 **Country:** Iraq
Interventions	**Group A:** CC for 6 months with a dose between 100 mg to 200 mg for 5 days beginning on day 3 of the menstrual cycle **Group B:** letrozole 2.5 mg to 5 mg daily for 5 days starting from the 3rd day of a spontaneous or progesterone-induced menstrual bleeding
Outcomes	Pregnancy rate, multiple pregnancies, follicular development, number of follicles, serum E2 on day of hCG, endometrial thickness, ovulation rate
Notes	**Ethical approval:** approval was obtained from the ethical committee of the College of Medicine, University of Basrah, Iraq. **Informed consent:** not reported if informed consent was obtained **Source of funding:** not reported **Power calculation:** not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sharief 2015 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomised into two 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	Unclear risk	Not reported how many women were randomised in first instance
Selective reporting (reporting bias)	Unclear risk	No trial protocol was found
Other bias	Low risk	None

Sh-El-Arab Elsedeek 2011

Study characteristics	
Methods	Randomised controlled double-blind trial **Duration and location of the trial:** not stated
Participants	**Inclusion criteria:** diagnosis of PCOS based on Rotterdam criteria provided that anovulation is 1 of the 2 required criteria **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. **Number of centres:** 1, an infertility unit of a university hospital **Number of women randomised:** 124; group A letrozole: 62, group B CC: 62 **Number of women analysed:** group A letrozole: 59, group B CC: 57 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 3 in the letrozole and 5 in the CC group were reported as lost to follow-up, but no further explanation given **Age (y):** group A letrozole: 25.0 ± 3.1, group B CC: 25.0 ± 3.6 **BMI (kg/m^2):** group A letrozole: 27.7 ± 3.5, group B CC: 29.2 ± 3.5 **Duration of infertility (y):** not reported **Country:** India
Interventions	**Group A:** letrozole, 5 mg/day orally given for 5 days, cycle days not given

Sh-El-Arab Elsedeek 2011 *(Continued)*

	Group B: CC, 100 mg/day orally given for 5 days, cycle days not given
Outcomes	Pregnancy rate, ovulation rate, endometrial thickness (mm), mid-luteal progesterone level (ng/mL), number of follicles ≥ 12 mm
Notes	**Ethical approval:** yes, institutional review board (IRB) approval was obtained for the trial. **Informed consent:** yes, informed consent was taken from all included cases **Source of funding:** not reported, also no conflicts of interest given. **Power calculation:** not stated We contacted Dr Sheik-el-Arab Elsedeek by email about allocation concealment, blinding of outcome assessors, information on live birth, miscarriage rate, OHSS, multiple pregnancies and funding/COI, but he did not respond.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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 were blinded and how the participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "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 participants lost to follow-up, reasons unknown
Selective reporting (reporting bias)	Unclear risk	Only pregnancy was reported; we contacted the authors to get trial protocol
Other bias	Low risk	None

Shi 2019

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** recruited 96 women with CC-resistant PCOS among those attending the gynaecology outpatient clinic in The Fifth Affiliated Hospital, Sun Yat-Sen University, China; December 2015 to December 2018.
Participants	**Inclusion criteria:** women with PCOS according to the revised 2003 consensus on

Shi 2019 *(Continued)*

	diagnostic criteria and long-term health risks related to PCOS. Through salpingography or hydrotubation under transvaginal B ultrasound and other examinations, all cases were confirmed to have tubal patency on at least one side. The semen of male was normal. **Exclusion criteria:** 1) infertility patients caused by non-PCOS ovulatory disorder or other factors; 2) patients with history of ovarian surgery or complication with endometriosis or pelvic adhesion; 3) patients with liver, kidney or thyroid dysfunction; 4) patients who did not receive treatment after enrolment according to the established regimen or gave up in the midst of treatment. **Number of centres:** 1, an infertility unit of a university hospital **Number of women randomised:** 124; group A letrozole: 62, group B CC: 62 **Number of women analysed:** group A letrozole: 59, group B CC: 57 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 3 in the letrozole and 5 in the CC group were reported as lost to follow-up, but no further explanation given **Age (y):** group A letrozole: 26.1 ± 3.2, group B hMG: 26.3 ± 3.0 **BMI (kg/m^2):** group A letrozole: 25.7 ± 4.9, group B hMG: 24.9 ± 5.1 **Duration of infertility (y):** Not reported **Country:** China
Interventions	Group A: oral letrozole 5.0 mg/d 1 on the 3rd–5th days of menstrual cycle for 5 consecutive days Group B: hMG 75U/d1 intramuscular injection for 5 days starting from the 3rd day of menstrual cycle.
Outcomes	Number of growing and mature follicles, serum E2 (pg/mL), serum P (ng/mL), endometrial thickness, occurrence of pregnancy and miscarriage, live birth, OHSS, multiple pregnancies
Notes	**Ethical approval and Informed consent:** yes, quote: "This study has been approved by the ethics committee of our hospital, and written consent has been obtained from all patients." **Source of funding:** not reported, also no conflicts of interest given. **Power calculation:** not stated Quote: "The 2 groups were expected to receive the treatment of ovulation induction for 4 to 6 cycles, and patients with poor outcomes were treated by assisted reproductive technologies." Authors have been contacted about ART; no ART was used in this trial (shisq2001@126.com)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomly allocated using a computer generated random table into two treatment groups: LE group and hMG group (n = 48)."
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)	Unclear risk	Not stated

Shi 2019 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were also analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None

Sohrabvand 2006

Study characteristics	
Methods	Single-blinded randomised clinical trial **Duration and location of the trial:** quote: "In this single-blind randomized clinical trial, 120 ovarian cycles were studied in 60 clomiphene-resistant patients with PCOS, who were chosen among 115 PCOS patients attending the infertility clinic of Vali-e-Asr Hospital (Tehran, Iran) during the years 2003–2004."
Participants	**Inclusion criteria:** women with PCOS who had failed to become pregnant after 3 courses of 150 mg CC (considered as CC-resistant), whereas the values of hormonal tests were normal. Tests: thyroid function, prolactin level, hysterosalpingography and husband's sperm analysis **Exclusion criteria:** women with a history of liver and kidney failure, cardiovascular disease, diabetes (based on criteria set by the American Diabetic Association) or women who consumed metformin or drugs affecting insulin secretion or CC in the previous 2 months **Number of centres:** 1, infertility clinic of Vali-e-Asr Hospital, Tehran **Number of women randomised:** 60; group A metformin-letrozole: 30, group B metformin-CC: 30 **Number of women analysed:** group A metformin-letrozole: 29, group B metformin-CC: 30 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 1 because she got pregnant after metformin treatment before letrozole was started **Age (y):** group A metformin-letrozole: 28.2 ± 3.1, group B metformin-CC: 29.6 ± 3.5 **BMI (kg/m^2):** group A metformin-letrozole: 30.0 ± 4.8, group B metformin-CC: 30.2 ± 3.9 **Duration of infertility (y):** group A metformin-letrozole: 3.8, group B metformin-CC: 3.8 **Country:** Iran
Interventions	**Group A:** metformin 500 mg x 3/d for 6 - 8 weeks. If pregnancy did not occur, 2.5 mg letrozole from cycle days 3-7 was given orally. **Group B:** metformin 500 mg x 3/d for 6-8 weeks. If pregnancy did not occur, 100 mg CC from cycle days 3-7 was given orally. Treatment was continued for 2 cycles.
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 by mature follicle (pM/L), regular menses after metformin, adverse effects of metformin, live birth rate, pregnancy rate, miscarriage rate

Sohrabvand 2006 *(Continued)*

Notes	**Ethical approval:** yes, consent from the deputy of research and the medical ethics committee of Tehran University of Medical Sciences **Informed consent:** not obtained because quote: “it was the routine treatment protocol and it was just put in the frame of a structured study” (email with Dr Farnaz Sohrabvand) **Source of funding:** quote: "No funding was necessary" (email with Dr Farnaz Sohrabvand) **Power calculation:** not stated Authors were contacted about live birth, multiple pregnancies, OHSS, informed consent, funding. No data available on live birth, multiple pregnancies and OHSS. Information retrieved about informed consent and funding (email with Dr Farnaz Sohrabvand)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "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 plausible that outcome assessors were blinded if participants were not.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was excluded due to pregnancy after start of metformin treatment
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	None

Wu 2016

Study characteristics

Methods	Randomised clinical trial **Duration of the trial:** quote: "The trial was started on October 2009. Owing to the expiration of the study drug (berberine and matching placebo), the data safety and monitoring board decided to stop enrolment in November 2013“

Wu 2016 *(Continued)*

Participants	**Inclusion criteria:** quote: "Chinese women with PCOS attempting to get pregnant were eligible if they fulfilled the following criteria: 1) age 20–40 years; 2) diagnosis of PCOS according to two of the three Rotterdam 2003 criteria, including oligo-ovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries; 3) at least one open fallopian tube and normal uterine cavity documented by hysterosalpingography, sonohysterography, or diagnostic laparoscopy within the past 3 years; 4) a male partner with sperm concentration of 15 million/mL and motility of 40% in at least one ejaculate; and 5) at least 1 year of infertility." **Exclusion criteria:** quote: "Subjects were excluded if they used hormonal drugs or other medications, including Chinese herbal prescriptions, in the past 3 months; had known severe organ dysfunction or mental illness; were pregnant, post-miscarriage, postpartum, or breastfeeding within the past 6 weeks; or had congenital adrenal hyperplasia, clinically suspected Cushing syndrome, or an androgen-secreting neoplasm." **Number of women randomised:** 644 women **Number of women analysed:** 644 women were analysed, 215 in group A, 214 in group B, 215 in group C. **Number of withdrawals/exclusions/loss to follow-up and reasons:** 16/215 (7.4%) in the letrozole group, 25/214 (11.7%) in the berberine group, and 15/215 (7.0%) in the combination group (P = 0.16). Reasons for withdrawal were similar among the 3 groups (P = 0.16 for the 3 groups; P = 0.19 for lost to follow-up; P = 0.88 for dropout; P = 1.0 for protocol violations; and P = 0.33 for adverse events). **Number of centres:** multicentre trial, 19 hospitals **Age (y):** group A 27.8 ± 3.6; group B 27.8 ± 3.7; group C 27.8 ± 3.6 **BMI (kg/m^2):** group A 24.8 ± 4.5; group B 24.5 ± 4.1; group C 25.1 ± 5.0 **Duration of infertility (months):** group A 32.7 ± 24.0; group B 28.5 ± 21.6; group C 29.8 ± 21.3 **Country:** China
Interventions	**Group A:** 2.5 mg (1 tablet) of letrozole on days 3–7 of the first 3 treatment cycles. This dose was increased to 5 mg letrozole (2 tablets) or 2 tablets of letrozole placebo on days 3–7 of the last 3 treatment cycles if not pregnant **Group B:** berberine was administered orally at a daily dose of 1.5 g for 6 months. **Group C:** letrozole and berberine were administered in the same doses as reported above.
Outcomes	Cumulative live births, ovulation rate, conception rate, clinical pregnancy rate, multiple pregnancy rate, abortion rate, pregnancy complications, adverse events from trial medications
Notes	**Ethical approval:** the Institutional Review Boards at participating hospitals approved the protocol. **Informed consent:** every participant gave written informed consent. **Source of funding:** supported by National Public Welfare Projects for Chinese Medicine (200807021) of China, National Key Discipline of Chinese Medicine in Gynecolog, 2009–14, Heilongjiang Province Foundation for Outstanding Youths (JC200804), Intervention for Polycystic Ovary Syndrome Based on Traditional Chinese Medicine Theory–''TianGui Shi Xu'' (2011TD006), and National Clinical Research Base in Chinese Medicine, 2009–14, at First Affiliated Hospital, Heilongjiang University of Chinese Medicine. The funding sources had no involvement in the trial design, the collection, analysis, and interpretation of data, the writing of the report, or in the decision to submit the article for publication. **Power calculation:** the sample size calculation was based on anticipated live birth rate.

Risk of bias

Bias	Authors' judgement	Support for judgement

Wu 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was performed through a web-based computer program (http://210.76.97.192:8080/cjbyj) operated by an independent data coordinating centre, the Institute of Basic Clinical Medicine of the China Academy of Chinese Medical Sciences. The randomisation was stratified by the participating sites."
Allocation concealment (selection bias)	Unclear risk	No further information about allocation after randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, physicians taking care of the participants, laboratory technicians, and data analysers were blinded to the assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, physicians taking care of the participants, laboratory technicians, and data analysers were blinded to the assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% to 12% were lost to follow-up, had protocol violations or adverse events. ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	None, trial protocol was published prior to participant enrolment in the trial
Other bias	Low risk	None

Zarei 2015

Study characteristics	
Methods	Randomised controlled clinical trial **Duration of the trial:** quote: "They underwent intra uterine insemination (IUI) between August 2011 and December 2012.“
Participants	**Inclusion criteria:** quote: "patients with CC-resistant PCOS. According to Rotterdam criteria, patients with at least 2 out of 3 of below criteria were included as a PCOS: 1) chronic anovulation, 2) clinical and/or biochemical evidence of hyperandrogenism and 3) polycystic appearance of ovaries in Transvaginal Ultrasound (TVS) Moreover, infertility was defined as failure to conceive despite having unprotected and frequent intercourse for at least 1 year. CC-resistance was considered as absence of ultrasound evidence regarding ovarian response consumption of 150mg of CC between the 5th and the 9th day of menstruation cycle for three consecutive cycles. All participants had a documented normal blood test, renal function test, liver function test, hysterosalpingography (HSG) and negative pregnancy test before the trial. The partners should have at least two semen analyses. According to WHO, a normal semen analysis should have these properties: Sperm concentration ≥ 15 million/ml, total sperm count ≥ 39 million, mobility rate > 40%, progressive motility ≥ 32% and normal morphology ≥ 4%." **Exclusion criteria:** women with breast cancer, renal and liver diseases, autoimmune problems and endocrinological problems such as diabetes, hyperprolactinaemia, thyroid diseases, Cushing’s syndrome and smokers were excluded from the trial. **Number of women randomised:** 140 women **Number of women analysed:** 131 women were analysed, 67 patients in control group and 64 cases in letrozole group.

Zarei 2015 *(Continued)*

	Number of withdrawals/exclusions/loss to follow-up and reasons: quote: "during this study, we eliminated 6 patients from the control group, 4 fell out of the study and 2 were finally diagnosed for OHSS. Three patients were also eliminated from the letrozole group; one fell out of the study protocol and 2 due to OHSS." **Number of centres:** single-centre trial **Age (y):** aged 18-35: control group: 27.7 ± 1.8, letrozole group: 27.9 ± 1.9 **BMI (kg/m²):** control group: 25.6 ± 3.2, letrozole group: 25.1 ± 4.4 **Duration of infertility (y):** control group: 5.4 ± 1.9, letrozole group: 5.0 ± 3.0 **Country:** Shiraz, Iran
Interventions	**Group A:** control group. 75 IU/day highly purified recombinant FSH (Gonal-f, Serono, Hellas, Puregon, Greece) intramuscularly, from the 3rd day through the day of HCG injection **Group B:** letrozole group additionally received 5 mg/day letrozole (Razak Drug Laboratory, Tehran, Iran) since the 8th day of cycle up to the day of HCG injection.
Outcomes	Premature LH surge, pregnancy rate, abortion rate, ongoing pregnancy rate, number of follicles > 18 mm, endometrial thickness (mm)
Notes	**Ethical approval:** not reported **Informed consent:** not reported **Source of funding:** not reported **Power calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In this study, 140 cases with PCOS resistant to CC were enrolled and divided into two groups of control (n = 70) and letrozole (n = 70)."
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	Quote: "During this study, we eliminated 6 patients from the control group, 4 fell out of the study and 2 were finally diagnosed for OHSS. Three patients were also eliminated from the letrozole group; one fell out of the study protocol and 2 due to OHSS. Thus, 67 patients (age ranges 18-39 years) remained in control group and 64 cases (age ranges 21-37 years) remained in letrozole group."
Selective reporting (reporting bias)	Unclear risk	Unclear; quote: "This trial was registered in Islamic Republic Clinical Trials Database (IRCT2014010615102N2)."

Zarei 2015 *(Continued)*

		We were unable to find the protocol, because the given trial registry number leads to a study protocol for pain medication after rhinoplastic surgery.
Other bias	High risk	Methods not very well described, clinical trial registration number leads to wrong trial.

Zeinalzadeh 2010

Study characteristics	
Methods	Randomised controlled trial **Duration and location of the trial:** quote: "This clinical trial was performed on 107 infertile patients with PCOS who were referred to Fatemeh Zahra Infertility Center, Babol, Iran, in 2006 and 2007.“
Participants	**Inclusion criteria:** women with primary infertility, documented PCOS, age < 35 years, < 5 years infertility and BMI between 19 and 26. PCOS was defined on the basis of ultrasonography findings, oligomenorrhoea and an increased LH/FSH ratio (> 3) **Exclusion criteria:** moderate or severe case of OHSS during trial, infertility resulting from male factors, tubular factors and endometriosis **Number of centres:** 1, Fatemeh Zahra Infertility Center, Babol **Number of women randomised:** 107; group A letrozole: 50, group B CC: 57 **Number of women analysed:** 107; group A letrozole: 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/m^2):** not reported **Duration of infertility (y):** group A letrozole: 2.4 ± 1, group B CC: 2.6 ± 1.2 **Country:** Iran
Interventions	**Group A:** 5 mg letrozole from cycle days 3-7 was given orally **Group B:** 100 mg CC from cycle days 3-7 was given orally
Outcomes	Ovulation rate, pregnancy rate, number of follicles > 17 mm, 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 We contacted authors for additional information, but they did not respond.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Zeinalzadeh 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "The participants were assigned to two groups using systematic randomisation 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	None

ART: assisted reproductive technology; BMI: body mass index; CC: clomiphene citrate; DHEA: dehydroepiandrosterone; ESHRE/ASRM: European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; hMG: human menopausal gonadotropin; ITT: intention-to-treat; IU: intrauterine; LH: luteinising hormone; LOD: laparoscopic ovarian drilling; OHSS: ovarian hyperstimulation syndrome; PCOS: polycystic ovary syndrome; PI: pulsatility index; rFSH: recombinant follicle-stimulating hormone; s: seconds; RI: resistance index; SD: standard deviation; TSH: thyroid-stimulating hormone; uFSH: urinary follicle-stimulating hormone; W: watts; y: year

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu Hashim 2010	Trial had to be excluded due to retraction of the paper, concerns about validity of the data. Link to retraction notice: www.fertstert.org/article/S0015-0282(20)32164-6/fulltext
Akbari 2012	No PCOS
Al-Hussaini 2014	Only short conference abstract; we did not find a published study article. We were unable to retrieve any information from trial authors.
Al-Obaidi 2018	Pseudo-randomization, poor responders were excluded from analysis
Al-Shaikh 2017	Not a RCT
Angel 2014	RCT, but not about women with PCOS
Anwary 2012	Not a RCT
Azargoon 2012	Not a RCT
Azmoodeh 2015	No PCOS

Study	Reason for exclusion
Badawy 2008	Trial had to be excluded due to retraction of the paper, concerns about validity of the data. Link to retraction notice: www.fertstert.org/article/S0015-0282(07)01038-2/fulltext
Badawy 2009a	Trial had to be excluded due to an expression concern of the paper, concerns about validity of the data. Link to the expression of concern: doi.org/10.1016/j.fertnstert.2020.07.035
Badawy 2009b	Trial had to be excluded due to an expression of concern of the paper, concerns about validity of the data. Link to the expression of concern: www.sciencedirect.com/science/article/pii/S0015028220306889
Badawy 2009c	Not a RCT
Baruah 2009	Quasi-randomised trial (quote: "Based on attendance order, patients with odd numbers were given letrozole and those with even numbers were given CC")
El Bigawy 2008	Quasi-randomised trial
Foroozanfard 2013	Not randomised for clomiphene or letrozole
Huang 2019	Non-PCOS
IRCT6517	Not randomised for letrozole
Khanna 2013	Not a RCT, no PCOS
Li 2016	Not randomised for letrozole
Mittal 2004	Not a RCT
Nahid 2012	Suspected quasi-randomisation based on attendance order
NCT00610077	No published data found, last updated on clinicaltrials.gov in 2008. No response from trial authors
NCT01315912	Not a RCT
NCT01431352	For the 2018 update, there was no update on clinicaltrials.gov. No trial data available, and no response from authors.
NCT01577017	No trial results found, unable to obtain more information from trial authors
NCT01679574	Trial should be finished. We contacted authors by email found through Google because no contact information was written in the trial protocol: abd_ellah98@yahoo.com. For the 2018 update, there was no update on clinicaltrials.gov and still no response from the author.
NCT01793038	Unable to obtain information from trial authors. No trial data found, no update on clinicaltrials.gov.
NCT03135301	Letrozole in both arms
Ozdemir 2013	RCT, but not about women with PCOS

Study	Reason for exclusion
Pakrashi 2014	Not randomised for letrozole
Palihawadana 2015	Women with PCOS were excluded from the trial
Pourali 2017	Women with PCOS were excluded from the trial
Sharma 2010	Only conference abstract available, full article could not be found. Contact address of authors unknown
Wang 2019	Quasi-randomised trial: participants excluded after randomisation when intervention was not successful (~30% of participants)
Xi 2015	Not a RCT
Yang 2008	Not a RCT (quote: "the allocation depended on the patients' choice" - translated by Prof Taixiang Wu)
Yun 2015	Not a RCT

CC: clomiphene citrate; PCOS: polycystic ovary syndrome; RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Abdellah 2011

Methods	Randomised controlled trial **Duration and location of the trial:** quote: "The present study was conducted from July 15, 2007, to February 28, 2010, at the Women's Health Center, Assiut University, Assiut, Egypt, after approval was received from the Ethics Committee of Assiut University."
Participants	**Inclusion criteria:** all participants 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. CC resistance was defined as lack of ovulation after 6 consecutive induction cycles with 50 mg 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. **Exclusion criteria:** exclusion criteria included age below 20 years or above 35 years; hormonal treatment within 3 months prior to the trial; hyperprolactinaemia (morning plasma prolactin concentration 30 ng/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. **Number of women randomised:** 147, 74 in the letrozole group and 73 in the LOD group **Number of women analysed:** 70 in the letrozole group and 70 in the LOD group **Number of withdrawals/exclusions/loss to follow-up and reasons:** 7 women were lost to follow-up. **Number of centres:** 1, Women's Health Center, Assiut University, Assiut **Age (y):** group A letrozole: 23.9 ± 3.2, group B LOD: 23.6 ± 3.2 **BMI (kg/m^2):** group A letrozole: 27.3 ± 2.6, group B LOD: 27.1 ± 2.6 **Duration of infertility (y):** group A letrozole: 4.2 ± 1.7, group B LOD: 4.2 ± 1.7

Abdellah 2011 *(Continued)*

	Country: Egypt
Interventions	**Group A:** letrozole, 5 mg/day given orally for 5 days during cycle days 3-7 for up to 6 cycles **Group B:** LOD, triple-puncture laparoscopy, monopolar diathermy, needle electrode set at 40 W pressed against border of ovary for 4 sec to achieve penetration depths of 7 mm to 8 mm, punctured at 4-6 points
Outcomes	**Primary outcomes:** ovulation rate **Secondary outcomes:** endometrial thickness on the day of hCG injection, rates of clinical pregnancy, spontaneous abortion, live birth and multiple pregnancies
Notes	**Ethical approval:** yes, the trial was approved by Mansoura University Hospital Research Ethics Committee. **Informed consent:** yes, all participants gave informed consent before inclusion in the trial. **Source of funding:** not stated **Conflicts of interest:** quote:“Conflict of interest statement: We declare that we have no conflict of interest” Authors contacted about information on OHSS **Power calculation:** quote: "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." Trial was moved to awaiting classification as there are concerns about the validity of the trial data.

Abu Hashim 2010a

Methods	Randomised controlled clinical trial **Duration and location of the trial:** quote: "The study comprised of 260 women with CC-resistant PCOS among those attending the Outpatient Clinic in Mansoura University Hospitals, and a private practice setting in the period from August 2006 to March 2009.“
Participants	**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. **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 programme of physical activity were also excluded. **Number of centres:** 2, outpatient clinic in Mansoura University hospitals and a private practice setting **Number of women randomised:** 260, 128 in the letrozole group and 132 in the LOD group **Number of women analysed:** 128 in the letrozole group and 132 in the LOD group **Number of withdrawals/exclusions/loss to follow-up and reasons:** none **Age (y):** group A letrozole: 27.3 ± 2.6, group B LOD: 26.4 ± 2.4 **BMI (kg/m^2):** group A letrozole: 26.4 ± 3.3, group B LOD: 26.6 ± 3.6 **Duration of infertility (y):** group A letrozole: 4.3 ± 1.11, group B LOD: 4.5 ± 1.24

Abu Hashim 2010a *(Continued)*

	Country: Egypt
Interventions	**Group A:** letrozole, 2.5 mg/day orally given for 5 days starting from day 3 of the cycle **Group B:** LOD, laparoscopy was performed using 3-puncture technique. Each ovary was cauterised at 4 points, each for 4 s at 40 W for a depth of 4 mm with a mixed current, using a monopolar electrosurgical needle.
Outcomes	**Primary outcome:** ovulation rate **Secondary outcomes:** midcycle endometrial thickness (mm), biochemical pregnancy/cycle, clinical pregnancy/participant, biochemical miscarriage/cycle, clinical miscarriage/participant and live birth rates
Notes	**Ethical approval:** yes, the trial was approved by Mansoura University Hospital Research Ethics Committee. **Informed consent:** yes, all participants gave informed consent before inclusion in the trial. **Source of funding:** not stated **Conflicts of interest:** quote:“Conflict of interest statement: We declare that we have no conflict of interest” **Power calculation:** quote: "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)." Trial was moved to awaiting classification as there are concerns about the validity of the trial data.

Aygen 2007

Methods	Randomised clinical trial
Participants	15 infertile women with PCOS
Interventions	Women were randomised into 3 treatment groups: **Group 1:** continuous metformin was used at the dose of 850 mg/tid/day for 6 months; afterwards, daily 2.5 mg letrozole between 3 and 7 days of the menstrual cycle was added to the metformin therapy. **Group 2:** participants received only daily 2.5 mg letrozole between days 3 and 7 of the menstrual cycle. **Group 3:** participants received daily 100 mg CC only between days 3 and 7 of the menstrual cycle.
Outcomes	Unclear
Notes	The article was written in Turkish, and we were not able to have it translated properly.

Ghoneim 2020

Methods	Randomised controlled clinical trial

Ghoneim 2020 *(Continued)*

	Duration and location of the trial: quote: "The study included a total of 120 overweight women complaining of polycystic ovary syndrome and attending infertility outpatient clinic of Tanta University Hospital, from January 2017 to December 2019 for the treatment of infertility.“
Participants	**Inclusion criteria:** quote: "All patients fulfilled the following inclusion criteria: Age 18-30 years. Polycystic ovarian syndrome women according to Rotterdam Criteria 2003." **Exclusion criteria:** quote: "1. Patients with a history of cardiovascular disease, diabetes or liver, and kidney failure were excluded. 2. Similarly, patients whose partner's sperm count was less than 20 million/ ml and sperm motility less than 20% were also not included in the study. 3. Patients who had undergone surgical treatment of infertility. 4. Recent history of ovulatory inducing drugs within the last 3 months." **Number of women randomised:** 120 **Number of women analysed:** 120 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 0 **Number of centres:** single-centre trial **Age (y):** mean age was 26.40 ± 5.20 years and in CC group and mean age was 26.50 ± 5.10years in the let group. **BMI (kg/m^2):** mean BMI was 27.50 ± 1.43 in CC group and mean BMI was 27.45 ± 1.36 in letrozole group. **Duration of infertility (y):** mean duration of infertility was 2.90 ± 1.40 years in CC group and mean duration of infertility was 2.88 ± 1.21 years in letrozole group. **Country:** Egypt
Interventions	**Group A:** quote: "Metformin–CC group (envelopes number 1– 60): All patients of both groups were received 1500 mg metformin HCl daily, 500 mg three times a day (Cidophage; Chemical Industries Development, Cairo, Egypt). Also, the patients of the metformin– CC group (CC Group) received 100 mg CC (Clomid; Global Napi Pharmaceuticals, Cairo, Egypt) for 5 days starting from 3rd day of their menstrual cycle." **Group B:** quote: "Metformin–Letrozole group (envelopes number 61–120). .... and those in the metformin–letrozole group (letrozole Group) received 5 mg letrozole (Letrozole, Technopharma, Cairo, Egypt) for 5 days from 3rd day of their menstrual cycle."
Outcomes	**Primary outcomes:** clinical pregnancy rate **Secondary outcomes:** endometrial thickness, ovulation rate, no. of follicles, no. of follicles > 18 mm, mean follicular diameter
Notes	**Ethical approval:** not reported **Informed consent:** quote: "Informed written consents were obtained from the patients participating in this study after informing them about aims of study, the steps of study, drugs given and the capability to withdraw at any time." **Source of funding:** not reported **Power calculation:** not reported Trial was moved to awaiting classification as there are concerns about the validity of the trial data.

Jindal 2019

Methods	prospective clinical trial
Participants	236 infertile patients (2016-2018) who were diagnosed as having anovulation due to PCOS
Interventions	Quote: "All patients were randomised by computer in two groups -Letrazole group (2.5-5mg) and CC group (50 mg to 100 mg) given for 5 days."
Outcomes	Ovulation rate
Notes	No trial data available, only conference abstract from ESHRE 2019 without any further information

Kamel 2019

Methods	Randomised controlled trial **Duration and location of the trial:** quote: "The current study was a randomized open-labeled controlled study conducted in Assiut Women Health Hospital between April 2017 and October 2018."
Participants	**Inclusion criteria:** all primary and secondary infertile women less than 39 years due to anovulation due to PCOD according to Rotterdam diagnostic criteria • Primary or secondary infertility. • Absence of galactorrhoea • Normal serum prolactin • Normal Hysterosalpinography • Husband has normal semen analysis **Exclusion criteria:** • Male factor infertility, tubal factor infertility • Endocrinopathy as (hypothyroidism, hyperprolactinemia) • BMI > 35 kg/m^2 • Patients with previous ovarian surgery including LOD **Number of centres:** single-centre trial **Number of women randomised:** 120 **Number of women analysed:** 110 **Number of withdrawals/exclusions/loss to follow-up and reasons:** 5 in each group respectively, lost to follow-up **Age (y):** group A CC + NAC: 27.89 ± 5.92; Group B Let: 27.84 ± 5.17 **BMI (kg/m^2):** group A CC + NAC: 28.67 ± 3.0; Group B Let: 27.28 ± 3.43 **Duration of infertility (y):** Group A CC + NAC: 3.08 ± 2.17; Group B Let: 2.96 ± 1.75 **Country:** Egypt
Interventions	**Group A:** quote: "CC 100 mg +NAC 600 mg started from third day of cycle for 5 days." **Group B:** quote: "Lertozole 5 mg alone started from third day of cycle for 5 days."
Outcomes	**Primary outcome:** ovulation rate in both groups

Kamel 2019 *(Continued)*

	Secondary outcomes: mid-cyclic endometrial thickness, OHSS, clinical pregnancy and miscarriage rates
Notes	**Ethical approval:** yes, quote: "The Institutional Ethical Review board approved the study." **Informed consent:** yes, quote: "All patients signed informed written consent before participation in the study." **Source of funding:** not stated **Conflicts of interest:** not stated **Power calculation:** not stated Trial was moved to awaiting classification as there are concerns about the validity of the trial data.

Lorzadeh 2011

Methods	Randomised clinical trial
Participants	100 infertile women with PCOS referred to Asali Hospital and private clinic in 2008
Interventions	Women were randomised into 2 groups of 50 that were treated with 5 mg letrozole or 100 mg CC from day 3 to 7 of the menstrual cycle.
Outcomes	Pregnancy rate
Notes	The article was written in Persian, but we were not able to have it translated properly.

NCT02551367

Methods	Randomised controlled trial
Participants	110 infertile women diagnosed with PCOS, aged 20-35, distributed randomly
Interventions	55 women will receive letrozole 2.5 mg twice daily orally from the 2nd to the 6th day of the cycle for 3 successive cycles. 55 women will receive CC 50 mg twice daily orally from the 2nd to the 6th day of the cycle for 3 successive cycles.
Outcomes	• Rate of ovulation assessed by number of mature follicles produced per cycle • Serum progesterone level on day 21 (assessed up to 24 weeks) • Mean endometrial thickness (assessed up to 24 weeks) • Chemical pregnancy (assessed up to 24 weeks) • Ongoing pregnancy (assessed up to 24 weeks)
Notes	We found no trial data, although trial completed since 2016 on clinicaltrials.gov

NCT02703649

Methods	A prospective randomised clinical trial

NCT02703649 *(Continued)*

Participants	PCOS patients who require induction of ovulation will prospectively randomised into two groups
Interventions	• Single 20 mg dose of Letrozole on day 3 of the menstrual cycle. Monitoring for response will include the usual measurements of serum Estradiol (E2), FSH, LH, progesterone and transvaginal ultrasound for follicular count and endometrial thickness measurement. First monitoring will be on day 7 of the cycle and the rest of the monitoring will be determined according to response. • Daily dose of Letrozole 2.5 mg starting day 3 for 5 days. Monitoring for response will include serum estradiol, FSH, LH, progesterone and transvaginal ultrasound for follicular count and endometrial thickness measurement. First day of monitoring will be on day 7 and the rest of monitoring will be determined according to response.
Outcomes	Primary outcomes: • Comparison of the number of follicle > 15 mm at day of ovulation Secondary outcomes: • Pregnancy rate • Comparison between the two groups • Estradiol levels at day of ovulation triggering OHSS • Clinical pregnancy rate
Notes	Estimated trial completion date 2018, no data available; author has been contacted, no response

NCT03664050

Methods	Randomised controlled clinical trial
Participants	90 women with PCOS
Interventions	Drug: group A 2.5 mg letrozole oral tablets Procedure: group B LOD
Outcomes	Ovulation rate, biochemical pregnancy rate, clinical pregnancy rate
Notes	Contact: Ahmed Abdelshafy ahmedshafy@hotmail.com Trial was registered in 2018, no update since

Rezk 2018

Methods	Randomised clinical trial **Duration and location of the trial:** quote: "This was a single center balanced randomized parallel group study carried out at the Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Shibin El-kom city, Menoufia governorate, Egypt during the period between the middle of October 2016 and the beginning of May 2017."
Participants	**Inclusion criteria: quote:** "Two hundred and nine patients diagnosed with PCOS based on the revised Rotterdam criteria with LH/FSH ratio above 2, who failed to respond to CC 150 mg daily for five days after 3–6 cycles of stimulation were recruited. A normal semen analysis, normal uterine cavity, and bilateral tubal patency were other criteria for inclusion."

Rezk 2018 *(Continued)*

	Exclusion criteria:"Patients with endocrine disorders affecting ovulation as hyperprolactinemia, thyroid, and adrenal gland diseases as well as those with anatomic abnormalities as uterine fibroids, endometriosis, ovarian cyst, and pelvic inflammatory disease were excluded from the study." **Number of centres:** single-centre trial **Number of women randomised:** 209, group A CC/metformin: 105, group B letrozole: 104 **Number of women analysed:** CC/metformin 102, letrozole 100 **Number of withdrawals/exclusions/loss to follow-up and reasons:** group A = 3, group B = 4 **Age (y):** group A CC/metformin: 24.6 ± 2.1, group B letrozole 24.2 ± 2.8 **BMI (kg/m²):** group A CC/metformin: 24.2 ± 4.3, group B letrozole 23.7 ± 4.8 **Duration of infertility (y):** group A CC/metformin: 28.2 ± 6.9, group B letrozole 27.8 ± 7.1 **Country:** Egypt
Interventions	**Group A:** (CC and metformin group, n = 102): received CC 100 mg (clomid, 50 mg tablets, Sanofi-aventis) daily from the 3rd day of the cycle for 5 days combined with metformin 500 mg (cidophage 500 mg, Cid Pharmaceuticals, Egypt) three times daily throughout the whole cycle. **Group B:** (letrozole group, n = 100): received letrozole 2.5 mg (letrozole 2.5 mg, Acdima International, Egypt) twice daily from the 3rd day of the cycle for 5 days.
Outcomes	• Ovulation rate, number of mature follicles and endometrial thickness on the day of hCG administration • Pregnancy rate during the three cycles of stimulation: pregnancy was diagnosed by positive pregnancy test in the serum to be confirmed by transvaginal ultrasound for confirmation of foetal cardiac activity • Adverse effects of the drugs used for induction of ovulation • Patient acceptability in terms of overall discomfort, overall satisfaction with treatment and advisability of the regimen to other women with similar condition
Notes	**Ethical approval and informed consent:** quote: "The study protocol was formally reviewed and approved by the local review board and the ethical committee at Menoufia faculty of Medicine with an informed consent obtained from all patients before commencement of the study." **Sample size calculation:** quote: "The sample size was calculated based on the assumption of a difference of 10% between the two groups regarding the success rate of inducing ovulation. The study was designed to have 90% power at the 5% significance level via enrolment of 100 patients in each group." **Funding**: not reported **Conflicts of interest**: none **Notes from reviewers:** trial was moved to awaiting classification due to concerns about validity of the trial data, more than 200 inclusions within a few months. Authors have been contacted about trial data.

Safdarian 2012

Methods	Double-blind randomised clinical trial

Safdarian 2012 *(Continued)*

Participants	59 infertile women who met inclusion criteria for PCOS were evaluated in the Infertility Clinic of Shariati Hospital in Tehran, Iran in 2010-2011
Interventions	Participants assigned to 2 letrozole and 1 letrozole-plus-hMG groups
Outcomes	Reported no outcomes of interest to our review
Notes	The article was written in Persian, but we were not able to have it translated properly.

Saha 2020

Methods	Randomised controlled trial
Participants	Total 108 anovulatory PCO women in the age group 20 to 36 years who had previous R3 failed treatment cycles with CC
Interventions	Group A: letrozole plus 3 doses of gonadotropin Group B: continuous gonadotropin 54 patients in each group
Outcomes	Both groups were evaluated in respect of terminal endocrinological profile, number of follicles, ovulation rate, pregnancy rate and outcome, adverse effects and cost-effectivity.
Notes	Only conference abstract found, no full article available; no further trial or author information

Shirin 2009

Methods	Randomised clinical trial, quote: "The cases were assigned to two groups through simple random sampling"
Participants	100 infertile, 20 to 35-year-old women with PCOS attending Vali-e-Asr Infertility Clinic from April 2003 to April 2007
Interventions	Group A: CC plus hMG Group B: letrozole plus hMG
Outcomes	Pregnancy, miscarriage and multiple pregnancy rates
Notes	The article was written in Persian, but we were not able to have it translated properly.

BMI: body mass index; CC: clomiphene citrate; ESHRE/ASRM: European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; hCG: human chorionic gonadotropin; hMG: human menopausal gonadotropin; LH: luteinising hormone; FSH: follicle-stimulating hormone; NAC: N-acetyl cysteine; PCO: polycystic ovaries; PCOS: polycystic ovary syndrome; PCOD: polycystic ovary disease; LOD: laparoscopic ovarian drilling; OHSS: ovarian hyperstimulation syndrome; W: watts; WHO: World Health Organisation

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

ChiCTR2100042082

Study name	Comparison of the clinical outcomes with different doses of letrozole in PCOS patients undergoing ovulation induction: a prospective, randomized, controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria**: aged 20-35 years, PCOS patients **Exclusion criteria**: clinically significant systemic disease such as renal failure; nonclassic congenital adrenal hyperplasia, primary hypothyroidism, hyperprolactinemia, Cushing syndrome, virilising adrenal or ovarian tumours; administration of hormonal treatments in the previous 3 months
Interventions	Experimental group: letrozole (high dose) Control group: letrozole (low dose)
Outcomes	• Ovulation rate • Clinical pregnancy rate • Number of preovulatory follicles • Multiple pregnancy rate
Starting date	20 January 2021
Contact information	Fu Yonglun: fuyonglunivf@163.com
Notes	

CTRI/2018/04/013343

Study name	A randomized controlled trial comparing the effect of letrozole and CC on endometrial development in infertile women with polycystic ovarian disease
Methods	Randomised, parallel group trial
Participants	Infertile women with PCOS; total sample size = 90 women
Interventions	There will be two groups: • letrozole (2.5 mg to 7.5 mg) from day 2 to day 5 x 3 cycles • CC (50 mg to 150 mg) from day 2 to day 5 x 3 cycles
Outcomes	**Primary outcome**: endometrial thickness **Secondary outcomes**: ovulation rate, pregnancy rate
Starting date	20 April 2018 (first enrolment)
Contact information	Dr Shavina Bansal Department of Obs and Gynae, AIIMS hospital, JODHPUR Basni, phase 2, Jodhpur, Rajasthan, Jodhpur, RAJASTHAN, 342005, India ananyasworld888@gmail.com
Notes	Estimated duration of trial: 2 years and 1 month, until May 2020

Cutler 2018

Study name	A randomized controlled trial comparing lifestyle intervention to letrozole for ovulation in women with polycystic ovary syndrome: a trial protocol
Methods	Randomised controlled trial
Participants	240 women diagnosed with PCOS, according to the Rotterdam criteria, who are trying to conceive
Interventions	Participants will be randomised to either a comprehensive lifestyle intervention programme or prescribed an oral fertility medication, letrozole. These two groups will be further randomised to consume either myo-inositol or a placebo.
Outcomes	Primary outcome: ovulation rate Secondary outcome: conception Other outcomes: miscarriage rates, validated rating measures of overall quality of life (including social, relational, mind/body and emotional subcategories) and mental health scores (depression, anxiety, and stress)
Starting date	2015, estimated end date 2018
Contact information	Contact: Anthony P Cheung, MBBS MPH MBA; email: ACheung@fertilitywithgrace.com Contact: Dylan A Cutler, BSc dacutl08@gmail.com
Notes	

Huang 2020

Study name	A multicenter randomized trial of personalized acupuncture, fixed acupuncture, letrozole, and placebo letrozole on live birth in infertile women with polycystic ovary syndrome
Methods	The trial is designed as an assessor-blinded RCT
Participants	A total of 1100 infertile women with PCOS will be recruited from 28 hospitals
Interventions	Participants will be randomly allocated to 4 groups: personalised acupuncture, fixed acupuncture, letrozole, or placebo letrozole. They will receive treatment for 16 weeks.
Outcomes	Primary outcome: live birth Secondary outcomes: ovulation rate, conception rate, pregnancy rate, pregnancy loss rate, changes in hormonal and metabolic parameters, and changes in quality of life scores Adverse events will be recorded throughout the trial.
Starting date	August 2018
Contact information	Jie Qiao, jie.qiao@263.net
Notes	

IRCT2016030926962N2

Study name	Comparing the efficacy of long-term and short-term doses of letrozole in ovulation induction among patients with polycystic ovary syndrome
Methods	Randomised single blinded trial
Participants	200 participants **Inclusion criteria**: • age 38-18 years • PCOS proven • resistance to CC • thyroid - tested normal • normal prolactin • absence of other causes of infertility, including male factor • normal hysterosalpangiography **Exclusion criteria**: • ovarian cysts • FSH > 10 • OHSS
Interventions	Group I: (short-term letrozole group; patients will receive oral letrozole 7.5 mg, from day 3 to 7 of menstruation) Group II: (long-term letrozole group; patients will receive 5 mg oral letrozole from day 2 or 3 of menstruation until 10 days (all participants will receive oral letrozole for three menstrual cycles)
Outcomes	**Primary outcomes**: no. of mature follicles, endometrial thickness **Secondary outcomes**: biochemical pregnancy by b-hCG, abortion rate, "Multiple event"
Starting date	2016, registered while recruiting
Contact information	Tahereh Behroozi Lak; Mail: t.behrooz2@yahoo.com Urmia University of Medical Sciences
Notes	

NCT03009838

Study name	Letrozole versus laparoscopic ovarian drilling in polycystic ovary syndrome
Methods	Randomised, open-label, clinical trial
Participants	**Inclusion criteria** • History of at least 1 year of infertility, either primary or secondary • BMI: 25 kg/m^{2}to35 kg/m^2 • Normal fallopian tubes • Normal semen analysis of the husband • Women who will agree to participate in the trial

NCT03009838 *(Continued)*

	Exclusion criteria • BMI > 35 kg/m^2 • Contraindication to general anaesthesia • Previous LOD • Presence of other causes of infertility • Women who had received metformin, gonadotropin, oral contraceptives or other hormonal drugs during the preceding 6 months • Women who intended to start a diet programme • Women who refuse to participate in the trial
Interventions	Group A: letrozole 2.5 mg Group B: LOD
Outcomes	Ovulation rate
Starting date	January 2017
Contact information	Responsible party: Ahmed Mohamed Abbas, Assiut University
Notes	Estimated primary completion date: December 2018

Priest 2019

Study name	Comparison of letrozole or clomifene for ovulation induction in women with polycystic ovarian syndrome
Methods	Interventional randomised controlled trial
Participants	Adult women diagnosed with PCOS seeking fertility treatment to participate in this trial
Interventions	Participants will be randomised online via a secure Internet facility at the level of the individual in a 1:1 ratio to either letrozole or clomifene and at the same time randomised to metformin or placebo. Planned IMP interventions: letrozole oral tablet 2.5 mg to 7.5 mg daily or clomifene 50 mg to 150 mg daily for 5 days of each menstrual cycle for up to 6 treatment cycles, with concomitant randomisation to an escalating dose of metformin to 1500 mg or placebo daily. Letrozole, clomifene, metformin and placebo will be provided as over-encapsulated tablets in numbered treatment packages. The metformin/placebo will be provided at the same time as letrozole/clomifene.
Outcomes	**Primary outcome** • Live births at and beyond 34 completed weeks of gestation measured using patient records **Secondary outcomes** • Miscarriage rate (defined as delivery before 24 weeks of gestation) • Ongoing pregnancy at 12 weeks (range 11 to 14 weeks) of gestation • Multiple pregnancies • Ovulation rate • Time to pregnancy
Starting date	March 2020, expected end date July 2023

Priest 2019 *(Continued)*

Contact information	Lee Priest l.priest.1@bham.ac.uk
Notes	

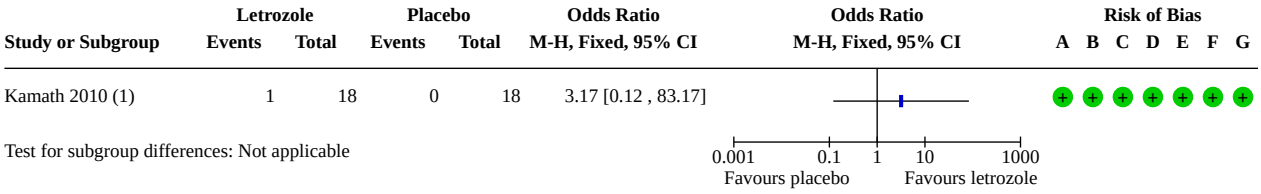
BMI: body mass index; CC: clomiphene citrate; FSH: follicle-stimulating hormone; hCG: hCG: human chorionic gonadotropin; LOD: laparoscopic ovarian drilling; PCOS: polycystic ovary syndrome; OHSS: ovarian hyperstimulation syndrome; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Letrozole compared to placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2 Ovarian hyperstimulation syndrome rate	2	167	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.05, 0.05]
1.3 Clinical pregnancy rate	2	167	Odds Ratio (M-H, Fixed, 95% CI)	2.88 [1.08, 7.66]
1.4 Miscarriage rate per woman	2	167	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.26, 9.89]
1.5 Miscarriage rate per pregnancy	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Letrozole compared to placebo, Outcome 1: Live birth rate



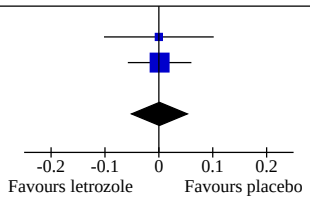
Footnotes
(1) Clomiphene-resistant women; letrozole, 2.5 mg/day versus placebo

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Letrozole compared to placebo, Outcome 2: Ovarian hyperstimulation syndrome rate

Study or Subgroup	Letrozole Events	Letrozole Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Kamath 2010 (1)	0	18	0	18	21.6%	0.00 [-0.10 , 0.10]
Zarei 2015 (2)	2	64	2	67	78.4%	0.00 [-0.06 , 0.06]
Total (95% CI)		**82**		**85**	**100.0%**	**0.00 [-0.05 , 0.05]**
Total events:	2		2			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



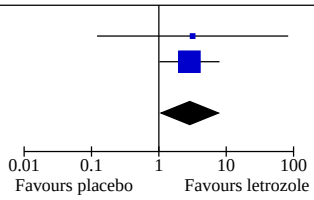
Footnotes
(1) Clomiphene-resistant women; letrozole, 2.5 mg/day versus placebo
(2) Clomiphene-resistant women; letrozole 5 mg versus placebo, followed by IUI

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Letrozole compared to placebo, Outcome 3: Clinical pregnancy rate

Study or Subgroup	Letrozole Events	Letrozole Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kamath 2010 (1)	1	18	0	18	9.1%	3.17 [0.12 , 83.17]
Zarei 2015 (2)	14	64	6	67	90.9%	2.85 [1.02 , 7.95]
Total (95% CI)		**82**		**85**	**100.0%**	**2.88 [1.08 , 7.66]**
Total events:	15		6			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Not applicable



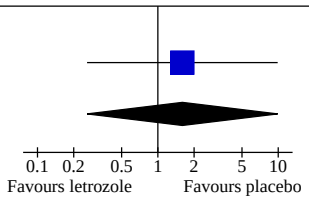
Footnotes
(1) Clomiphene-resistant women; letrozole, 2.5 mg/day versus placebo
(2) Clomiphene-resistant women; letrozole 5 mg versus placebo, followed by IUI

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Letrozole compared to placebo, Outcome 4: Miscarriage rate per woman

Study or Subgroup	Letrozole Events	Letrozole Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kamath 2010 (1)	0	18	0	18		Not estimable
Zarei 2015 (2)	3	64	2	67	100.0%	1.60 [0.26 , 9.89]
Total (95% CI)		**82**		**85**	**100.0%**	**1.60 [0.26 , 9.89]**
Total events:	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable



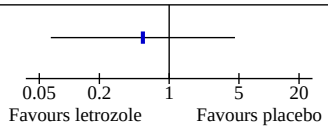
Footnotes
(1) Clomiphene-resistant women; letrozole, 2.5 mg/day versus placebo
(2) Clomiphene-resistant women; letrozole 5 mg versus placebo, followed by IUI

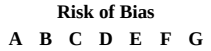
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Letrozole compared to placebo, Outcome 5: Miscarriage rate per pregnancy

Study or Subgroup	Letrozole Events	Letrozole Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI
Zarei 2015 (1)	3	14	2	6	0.55 [0.07 , 4.56]

Test for subgroup differences: Not applicable



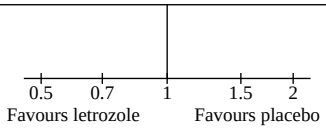


Footnotes
(1) Clomiphene-resistant women; letrozole 5 mg versus placebo, followed by IUI

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Letrozole compared to placebo, Outcome 6: Multiple pregnancy rate

Study or Subgroup	Letrozole Events	Letrozole Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
Kamath 2010 (1)	0	18	0	18	Not estimable		+	+	+	+	+	+	+



Footnotes

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

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Letrozole compared to SERM with or without adjuncts, followed by timed intercourse

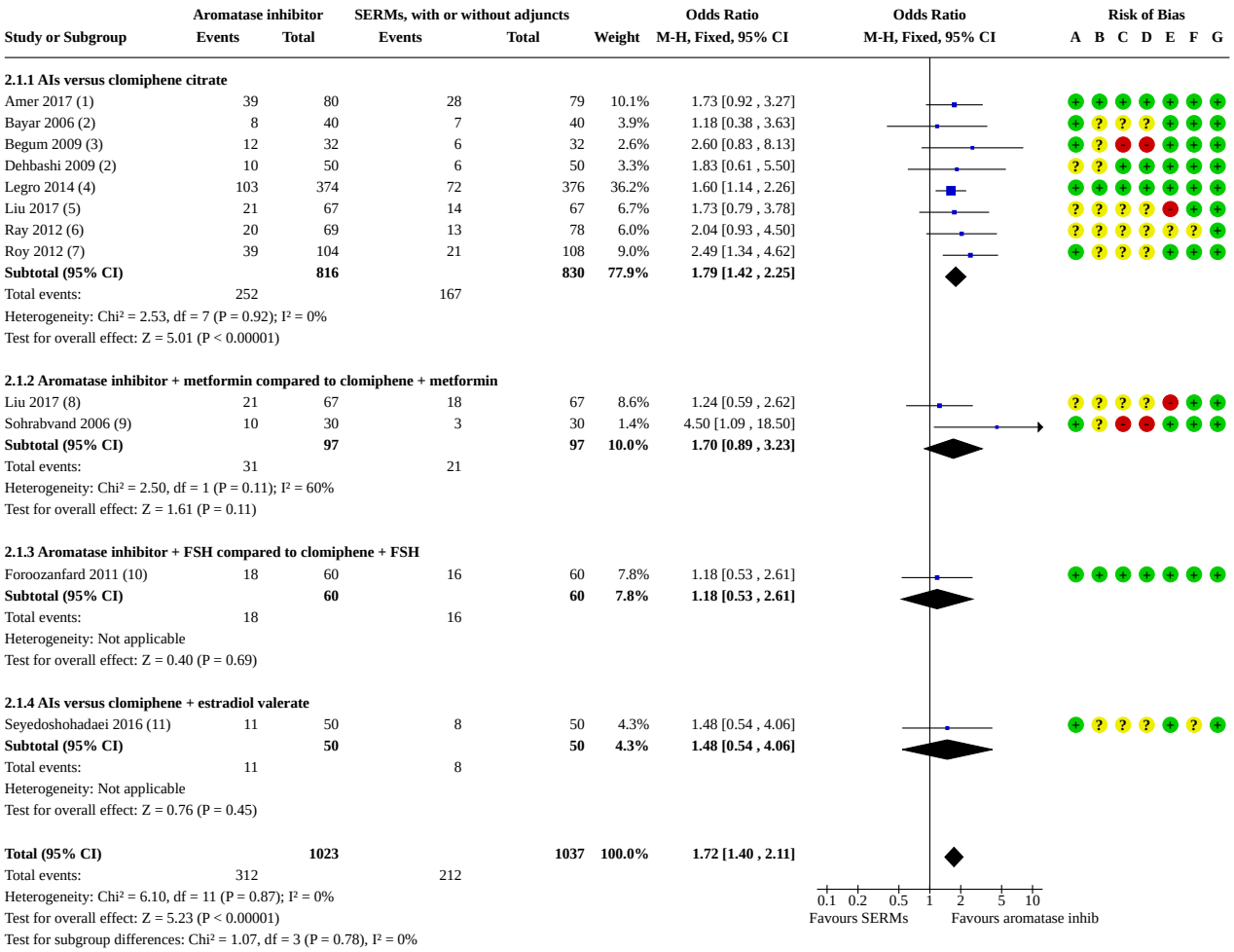
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth rate	11	2060	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [1.40, 2.11]
2.1.1 AIs versus clomiphene citrate	8	1646	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [1.42, 2.25]
2.1.2 Aromatase inhibitor + metformin compared to clomiphene + metformin	2	194	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.89, 3.23]
2.1.3 Aromatase inhibitor + FSH compared to clomiphene + FSH	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.53, 2.61]
2.1.4 AIs versus clomiphene + estradiol valerate	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.54, 4.06]
2.2 Live birth rate by BMI	9	1880	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [1.41, 2.15]
2.2.1 BMI > 25	6	1428	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [1.44, 2.35]
2.2.2 BMI < 25	3	452	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.98, 2.25]
2.3 Live birth rate by first- or second-line treatment	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 No previous ovulation induction	4	1089	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [1.22, 2.14]
2.3.2 CC-resistant women	4	344	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [1.08, 2.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.3 Unclear or mixed study cohort	3	627	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [1.31, 2.69]
2.4 Impact of allocation bias for live birth rate	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 Unclear risk of allocation	8	1031	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.42, 2.54]
2.4.2 Low risk of allocation	3	1029	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [1.18, 2.08]
2.5 Impact of detection bias for live birth rate	11	2060	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [1.40, 2.11]
2.5.1 High risk of detection	1	64	Odds Ratio (M-H, Fixed, 95% CI)	2.60 [0.83, 8.13]
2.5.2 Low risk of detection	5	1189	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [1.26, 2.16]
2.5.3 Unclear risk of detection	5	807	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [1.27, 2.44]
2.6 Impact of attrition bias for live birth rate	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.6.1 Unclear risk of attrition	1	147	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.93, 4.50]
2.6.2 Low risk of attrition	9	1645	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [1.39, 2.19]
2.6.3 High risk of attrition	1	268	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.85, 2.50]
2.7 Ovarian hyperstimulation syndrome rate	10	1848	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.01]
2.7.1 AIs versus clomiphene citrate	8	1572	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
2.7.2 Aromatase inhibitor + hMG versus clomiphene + hMG	2	276	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.04, 0.04]
2.8 Ovarian hyperstimulation syndrome rate by BMI	9		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
2.8.1 BMI > 25	4	1163	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.01, 0.00]
2.8.2 BMI < 25	5	605	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Clinical pregnancy rate	23	3321	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.45, 1.98]
2.9.1 Aromatase inhibitor versus clomiphene citrate	17	2516	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [1.42, 2.03]
2.9.2 Aromatase inhibitor + metformin versus clomiphene + metformin	3	294	Odds Ratio (M-H, Fixed, 95% CI)	1.86 [1.05, 3.29]
2.9.3 Aromatase inhibitor + hMG versus clomiphene + hMG	2	276	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.82, 2.27]
2.9.4 AIs versus tamoxifen	2	135	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.64, 3.90]
2.9.5 AIs versus clomiphene + estradiol valerate	1	100	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [0.94, 6.46]
2.10 Impact of allocation bias for clinical pregnancy rate	21		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.10.1 Unclear risk of allocation	17	1931	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [1.41, 2.14]
2.10.2 Low risk of allocation	4	580	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [1.10, 2.21]
2.11 Miscarriage rate per woman	15	2422	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [1.01, 1.87]
2.11.1 AIs versus clomiphene citrate	10	1752	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.98, 1.99]
2.11.2 Aromatase inhibitor + metformin versus clomiphene + metformin	3	294	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.52, 2.82]
2.11.3 Aromatase inhibitor + hMG versus clomiphene + hMG	2	276	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.31, 2.27]
2.11.4 AIs versus clomiphene + estradiol valerate	1	100	Odds Ratio (M-H, Fixed, 95% CI)	12.21 [0.66, 226.97]
2.12 Miscarriage rate per pregnancy	15	736	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.32]
2.12.1 AIs versus clomiphene citrate	10	529	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.63, 1.42]
2.12.2 Aromatase inhibitor + metformin versus clomiphene + metformin	3	79	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 2.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.12.3 Aromatase inhibitor + hMG versus clomiphene + hMG	2	104	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.23, 1.96]
2.12.4 AIs versus clomiphene + estradiol valerate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	8.13 [0.39, 167.90]
2.13 Multiple pregnancy rate	14	2247	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.42, 1.32]
2.13.1 Aromatase inhibitor versus clomiphene citrate	12	1971	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.35, 1.34]
2.13.2 Aromatase inhibitor + hMG versus clomiphene + hMG	2	276	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.29, 3.05]

Analysis 2.1. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 1: Live birth rate



Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 AIs versus clomiphene citrate						
Amer 2017 (1)	39	80	28	79	10.1%	1.73 [0.92 , 3.27]
Bayar 2006 (2)	8	40	7	40	3.9%	1.18 [0.38 , 3.63]
Begum 2009 (3)	12	32	6	32	2.6%	2.60 [0.83 , 8.13]
Dehbashi 2009 (2)	10	50	6	50	3.3%	1.83 [0.61 , 5.50]
Legro 2014 (4)	103	374	72	376	36.2%	1.60 [1.14 , 2.26]
Liu 2017 (5)	21	67	14	67	6.7%	1.73 [0.79 , 3.78]
Ray 2012 (6)	20	69	13	78	6.0%	2.04 [0.93 , 4.50]
Roy 2012 (7)	39	104	21	108	9.0%	2.49 [1.34 , 4.62]
Subtotal (95% CI)		**816**		**830**	**77.9%**	**1.79 [1.42 , 2.25]**
Total events:	252		167			
Heterogeneity: Chi² = 2.53, df = 7 (P = 0.92); I² = 0%						
Test for overall effect: Z = 5.01 (P < 0.00001)						
2.1.2 Aromatase inhibitor + metformin compared to clomiphene + metformin						
Liu 2017 (8)	21	67	18	67	8.6%	1.24 [0.59 , 2.62]
Sohrabvand 2006 (9)	10	30	3	30	1.4%	4.50 [1.09 , 18.50]
Subtotal (95% CI)		**97**		**97**	**10.0%**	**1.70 [0.89 , 3.23]**
Total events:	31		21			
Heterogeneity: Chi² = 2.50, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 1.61 (P = 0.11)						
2.1.3 Aromatase inhibitor + FSH compared to clomiphene + FSH						
Foroozanfard 2011 (10)	18	60	16	60	7.8%	1.18 [0.53 , 2.61]
Subtotal (95% CI)		**60**		**60**	**7.8%**	**1.18 [0.53 , 2.61]**
Total events:	18		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
2.1.4 AIs versus clomiphene + estradiol valerate						
Seyedoshohadaei 2016 (11)	11	50	8	50	4.3%	1.48 [0.54 , 4.06]
Subtotal (95% CI)		**50**		**50**	**4.3%**	**1.48 [0.54 , 4.06]**
Total events:	11		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**1023**		**1037**	**100.0%**	**1.72 [1.40 , 2.11]**
Total events:	312		212			
Heterogeneity: Chi² = 6.10, df = 11 (P = 0.87); I² = 0%						
Test for overall effect: Z = 5.23 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.07, df = 3 (P = 0.78), I² = 0%						

Footnotes

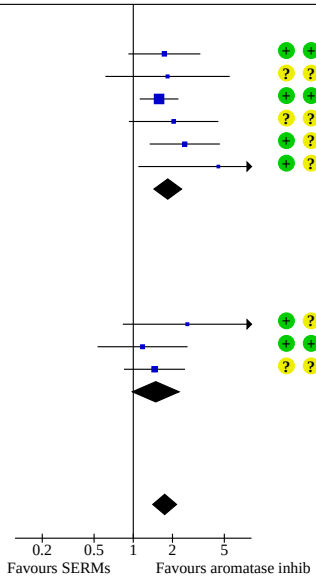
(1) Previous subfertility treatment unknown; starting dose 2.5 mg letrozole vs 50 mg clomiphene citrate/day
(2) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene 100 mg/day
(3) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(4) Cumulative live birth rate; treatment naïve patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(5) Previous treatment for subfertility unknown; clomiphene 50 - 150 mg versus letrozole 5 mg
(6) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene 100 mg/day
(7) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 - 5 mg/day versus clomiphene 50 - 100 mg/day
(8) Previous treatment for subfertility unknown; clomiphene 50 - 150 mg versus letrozole 5 mg; both groups received 1000 - 1500 mg metformin daily
(9) Clomiphene-resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500mg/day
(10) Clomiphene-resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG
(11) Clomiphene-resistant women; letrozole 5mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 2: Live birth rate by BMI

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
2.2.1 BMI > 25							
Amer 2017 (1)	39	80	28	79	10.9%	1.73 [0.92 , 3.27]	+ + + + + + +
Dehbashi 2009 (2)	10	50	6	50	3.6%	1.83 [0.61 , 5.50]	? ? + + + + +
Legro 2014 (3)	103	374	73	376	39.8%	1.58 [1.12 , 2.22]	+ + + + + + +
Ray 2012 (4)	20	69	13	78	6.5%	2.04 [0.93 , 4.50]	? ? ? ? ? ? +
Roy 2012 (5)	39	104	21	108	9.7%	2.49 [1.34 , 4.62]	+ ? ? ? + + +
Sohrabvand 2006 (6)	10	30	3	30	1.5%	4.50 [1.09 , 18.50]	+ ? - - + + +
Subtotal (95% CI)		**707**		**721**	**72.1%**	**1.84 [1.44 , 2.35]**	
Total events:	221		144				
Heterogeneity: Chi² = 3.32, df = 5 (P = 0.65); I² = 0%							
Test for overall effect: Z = 4.88 (P < 0.00001)							
2.2.2 BMI < 25							
Begum 2009 (7)	12	32	6	32	2.8%	2.60 [0.83 , 8.13]	+ ? - - + + +
Foroozanfard 2011 (8)	18	60	16	60	8.5%	1.18 [0.53 , 2.61]	+ + + + + + +
Liu 2017 (9)	42	134	32	134	16.6%	1.46 [0.85 , 2.50]	? ? ? ? - + +
Subtotal (95% CI)		**226**		**226**	**27.9%**	**1.49 [0.98 , 2.25]**	
Total events:	72		54				
Heterogeneity: Chi² = 1.26, df = 2 (P = 0.53); I² = 0%							
Test for overall effect: Z = 1.88 (P = 0.06)							
Total (95% CI)		**933**		**947**	**100.0%**	**1.74 [1.41 , 2.15]**	
Total events:	293		198				
Heterogeneity: Chi² = 5.31, df = 8 (P = 0.72); I² = 0%							
Test for overall effect: Z = 5.16 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.75, df = 1 (P = 0.39), I² = 0%							



Footnotes

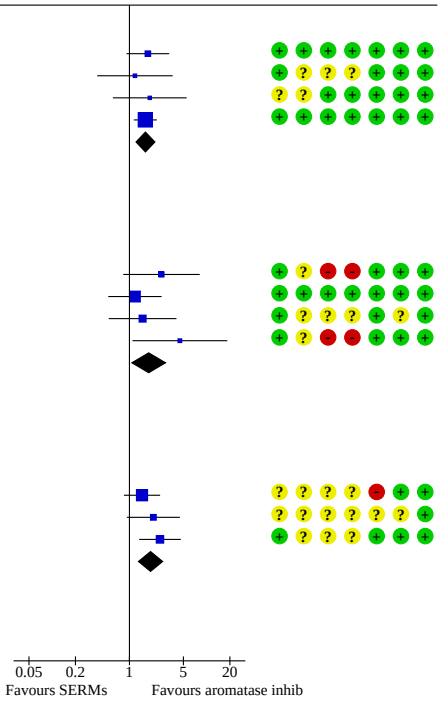
(1) No previous ovulation induction; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(2) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(3) Cumulative live birth rate; treatment naïve patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(4) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(5) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(6) Clomiphene resistant women; Letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(7) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(8) Clomiphene resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(9) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500 mg metformin daily

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 3: Live birth rate by first- or second-line treatment

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 No previous ovulation induction						
Amer 2017 (1)	39	80	28	79	18.8%	1.73 [0.92 , 3.27]
Bayar 2006 (2)	8	40	7	40	7.3%	1.18 [0.38 , 3.63]
Dehbashi 2009 (2)	10	50	6	50	6.2%	1.83 [0.61 , 5.50]
Legro 2014 (3)	103	374	72	376	67.7%	1.60 [1.14 , 2.26]
Subtotal (95% CI)		**544**		**545**	**100.0%**	**1.61 [1.22 , 2.14]**
Total events:	160		113			
Heterogeneity: Chi² = 0.40, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
2.3.2 CC-resistant women						
Begum 2009 (4)	12	32	6	32	16.2%	2.60 [0.83 , 8.13]
Foroozanfard 2011 (5)	18	60	16	60	48.3%	1.18 [0.53 , 2.61]
Seyedoshohadaei 2016 (6)	11	50	8	50	26.9%	1.48 [0.54 , 4.06]
Sohrabvand 2006 (7)	10	30	3	30	8.6%	4.50 [1.09 , 18.50]
Subtotal (95% CI)		**172**		**172**	**100.0%**	**1.78 [1.08 , 2.93]**
Total events:	51		33			
Heterogeneity: Chi² = 3.24, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 2.24 (P = 0.02)						
2.3.3 Unclear or mixed study cohort						
Liu 2017 (8)	42	134	32	134	50.5%	1.46 [0.85 , 2.50]
Ray 2012 (9)	20	69	13	78	19.9%	2.04 [0.93 , 4.50]
Roy 2012 (10)	39	104	21	108	29.6%	2.49 [1.34 , 4.62]
Subtotal (95% CI)		**307**		**320**	**100.0%**	**1.88 [1.31 , 2.69]**
Total events:	101		66			
Heterogeneity: Chi² = 1.69, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
Test for subgroup differences: Chi² = 0.44, df = 2 (P = 0.80), I² = 0%						



Footnotes

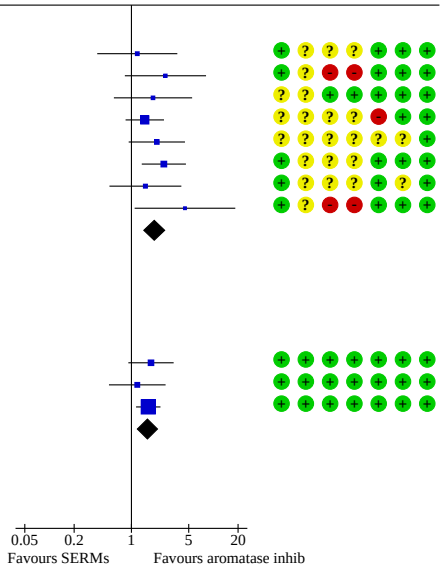
(1) No previous ovulation induction; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(2) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(3) Cumulative live birth rate; treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(4) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(5) Clomiphene resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(6) Clomiphene resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg
(7) Clomiphene resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(8) Previous treatment for subfertility unknown; clomiphene 50-150 mg versus letrozole 5 mg; both groups received 1000-1500 mg metformin daily
(9) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(10) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 4: Impact of allocation bias for live birth rate

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 Unclear risk of allocation						
Bayar 2006 (1)	8	40	7	40	8.5%	1.18 [0.38 , 3.63]
Begum 2009 (2)	12	32	6	32	5.7%	2.60 [0.83 , 8.13]
Dehbashi 2009 (1)	10	50	6	50	7.3%	1.83 [0.61 , 5.50]
Liu 2017 (3)	42	134	32	134	33.3%	1.46 [0.85 , 2.50]
Ray 2012 (4)	20	69	13	78	13.2%	2.04 [0.93 , 4.50]
Roy 2012 (5)	39	104	21	108	19.5%	2.49 [1.34 , 4.62]
Seyedoshohadaei 2016 (6)	11	50	8	50	9.5%	1.48 [0.54 , 4.06]
Sohrabvand 2006 (7)	10	30	3	30	3.0%	4.50 [1.09 , 18.50]
Subtotal (95% CI)		**509**		**522**	**100.0%**	**1.90 [1.42 , 2.54]**
Total events:	152		96			
Heterogeneity: Chi² = 4.34, df = 7 (P = 0.74); I² = 0%						
Test for overall effect: Z = 4.29 (P < 0.0001)						
2.4.2 Low risk of allocation						
Amer 2017 (8)	39	80	28	79	18.6%	1.73 [0.92 , 3.27]
Foroozanfard 2011 (9)	18	60	16	60	14.4%	1.18 [0.53 , 2.61]
Legro 2014 (10)	103	374	72	376	67.0%	1.60 [1.14 , 2.26]
Subtotal (95% CI)		**514**		**515**	**100.0%**	**1.57 [1.18 , 2.08]**
Total events:	160		116			
Heterogeneity: Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.12 (P = 0.002)						
Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0%						



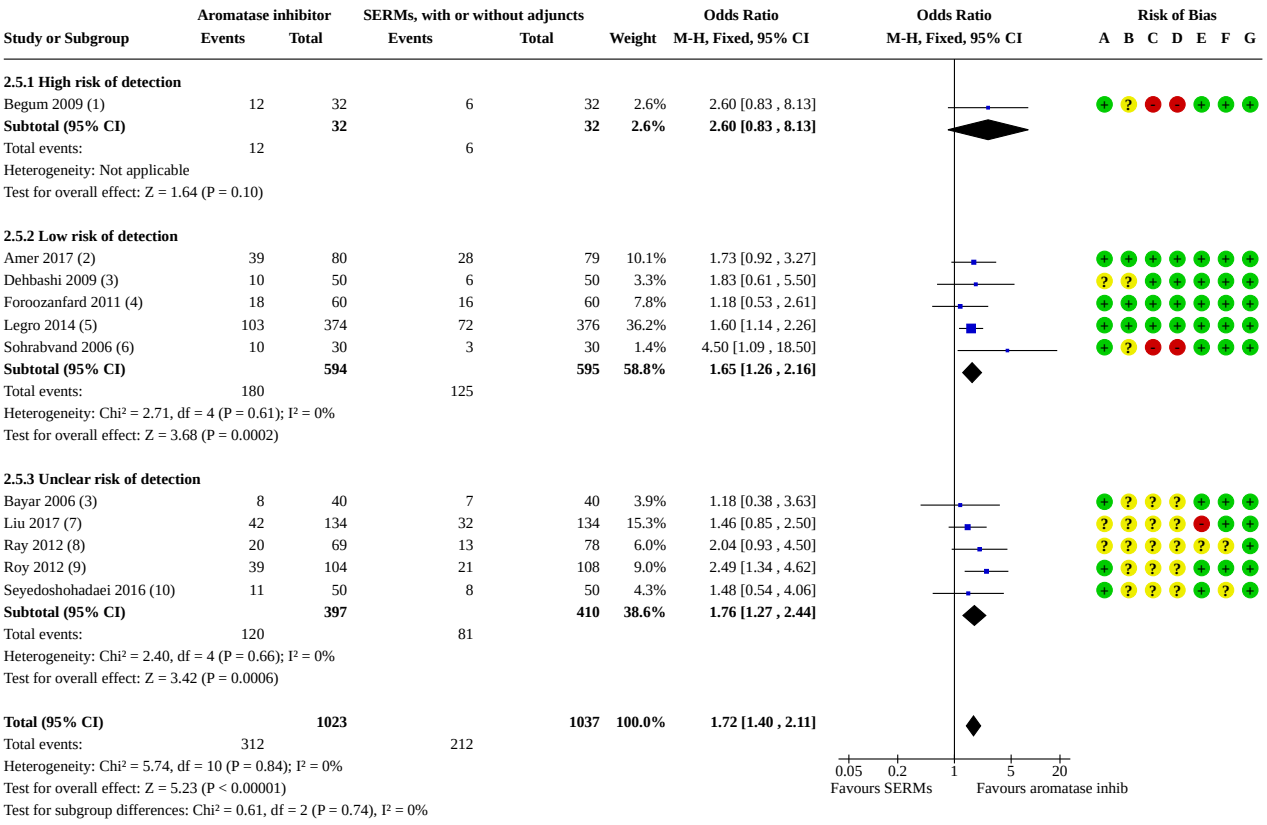
Footnotes

(1) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(2) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(3) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500mg metformin daily
(4) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(5) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(6) Clomiphene resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg
(7) Clomiphene resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(8) No previous ovulation induction; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(9) Clomiphene resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(10) Cumulative live birth rate; treatment naive patients; Letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 5: Impact of detection bias for live birth rate



Footnotes

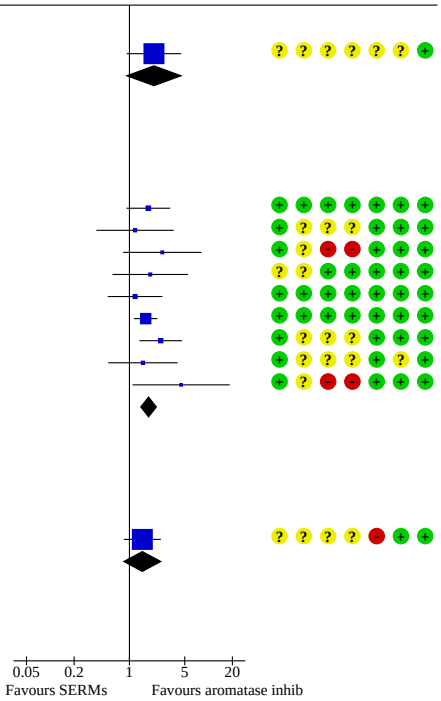
(1) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(2) No previous ovulation induction; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(3) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(4) Clomiphene resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(5) Cumulative live birth rate; treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(6) Clomiphene resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(7) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500 mg metformin daily
(8) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(9) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(10) Clomiphene resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 6: Impact of attrition bias for live birth rate

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.6.1 Unclear risk of attrition						
Ray 2012 (1)	20	69	13	78	100.0%	2.04 [0.93 , 4.50]
Subtotal (95% CI)		**69**		**78**	**100.0%**	**2.04 [0.93 , 4.50]**
Total events:	20		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
2.6.2 Low risk of attrition						
Amer 2017 (2)	39	80	28	79	12.8%	1.73 [0.92 , 3.27]
Bayar 2006 (3)	8	40	7	40	5.0%	1.18 [0.38 , 3.63]
Begum 2009 (4)	12	32	6	32	3.3%	2.60 [0.83 , 8.13]
Dehbashi 2009 (3)	10	50	6	50	4.3%	1.83 [0.61 , 5.50]
Foroozanfard 2011 (5)	18	60	16	60	9.9%	1.18 [0.53 , 2.61]
Legro 2014 (6)	103	374	72	376	46.1%	1.60 [1.14 , 2.26]
Roy 2012 (7)	39	104	21	108	11.4%	2.49 [1.34 , 4.62]
Seyedoshohadaei 2016 (8)	11	50	8	50	5.5%	1.48 [0.54 , 4.06]
Sohrabvand 2006 (9)	10	30	3	30	1.8%	4.50 [1.09 , 18.50]
Subtotal (95% CI)		**820**		**825**	**100.0%**	**1.75 [1.39 , 2.19]**
Total events:	250		167			
Heterogeneity: Chi² = 5.19, df = 8 (P = 0.74); I² = 0%						
Test for overall effect: Z = 4.79 (P < 0.00001)						
2.6.3 High risk of attrition						
Liu 2017 (10)	42	134	32	134	100.0%	1.46 [0.85 , 2.50]
Subtotal (95% CI)		**134**		**134**	**100.0%**	**1.46 [0.85 , 2.50]**
Total events:	42		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
Test for subgroup differences: Chi² = 0.56, df = 2 (P = 0.75), I² = 0%						



Footnotes

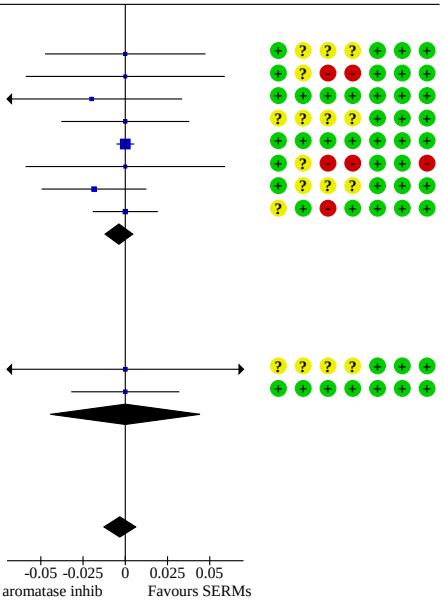
(1) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(2) No previous ovulation induction; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(3) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(4) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(5) Clomiphene-resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(6) Cumulative live birth rate; treatment naive patients; Letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(7) Unknown if primary fertility treatment or CC-resistant; Letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(8) Clomiphene-resistant women; letrozole 5mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg
(9) Clomiphene-resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(10) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500 mg metformin daily

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 7: Ovarian hyperstimulation syndrome rate

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
2.7.1 AIs versus clomiphene citrate						
Bayar 2006 (1)	0	40	0	40	4.4%	0.00 [-0.05 , 0.05]
Begum 2009 (2)	0	32	0	32	3.5%	0.00 [-0.06 , 0.06]
El-Khayat 2016 (3)	0	50	1	50	5.5%	-0.02 [-0.07 , 0.03]
Ghahiri 2016 (4)	0	50	0	51	5.5%	0.00 [-0.04 , 0.04]
Legro 2014 (5)	0	374	0	376	41.0%	0.00 [-0.01 , 0.01]
Nazik 2012 (6)	0	31	0	33	3.5%	0.00 [-0.06 , 0.06]
Roy 2012 (7)	0	104	2	108	11.6%	-0.02 [-0.05 , 0.01]
Selim 2012 (8)	0	102	0	99	11.0%	0.00 [-0.02 , 0.02]
Subtotal (95% CI)		**783**		**789**	**85.9%**	**-0.00 [-0.01 , 0.00]**
Total events:	0		3			
Heterogeneity: Chi² = 3.47, df = 7 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.7.2 Aromatase inhibitor + hMG versus clomiphene + hMG						
Chen 2016 (9)	6	104	3	52	7.6%	0.00 [-0.08 , 0.08]
Foroozanfard 2011 (10)	0	60	0	60	6.6%	0.00 [-0.03 , 0.03]
Subtotal (95% CI)		**164**		**112**	**14.1%**	**0.00 [-0.04 , 0.04]**
Total events:	6		3			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**947**		**901**	**100.0%**	**-0.00 [-0.01 , 0.01]**
Total events:	6		6			
Heterogeneity: Chi² = 3.01, df = 9 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



Footnotes

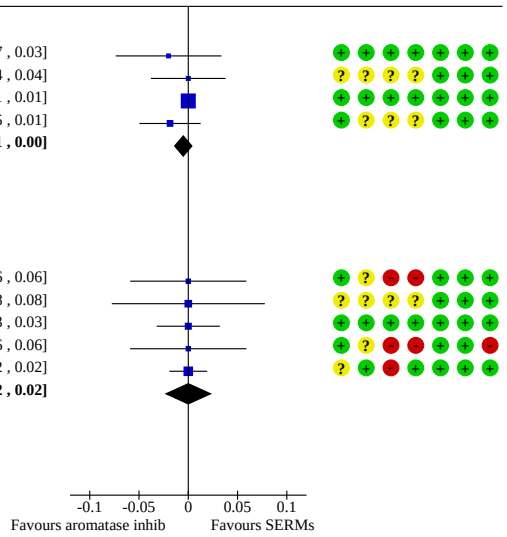
(1) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(2) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(3) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(4) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(5) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(6) No previous ovulation induction; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(7) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(8) Unknown if primary fertility treatment or CC-resistant; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(9) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(10) Clomiphene resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.8. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 8: Ovarian hyperstimulation syndrome rate by BMI

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
2.8.1 BMI > 25						
El-Khayat 2016 (1)	0	50	1	50	8.6%	-0.02 [-0.07 , 0.03]
Ghahiri 2016 (2)	0	50	0	51	8.7%	0.00 [-0.04 , 0.04]
Legro 2014 (3)	0	374	0	376	64.5%	0.00 [-0.01 , 0.01]
Roy 2012 (4)	0	104	2	108	18.2%	-0.02 [-0.05 , 0.01]
Subtotal (95% CI)		**578**		**585**	**100.0%**	**-0.01 [-0.01 , 0.00]**
Total events:	0		3			
Heterogeneity: Chi² = 4.76, df = 3 (P = 0.19); I² = 37%						
Test for overall effect: Z = 1.14 (P = 0.26)						
2.8.2 BMI < 25						
Begum 2009 (5)	0	32	0	32	10.9%	0.00 [-0.06 , 0.06]
Chen 2016 (6)	6	104	3	52	23.6%	0.00 [-0.08 , 0.08]
Foroozanfard 2011 (7)	0	60	0	60	20.4%	0.00 [-0.03 , 0.03]
Nazik 2012 (8)	0	31	0	33	10.9%	0.00 [-0.06 , 0.06]
Selim 2012 (9)	0	102	0	99	34.2%	0.00 [-0.02 , 0.02]
Subtotal (95% CI)		**329**		**276**	**100.0%**	**0.00 [-0.02 , 0.02]**
Total events:	6		3			
Heterogeneity: Chi² = 0.00, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



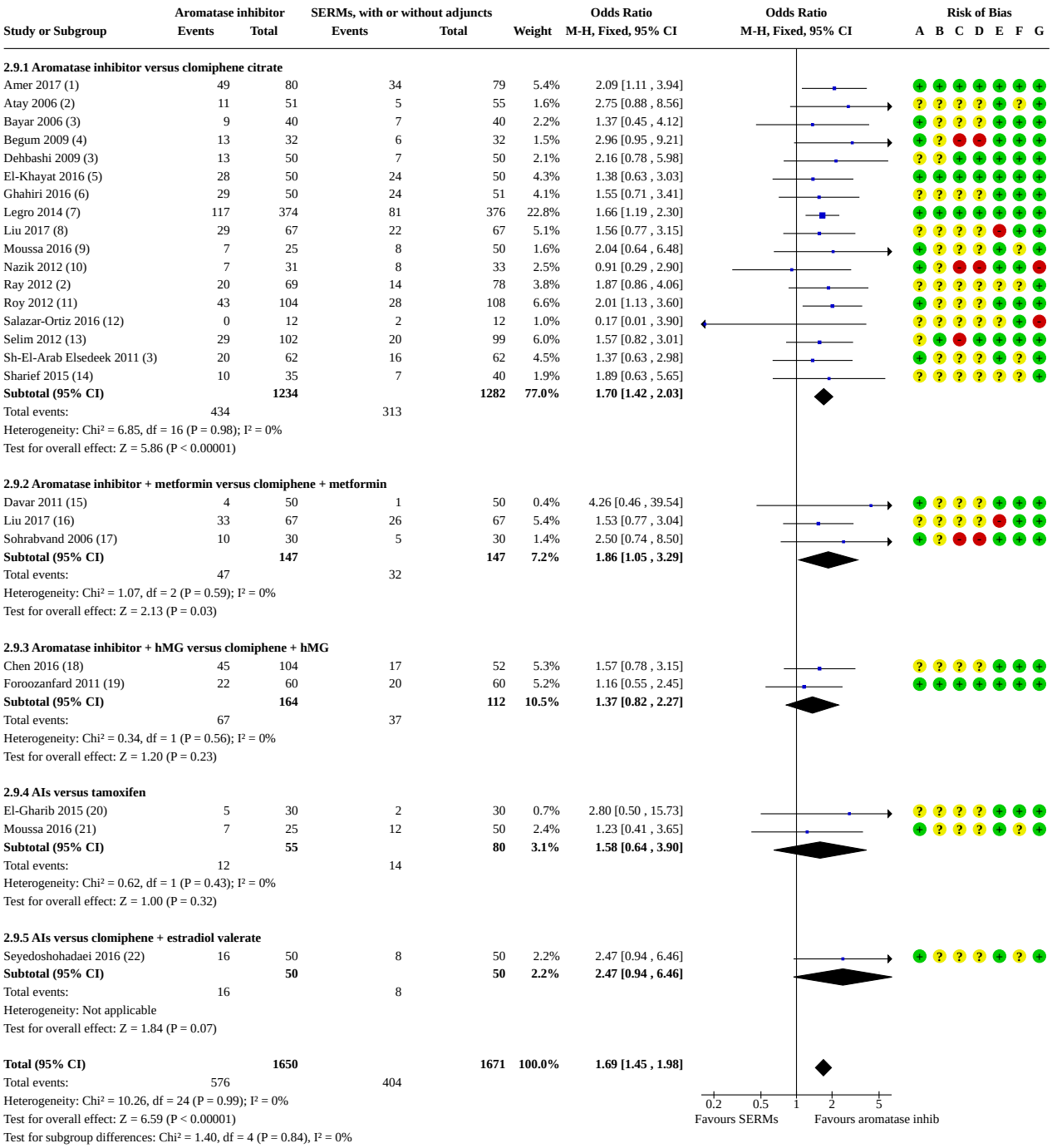
Footnotes

(1) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(2) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(3) Cumulative live birth rate
(4) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(5) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(6) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(7) Clomiphene-resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(8) No previous ovulation induction; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(9) Unknown if primary fertility treatment or CC-resistant; letrozole, 5 mg/day versus clomiphene,100 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.9. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 9: Clinical pregnancy rate



Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.9.1 Aromatase inhibitor versus clomiphene citrate						
Amer 2017 (1)	49	80	34	79	5.4%	2.09 [1.11 , 3.94]
Atay 2006 (2)	11	51	5	55	1.6%	2.75 [0.88 , 8.56]
Bayar 2006 (3)	9	40	7	40	2.2%	1.37 [0.45 , 4.12]
Begum 2009 (4)	13	32	6	32	1.5%	2.96 [0.95 , 9.21]
Dehbashi 2009 (3)	13	50	7	50	2.1%	2.16 [0.78 , 5.98]
El-Khayat 2016 (5)	28	50	24	50	4.3%	1.38 [0.63 , 3.03]
Ghahiri 2016 (6)	29	50	24	51	4.1%	1.55 [0.71 , 3.41]
Legro 2014 (7)	117	374	81	376	22.8%	1.66 [1.19 , 2.30]
Liu 2017 (8)	29	67	22	67	5.1%	1.56 [0.77 , 3.15]
Moussa 2016 (9)	7	25	8	50	1.6%	2.04 [0.64 , 6.48]
Nazik 2012 (10)	7	31	8	33	2.5%	0.91 [0.29 , 2.90]
Ray 2012 (2)	20	69	14	78	3.8%	1.87 [0.86 , 4.06]
Roy 2012 (11)	43	104	28	108	6.6%	2.01 [1.13 , 3.60]
Salazar-Ortiz 2016 (12)	0	12	2	12	1.0%	0.17 [0.01 , 3.90]
Selim 2012 (13)	29	102	20	99	6.0%	1.57 [0.82 , 3.01]
Sh-El-Arab Elsedeek 2011 (3)	20	62	16	62	4.5%	1.37 [0.63 , 2.98]
Sharief 2015 (14)	10	35	7	40	1.9%	1.89 [0.63 , 5.65]
Subtotal (95% CI)		**1234**		**1282**	**77.0%**	**1.70 [1.42 , 2.03]**
Total events:	434		313			
Heterogeneity: Chi² = 6.85, df = 16 (P = 0.98); I² = 0%						
Test for overall effect: Z = 5.86 (P < 0.00001)						
2.9.2 Aromatase inhibitor + metformin versus clomiphene + metformin						
Davar 2011 (15)	4	50	1	50	0.4%	4.26 [0.46 , 39.54]
Liu 2017 (16)	33	67	26	67	5.4%	1.53 [0.77 , 3.04]
Sohrabvand 2006 (17)	10	30	5	30	1.4%	2.50 [0.74 , 8.50]
Subtotal (95% CI)		**147**		**147**	**7.2%**	**1.86 [1.05 , 3.29]**
Total events:	47		32			
Heterogeneity: Chi² = 1.07, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
2.9.3 Aromatase inhibitor + hMG versus clomiphene + hMG						
Chen 2016 (18)	45	104	17	52	5.3%	1.57 [0.78 , 3.15]
Foroozanfard 2011 (19)	22	60	20	60	5.2%	1.16 [0.55 , 2.45]
Subtotal (95% CI)		**164**		**112**	**10.5%**	**1.37 [0.82 , 2.27]**
Total events:	67		37			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
2.9.4 AIs versus tamoxifen						
El-Gharib 2015 (20)	5	30	2	30	0.7%	2.80 [0.50 , 15.73]
Moussa 2016 (21)	7	25	12	50	2.4%	1.23 [0.41 , 3.65]
Subtotal (95% CI)		**55**		**80**	**3.1%**	**1.58 [0.64 , 3.90]**
Total events:	12		14			
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
2.9.5 AIs versus clomiphene + estradiol valerate						
Seyedoshohadaei 2016 (22)	16	50	8	50	2.2%	2.47 [0.94 , 6.46]
Subtotal (95% CI)		**50**		**50**	**2.2%**	**2.47 [0.94 , 6.46]**
Total events:	16		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
Total (95% CI)		**1650**		**1671**	**100.0%**	**1.69 [1.45 , 1.98]**
Total events:	576		404			
Heterogeneity: Chi² = 10.26, df = 24 (P = 0.99); I² = 0%						
Test for overall effect: Z = 6.59 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.40, df = 4 (P = 0.84), I² = 0%						

Footnotes

(1) Unknown if previously treated for subfertility; letrozole 2,5 mg vs clomipheme 5 mg/day
(2) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(3) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(4) CC-resistant women; letrozole, 7.5 mg/day versus clomiphene, 150 mg/day
(5) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(6) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(7) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(8) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg
(9) Previous treatment for subfertility unknown; clomiphene 100 mg/day versus letrozole 5 mg/day
(10) No previous ovulation induction; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(11) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day

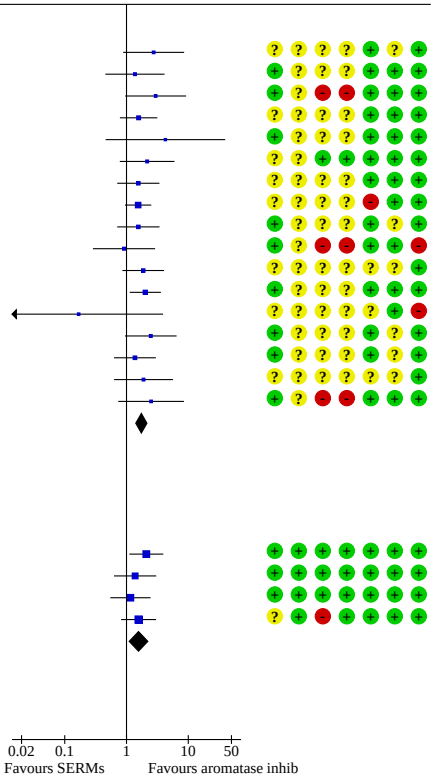
Analysis 2.9. (Continued)

(9) Previous treatment for subfertility unknown; clomiphene 100 mg/day versus letrozole 5 mg/day
(10) No previous ovulation induction; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(11) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(12) Treatment-naive women with PCOS; 2.5mg let vs 100mg cc daily for 5 days
(13) Unknown if primary fertility treatment or CC-resistant; letrozole, 5 mg/day versus clomiphene,100 mg/day
(14) Primary subfertility treatment unknown; letrozole 2.5 – 5mg/day vs clomiphene 100 – 200mg/day
(15) Clomiphene-resistant women; letrozole, 5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(16) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500 mg metformin daily
(17) Clomiphene-resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(18) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(19) Clomiphene-resistant women; letrozole, 5 mg/day + 150 UI hMG versus clomiphene, 100 mg/day + 150 UI hMG
(20) CC-resistant participants; letrozole 2.5 mg versus tamoxifen 20 mg/day
(21) Previous treatment for subfertility unknown; tamoxifen 20 mg/day versus letrozole 5 mg/day
(22) Clomiphene resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.10. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 10: Impact of allocation bias for clinical pregnancy rate

Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.10.1 Unclear risk of allocation						
Atay 2006 (1)	11	51	5	55	2.8%	2.75 [0.88 , 8.56]
Bayar 2006 (2)	9	40	7	40	4.0%	1.37 [0.45 , 4.12]
Begum 2009 (3)	13	32	6	32	2.6%	2.96 [0.95 , 9.21]
Chen 2016 (4)	45	104	17	52	9.5%	1.57 [0.78 , 3.15]
Davar 2011 (5)	4	50	1	50	0.7%	4.26 [0.46 , 39.54]
Dehbashi 2009 (2)	13	50	7	50	3.8%	2.16 [0.78 , 5.98]
Ghahiri 2016 (6)	29	50	24	51	7.4%	1.55 [0.71 , 3.41]
Liu 2017 (7)	62	134	48	134	19.1%	1.54 [0.95 , 2.52]
Moussa 2016 (8)	14	50	20	100	7.1%	1.56 [0.71 , 3.42]
Nazik 2012 (9)	7	31	8	33	4.4%	0.91 [0.29 , 2.90]
Ray 2012 (10)	20	69	14	78	6.9%	1.87 [0.86 , 4.06]
Roy 2012 (11)	43	104	28	108	11.9%	2.01 [1.13 , 3.60]
Salazar-Ortiz 2016 (12)	0	12	2	12	1.8%	0.17 [0.01 , 3.90]
Seyedoshohadaei 2016 (13)	16	50	8	50	4.0%	2.47 [0.94 , 6.46]
Sh-El-Arab Elsedeek 2011 (2)	20	62	16	62	8.0%	1.37 [0.63 , 2.98]
Sharief 2015 (14)	10	35	7	40	3.5%	1.89 [0.63 , 5.65]
Sohrabvand 2006 (15)	10	30	5	30	2.5%	2.50 [0.74 , 8.50]
Subtotal (95% CI)		**954**		**977**	**100.0%**	**1.74 [1.41 , 2.14]**
Total events:	326		223			
Heterogeneity: Chi² = 7.74, df = 16 (P = 0.96); I² = 0%						
Test for overall effect: Z = 5.21 (P < 0.00001)						
2.10.2 Low risk of allocation						
Amer 2017 (16)	49	80	34	79	26.0%	2.09 [1.11 , 3.94]
El-Khayat 2016 (17)	28	50	24	50	20.7%	1.38 [0.63 , 3.03]
Foroozanfard 2011 (18)	22	60	20	60	24.8%	1.16 [0.55 , 2.45]
Selim 2012 (19)	29	102	20	99	28.5%	1.57 [0.82 , 3.01]
Subtotal (95% CI)		**292**		**288**	**100.0%**	**1.56 [1.10 , 2.21]**
Total events:	128		98			
Heterogeneity: Chi² = 1.53, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						



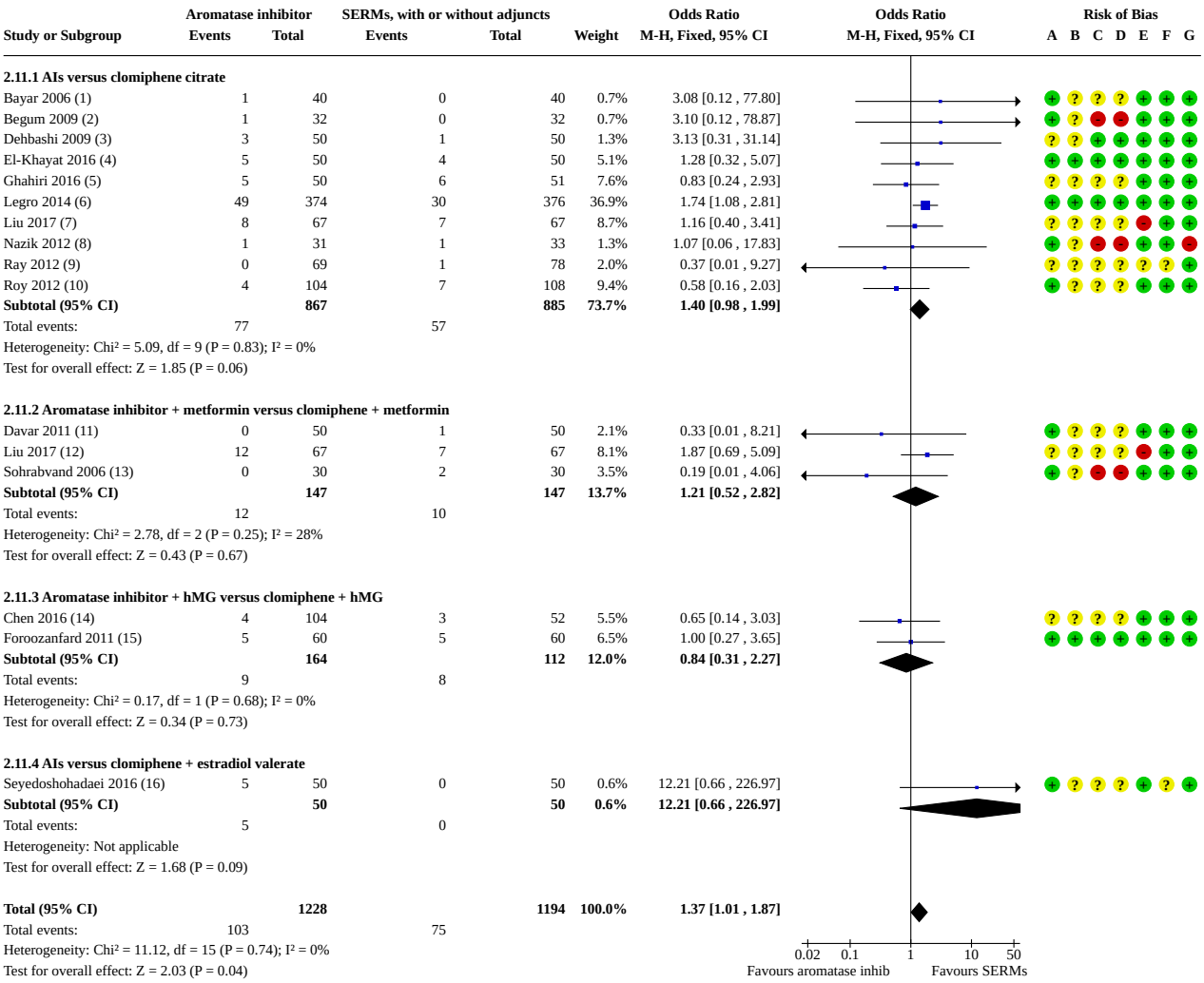
Footnotes

(1) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(2) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(3) CC-resistant women; letrozole 7.5 mg/day versus clomiphene 150 mg/day
(4) Previous treatment unknown; letrozole 2.5 – 5mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(5) Clomiphene-resistant women; letrozole, 5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(6) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(7) Previous treatment for subfertility unknown; clomiphene 50 – 150mg versus letrozole 5 mg; both groups received 1000 – 1500 mg metformin daily
(8) Previous treatment for subfertility unknown; tamoxifen 20 mg/day or clomiphene 100 mg/day versus letrozole 5 mg/day
(9) No previous ovulation induction; letrozole, 2.5 mg/day versus clomiphene, 100 mg/day
(10) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(11) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene, 50 – 100 mg/day
(12) Treatment-naive women with PCOS; 2.5mg let vs 100mg cc daily for 5 days
(13) Clomiphene-resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg
(14) Primary subfertility treatment unknown; letrozole 2.5 – 5 mg/day vs clomiphene 100 – 200 mg/day
(15) Clomiphene-resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(16) Unknown if previously treated for subfertility; letrozole 2.5 mg vs clomipheme 5 mg / day
(17) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(18) Clomiphene-resistant women; letrozole 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG
(19) Unknown if primary fertility treatment or CC-resistant; letrozole, 5 mg/day versus clomiphene,100 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.11. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 11: Miscarriage rate per woman



Footnotes

(1) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(2) CC-resistant women; letrozole 7.5 mg/day versus clomiphene 150 mg/day
(3) No previous ovulation induction; letrozole 5 mg/day versus clomiphene 100 mg/day
(4) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(5) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(6) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(7) Previous treatment for subfertility unknown; clomiphene 50-150 mg versus letrozole 5 mg
(8) No previous ovulation induction; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(9) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(10) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 – 5 mg/day versus clomiphene 50 – 100 mg/day
(11) Clomiphene-resistant women; letrozole, 5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(12) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500 mg metformin daily
(13) Clomiphene-resistant women; letrozole, 2.5 mg/day + metformin, 1500 mg/day versus clomiphene, 100 mg/day + metformin, 1500 mg/day
(14) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(15) Clomiphene-resistant women; letrozole 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG
(16) Clomiphene-resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg

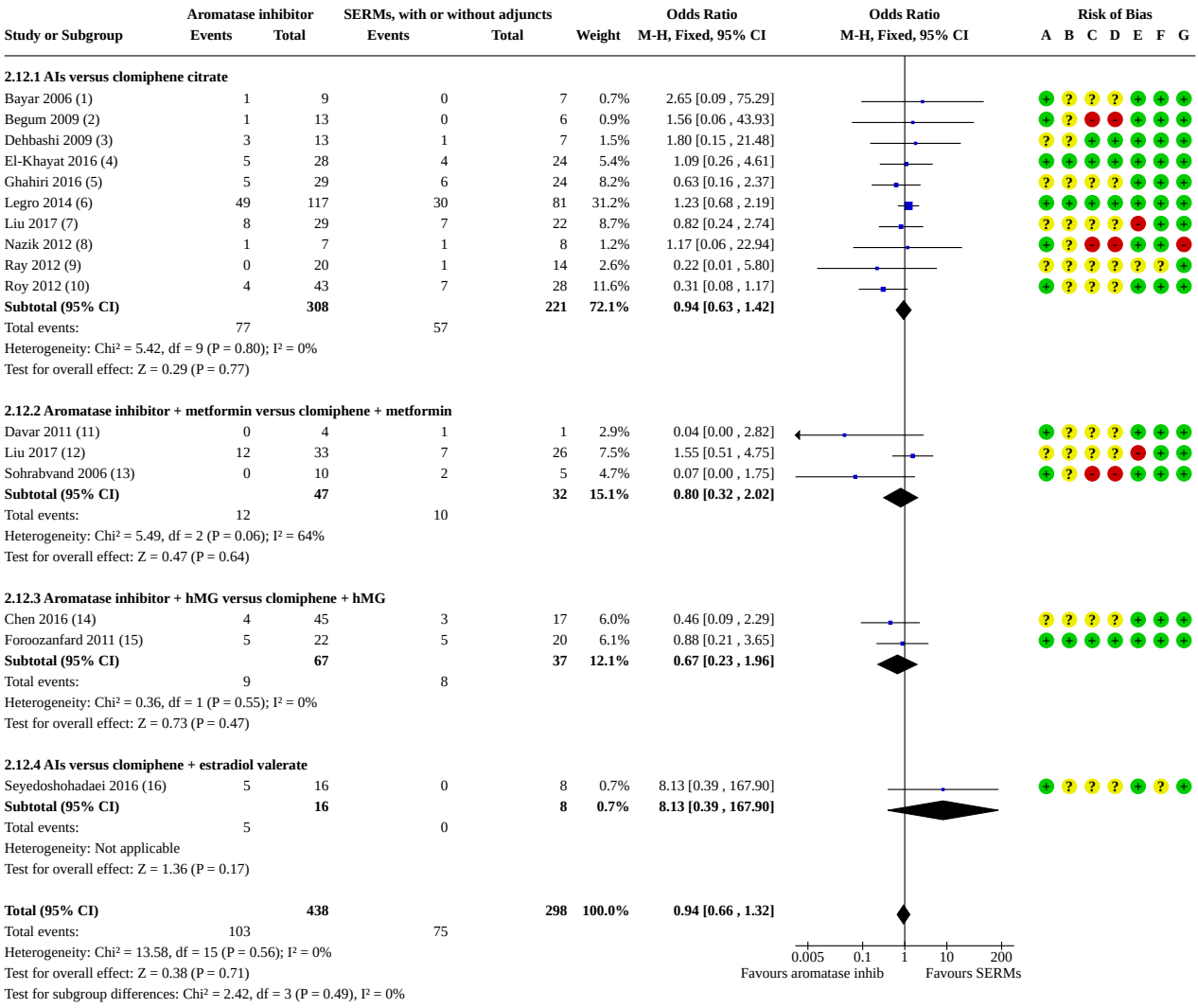
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.11. (Continued)

(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.12. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 12: Miscarriage rate per pregnancy



Study or Subgroup	Aromatase inhibitor Events	Aromatase inhibitor Total	SERMs, with or without adjuncts Events	SERMs, with or without adjuncts Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
2.12.1 AIs versus clomiphene citrate							
Bayar 2006 (1)	1	9	0	7	0.7%	2.65 [0.09 , 75.29]	+ ? ? ? + + +
Begum 2009 (2)	1	13	0	6	0.9%	1.56 [0.06 , 43.93]	+ ? - - + + +
Dehbashi 2009 (3)	3	13	1	7	1.5%	1.80 [0.15 , 21.48]	? ? + + + + +
El-Khayat 2016 (4)	5	28	4	24	5.4%	1.09 [0.26 , 4.61]	+ + + + + + +
Ghahiri 2016 (5)	5	29	6	24	8.2%	0.63 [0.16 , 2.37]	? ? ? ? + + +
Legro 2014 (6)	49	117	30	81	31.2%	1.23 [0.68 , 2.19]	+ + + + + + +
Liu 2017 (7)	8	29	7	22	8.7%	0.82 [0.24 , 2.74]	? ? ? ? - + +
Nazik 2012 (8)	1	7	1	8	1.2%	1.17 [0.06 , 22.94]	+ ? - - + + -
Ray 2012 (9)	0	20	1	14	2.6%	0.22 [0.01 , 5.80]	? ? ? ? ? ? +
Roy 2012 (10)	4	43	7	28	11.6%	0.31 [0.08 , 1.17]	+ ? ? ? + + +
Subtotal (95% CI)		**308**		**221**	**72.1%**	**0.94 [0.63 , 1.42]**	
Total events:	77		57				
Heterogeneity: Chi² = 5.42, df = 9 (P = 0.80); I² = 0%							
Test for overall effect: Z = 0.29 (P = 0.77)							
2.12.2 Aromatase inhibitor + metformin versus clomiphene + metformin							
Davar 2011 (11)	0	4	1	1	2.9%	0.04 [0.00 , 2.82]	+ ? ? ? + + +
Liu 2017 (12)	12	33	7	26	7.5%	1.55 [0.51 , 4.75]	? ? ? ? - + +
Sohrabvand 2006 (13)	0	10	2	5	4.7%	0.07 [0.00 , 1.75]	+ ? - - + + +
Subtotal (95% CI)		**47**		**32**	**15.1%**	**0.80 [0.32 , 2.02]**	
Total events:	12		10				
Heterogeneity: Chi² = 5.49, df = 2 (P = 0.06); I² = 64%							
Test for overall effect: Z = 0.47 (P = 0.64)							
2.12.3 Aromatase inhibitor + hMG versus clomiphene + hMG							
Chen 2016 (14)	4	45	3	17	6.0%	0.46 [0.09 , 2.29]	? ? ? ? + + +
Foroozanfard 2011 (15)	5	22	5	20	6.1%	0.88 [0.21 , 3.65]	+ + + + + + +
Subtotal (95% CI)		**67**		**37**	**12.1%**	**0.67 [0.23 , 1.96]**	
Total events:	9		8				
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%							
Test for overall effect: Z = 0.73 (P = 0.47)							
2.12.4 AIs versus clomiphene + estradiol valerate							
Seyedoshohadaei 2016 (16)	5	16	0	8	0.7%	8.13 [0.39 , 167.90]	+ ? ? ? + ? +
Subtotal (95% CI)		**16**		**8**	**0.7%**	**8.13 [0.39 , 167.90]**	
Total events:	5		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.36 (P = 0.17)							
Total (95% CI)		**438**		**298**	**100.0%**	**0.94 [0.66 , 1.32]**	
Total events:	103		75				
Heterogeneity: Chi² = 13.58, df = 15 (P = 0.56); I² = 0%							
Test for overall effect: Z = 0.38 (P = 0.71)							
Test for subgroup differences: Chi² = 2.42, df = 3 (P = 0.49), I² = 0%							

Footnotes

(1) No previous ovulation induction; letrozole, 5 mg/day versus clomiphene, 100 mg/day
(2) CC-resistant women; letrozole 7.5 mg/day versus clomiphene 150 mg/day
(3) No previous ovulation induction; letrozole 5 mg/day versus clomiphene 100 mg/day
(4) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(5) Previous subfertility treatment unknown; 5 mg letrozole versus 100 mg clomiphene/day
(6) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(7) Previous treatment for subfertility unknown; clomiphene 50 – 150mg versus letrozole 5 mg
(8) No previous ovulation induction; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(9) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(10) Unknown if primary fertility treatment or CC-resistant; letrozole, 2.5 – 5 mg/day versus clomiphene 50 – 100 mg/day
(11) Clomiphene-resistant women; letrozole 5 mg/day + metformin 1500 mg/day versus clomiphene 100 mg/day + metformin 1500 mg/day
(12) Previous treatment for subfertility unknown; clomiphene 50 – 150 mg versus letrozole 5 mg; both groups received 1000 – 1500mg metformin daily
(13) Clomiphene-resistant women; letrozole 2.5 mg/day + metformin 1500 mg/day versus clomiphene 100 mg/day + metformin 1500 mg/day
(14) Previous treatment unknown; letrozole 2.5 – 5mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(15) Clomiphene-resistant women; letrozole 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG
(16) Clomiphene-resistant women; letrozole 5 mg/day versus clomiphene 100 mg/day + estradiol valerate 4 mg

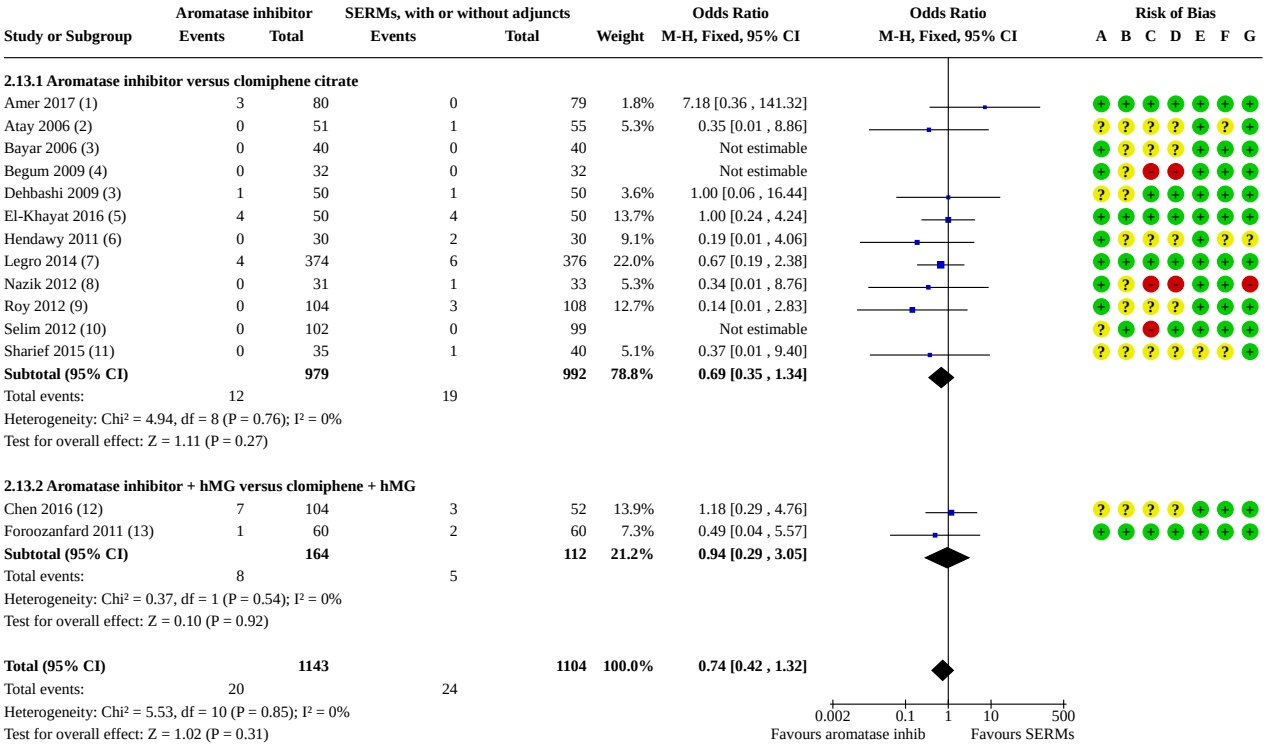
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.12. (Continued)

(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.13. Comparison 2: Letrozole compared to SERM with or without adjuncts, followed by timed intercourse, Outcome 13: Multiple pregnancy rate



Study or Subgroup	Aromatase inhibitor Events	Total	SERMs, with or without adjuncts Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
2.13.1 Aromatase inhibitor versus clomiphene citrate							
Amer 2017 (1)	3	80	0	79	1.8%	7.18 [0.36 , 141.32]	+ + + + + + +
Atay 2006 (2)	0	51	1	55	5.3%	0.35 [0.01 , 8.86]	? ? ? ? + ? +
Bayar 2006 (3)	0	40	0	40		Not estimable	+ ? ? ? + + +
Begum 2009 (4)	0	32	0	32		Not estimable	+ ? - - + + +
Dehbashi 2009 (3)	1	50	1	50	3.6%	1.00 [0.06 , 16.44]	? ? + + + + +
El-Khayat 2016 (5)	4	50	4	50	13.7%	1.00 [0.24 , 4.24]	+ + + + + + +
Hendawy 2011 (6)	0	30	2	30	9.1%	0.19 [0.01 , 4.06]	+ ? ? ? + ? ?
Legro 2014 (7)	4	374	6	376	22.0%	0.67 [0.19 , 2.38]	+ + + + + + +
Nazik 2012 (8)	0	31	1	33	5.3%	0.34 [0.01 , 8.76]	+ ? - - + + -
Roy 2012 (9)	0	104	3	108	12.7%	0.14 [0.01 , 2.83]	+ ? ? ? + + +
Selim 2012 (10)	0	102	0	99		Not estimable	? + - + + + +
Sharief 2015 (11)	0	35	1	40	5.1%	0.37 [0.01 , 9.40]	? ? ? ? ? ? +
Subtotal (95% CI)		**979**		**992**	**78.8%**	**0.69 [0.35 , 1.34]**	
Total events:	12		19				
Heterogeneity: Chi² = 4.94, df = 8 (P = 0.76); I² = 0%							
Test for overall effect: Z = 1.11 (P = 0.27)							
2.13.2 Aromatase inhibitor + hMG versus clomiphene + hMG							
Chen 2016 (12)	7	104	3	52	13.9%	1.18 [0.29 , 4.76]	? ? ? ? + + +
Foroozanfard 2011 (13)	1	60	2	60	7.3%	0.49 [0.04 , 5.57]	+ + + + + + +
Subtotal (95% CI)		**164**		**112**	**21.2%**	**0.94 [0.29 , 3.05]**	
Total events:	8		5				
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.10 (P = 0.92)							
Total (95% CI)		**1143**		**1104**	**100.0%**	**0.74 [0.42 , 1.32]**	
Total events:	20		24				
Heterogeneity: Chi² = 5.53, df = 10 (P = 0.85); I² = 0%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%							

Footnotes

(1) Previous subfertility treatment unknown; starting dose 2.5 mg letrozole vs 50 mg clomiphen citrate/day
(2) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(3) No previous ovulation induction; letrozole 5 mg/day versus clomiphene 100 mg/day
(4) CC-resistant women; letrozole 7.5 mg/day versus clomiphene 150 mg/day
(5) Unknown if previously treatet for subfertility; 5 mg letrozole versus 100 mg clomiphene/day
(6) Treatment naive women; starting dose letrozole 2.5 mg/day vs clomiphene 50mg/day
(7) Treatment naive patients; letrozole 2.5 mg/day vs clomiphene 50 mg/day starting dose
(8) No previous ovulation induction; letrozole 2.5 mg/day versus clomiphene 100 mg/day
(9) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 – 5 mg/day versus clomiphene 50 – 100 mg/day
(10) Unknown if primary fertility treatment or CC-resistant; letrozole 5 mg/day versus clomiphene 100 mg/day
(11) Primary subfertility treatment unknown; letrozole 2.5 – 5 mg/day vs clomiphene 100 – 200 mg/day
(12) Previous treatment unknown; letrozole 2.5 – 5 mg +/- 75 IU hMG versus CC 50 – 100 mg/day
(13) Clomiphene-resistant women; letrozole 5 mg/day + 150 UI hMG versus clomiphene 100 mg/day + 150 UI hMG

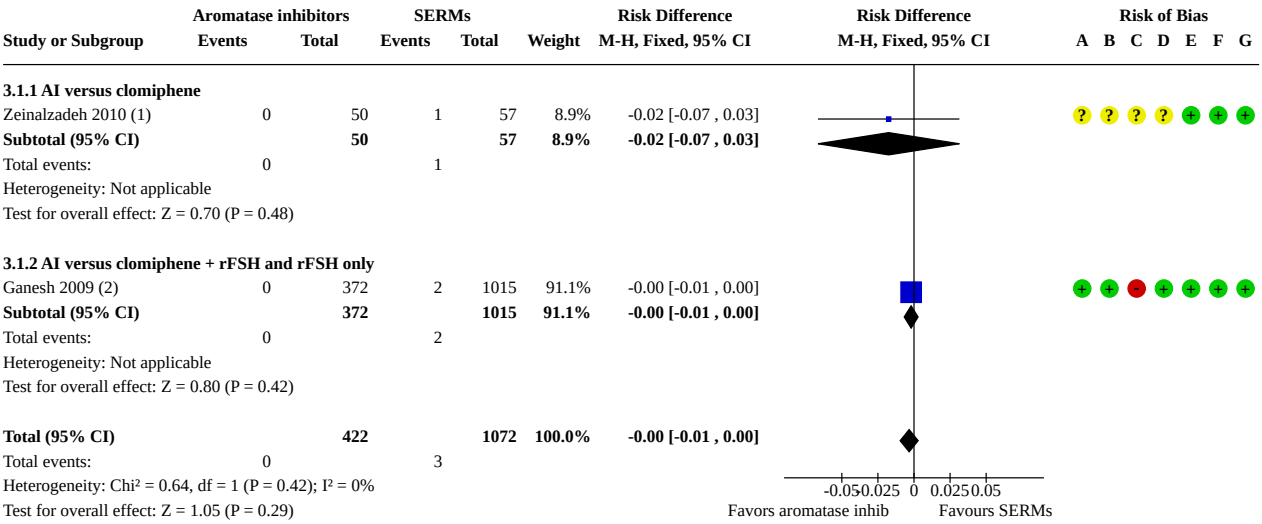
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Letrozole compared to SERMs with our without adjuncts, followed by IUI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Ovarian hyperstimulation syndrome rate	2	1494	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
3.1.1 AI versus clomiphene	1	107	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
3.1.2 AI versus clomiphene + rFSH and rFSH only	1	1387	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.00]
3.2 Clinical pregnancy rate	3	1597	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [1.30, 2.25]
3.2.1 AI versus clomiphene	2	210	Odds Ratio (M-H, Fixed, 95% CI)	2.09 [0.97, 4.53]
3.2.2 AI versus clomiphene + rFSH and rFSH only	1	1387	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [1.23, 2.22]
3.3 Miscarriage rate per woman	2	1490	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.62, 2.40]
3.3.1 AI versus clomiphene	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.06]
3.3.2 AI versus clomiphene + rFSH and rFSH only	1	1387	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.66, 2.65]
3.4 Miscarriage rate per pregnancy	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.37, 1.57]
3.4.1 AI versus clomiphene	1	15	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.00, 3.09]
3.4.2 AI versus clomiphene + rFSH and rFSH only	1	245	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.40, 1.79]
3.5 Multiple pregnancy rate	3	1597	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.49, 2.13]
3.5.1 AI versus clomiphene	2	210	Odds Ratio (M-H, Fixed, 95% CI)	3.48 [0.14, 87.49]
3.5.2 AI versus clomiphene + rFSH and rFSH only	1	1387	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.44, 2.03]

Analysis 3.1. Comparison 3: Letrozole compared to SERMs with our without adjuncts, followed by IUI, Outcome 1: Ovarian hyperstimulation syndrome rate



Footnotes

(1) 5 mg letrozole versus 100 mg clomiphene for 5 days during cycle days 3-7

(2) letrozole 5 mg/day versus clomiphene 100 mg/day + rFSH 75 – 100 IU versus rFSH 75 – 100 IU/day

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

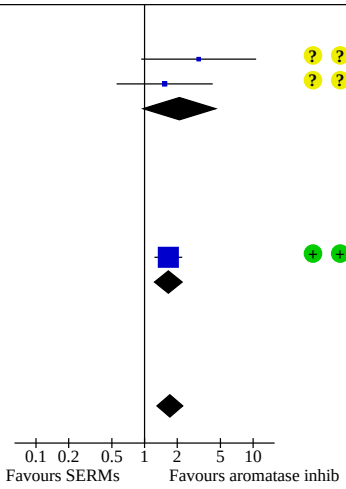
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 3.2. Comparison 3: Letrozole compared to SERMs with our without adjuncts, followed by IUI, Outcome 2: Clinical pregnancy rate

Study or Subgroup	aromatase inhibitors Events	Total	SERMs Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.2.1 AI versus clomiphene							
Kar 2012 (1)	11	52	4	51	4.3%	3.15 [0.93 , 10.66]	? ? ? ? + + +
Zeinalzadeh 2010 (2)	10	50	8	57	8.1%	1.53 [0.55 , 4.24]	? ? ? ? + + +
Subtotal (95% CI)		**102**		**108**	**12.4%**	**2.09 [0.97 , 4.53]**	
Total events:	21		12				
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%							
Test for overall effect: Z = 1.88 (P = 0.06)							
3.2.2 AI versus clomiphene + rFSH and rFSH only							
Ganesh 2009 (3)	87	372	158	1015	87.6%	1.66 [1.23 , 2.22]	+ + - + + + +
Subtotal (95% CI)		**372**		**1015**	**87.6%**	**1.66 [1.23 , 2.22]**	
Total events:	87		158				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.36 (P = 0.0008)							
Total (95% CI)		**474**		**1123**	**100.0%**	**1.71 [1.30 , 2.25]**	
Total events:	108		170				
Heterogeneity: Chi² = 1.06, df = 2 (P = 0.59); I² = 0%							
Test for overall effect: Z = 3.84 (P = 0.0001)							
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%							



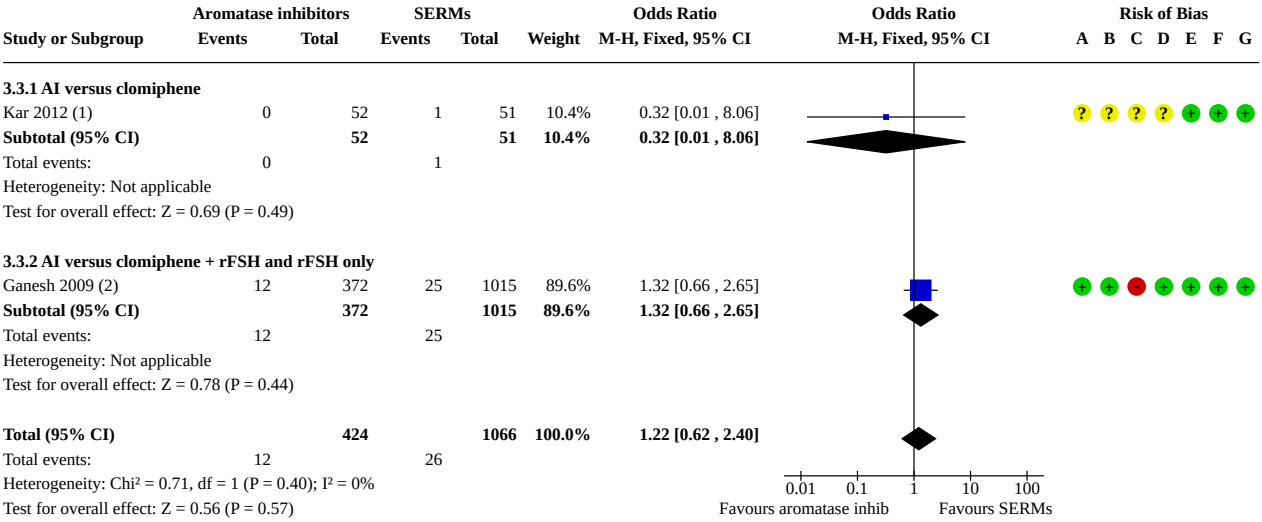
Footnotes

(1) Letrozole 5 mg per day versus clomiphene 100 mg per day for 5 days during cycle days 2 – 6
(2) 5 mg letrozole versus 100 mg clomiphene for 5 days during cycle days 3 – 7
(3) Letrozole 5 mg/day versus clomiphene 100 mg/day + rFSH 75 – 100 IU versus rFSH 75 – 100 IU/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.3. Comparison 3: Letrozole compared to SERMs with our without adjuncts, followed by IUI, Outcome 3: Miscarriage rate per woman



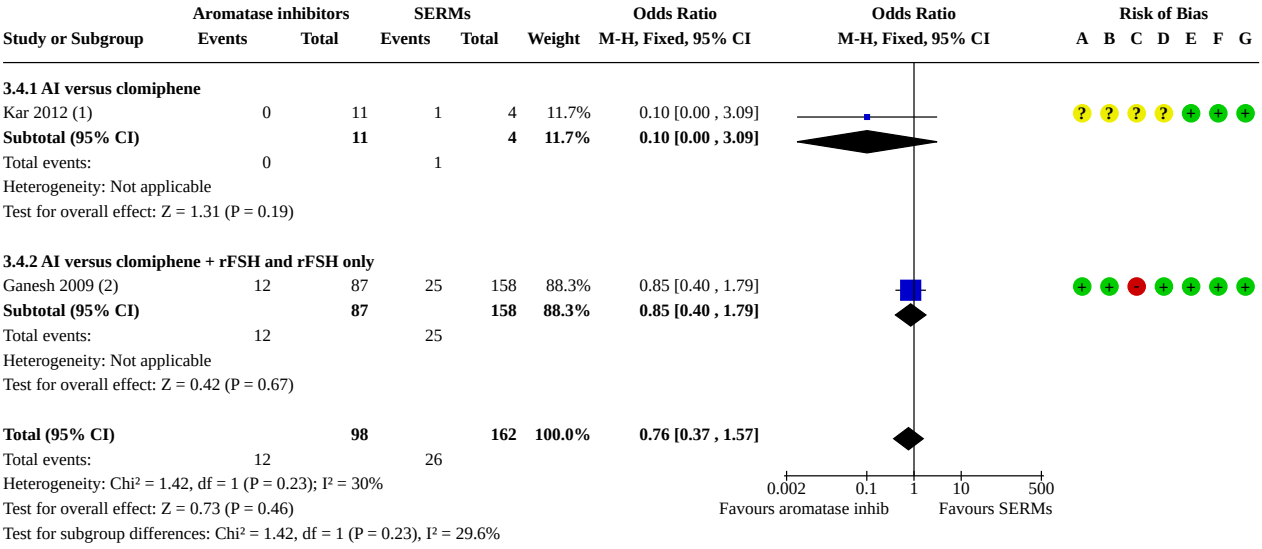
Footnotes

(1) Letrozole 5 mg per day versus clomiphene 100 mg per day for 5 days during cycle days 2 – 6
(2) Letrozole 5 mg/day versus clomiphene 100 mg/day + rFSH 75 – 100 IU versus rFSH 75 – 100 IU/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Letrozole compared to SERMs with our without adjuncts, followed by IUI, Outcome 4: Miscarriage rate per pregnancy



Footnotes

(1) Letrozole 5 mg per day versus clomiphene 100 mg per day for 5 days during cycle days 2 – 6

(2) Letrozole 5 mg/day versus clomiphene 100 mg/day + rFSH 75 – 100 IU versus rFSH 75 – 100 IU/day

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

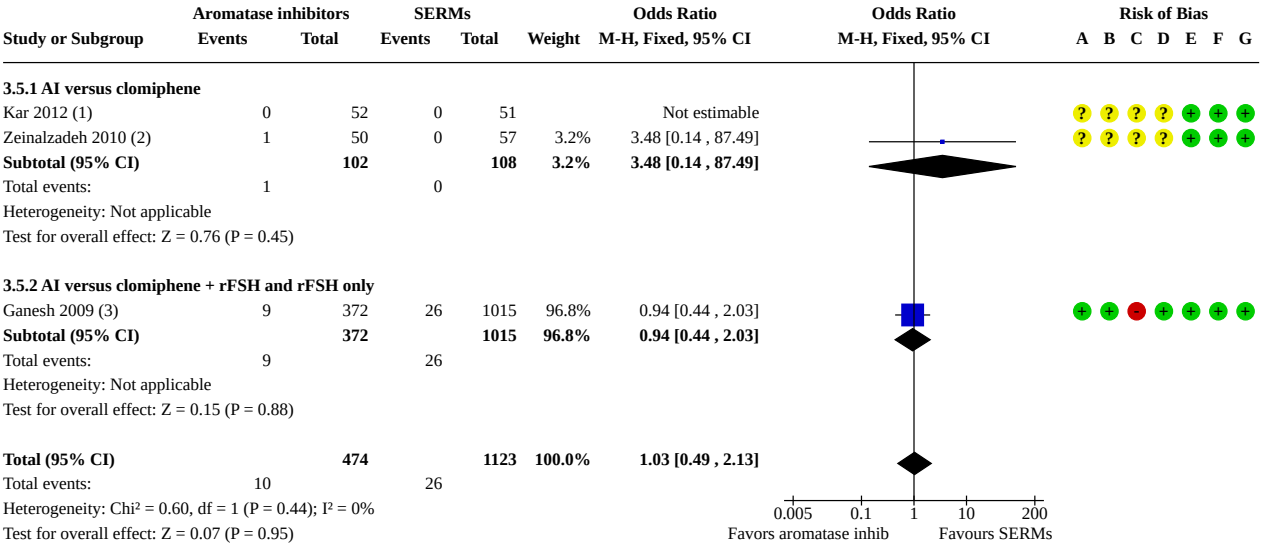
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 3.5. Comparison 3: Letrozole compared to SERMs with our without adjuncts, followed by IUI, Outcome 5: Multiple pregnancy rate



Footnotes

(1) Letrozole 5 mg per day versus clomiphene 100 mg per day for 5 days during cycle days 2 – 6
(2) 5 mg letrozole versus 100 mg clomiphene for 5 days during cycle days 3 – 7
(3) Letrozole 5 mg/day versus clomiphene 100 mg/day + rFSH 75 – 100 IU versus rFSH 75 – 100 IU/day

Risk of bias legend

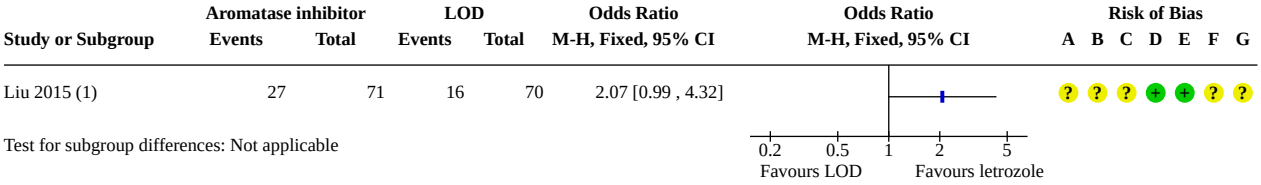
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4. Letrozole compared to laparoscopic ovarian drilling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Live birth rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2 Clinical pregnancy rate	3	367	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.95, 2.28]
4.2.1 AI versus LOD	2	221	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [0.96, 2.97]
4.2.2 AI + metformin versus LOD	1	146	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.60, 2.39]
4.3 Miscarriage rate per woman	3	367	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.31, 2.44]
4.3.1 AI versus LOD	2	221	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.50]
4.3.2 AI + metformin versus LOD	1	146	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.29, 6.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Miscarriage rate per pregnancy	3	122	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.22, 1.92]
4.4.1 AI versus LOD	2	73	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.72]
4.4.2 AI + metformin versus LOD	1	49	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.24, 6.09]
4.5 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

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

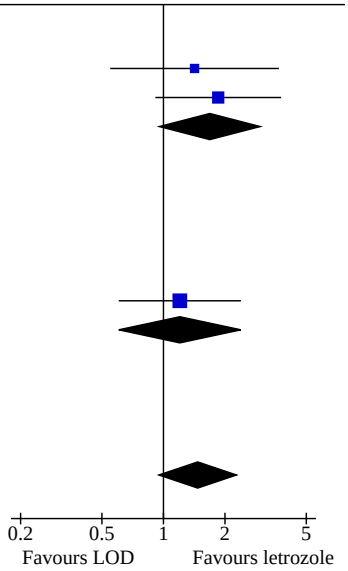


Footnotes
(1) Clomiphene-resistant women; 2.5 mg letrozole versus LOD

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Letrozole compared to laparoscopic ovarian drilling, Outcome 2: Clinical pregnancy rate

Study or Subgroup	Aromatase inhibitor Events	Total	LOD Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 AI versus LOD						
Ibrahim 2017 (1)	14	40	11	40	21.5%	1.42 [0.55 , 3.67]
Liu 2015 (2)	29	71	19	70	34.0%	1.85 [0.91 , 3.76]
Subtotal (95% CI)		**111**		**110**	**55.5%**	**1.69 [0.96 , 2.97]**
Total events:	43		30			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
4.2.2 AI + metformin versus LOD						
Elgafor 2013 (3)	26	73	23	73	44.5%	1.20 [0.60 , 2.39]
Subtotal (95% CI)		**73**		**73**	**44.5%**	**1.20 [0.60 , 2.39]**
Total events:	26		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**184**		**183**	**100.0%**	**1.47 [0.95 , 2.28]**
Total events:	69		53			
Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)						
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%						



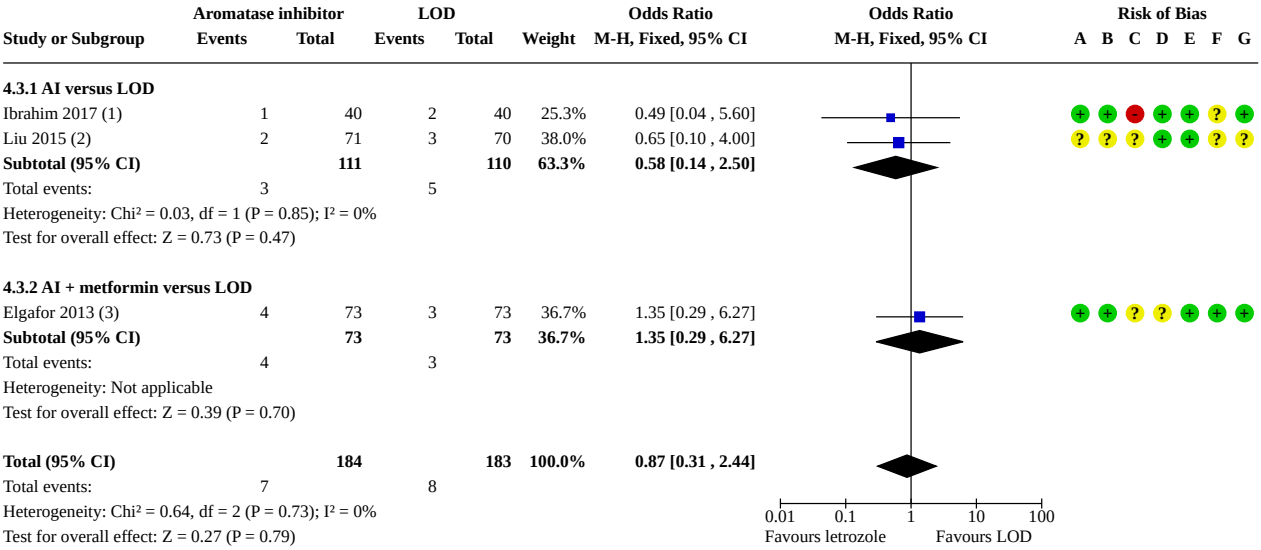
Footnotes

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

(2) Clomiphene-resistant women; 2.5 mg letrozole versus LOD

(3) Letrozole 5 mg/day for 5 days + metformin 850 – 1700 mg/day for 6 – 8 weeks versus LOD

Analysis 4.3. Comparison 4: Letrozole compared to laparoscopic ovarian drilling, Outcome 3: Miscarriage rate per woman



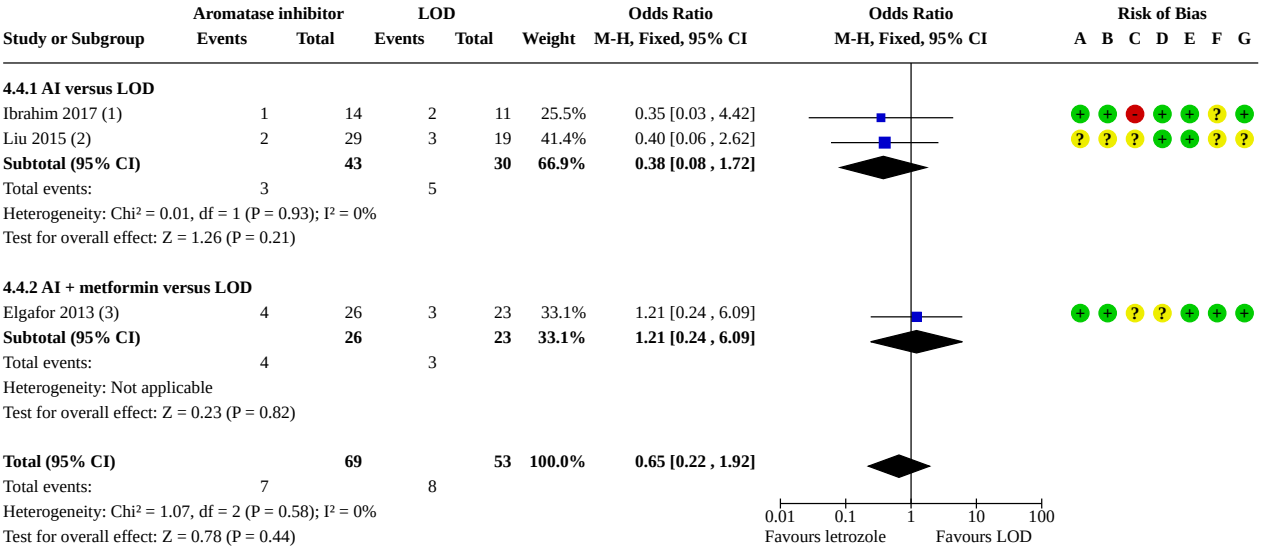
Footnotes

(1) Clomiphene-resistant women; letrozole 5 mg/day versus LOD
(2) Clomiphene-resistant women; 2.5 mg letrozole versus LOD
(3) letrozole 5 mg/day for 5 days + metformin 850 – 1700 mg/day for 6 – 8 weeks versus LOD

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: Letrozole compared to laparoscopic ovarian drilling, Outcome 4: Miscarriage rate per pregnancy



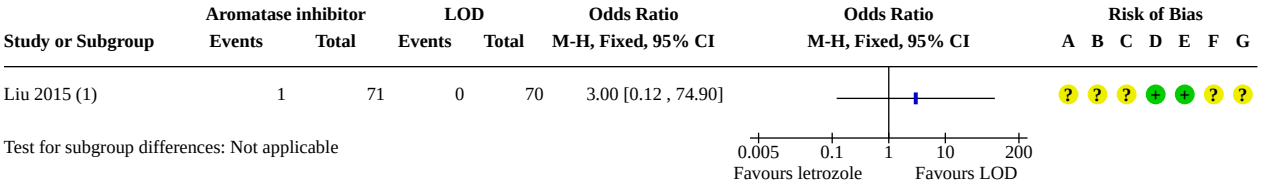
Footnotes

(1) Clomiphene-resistant women; letrozole 5 mg/day versus LOD
(2) Clomiphene-resistant women; 2.5 mg letrozole versus LOD
(3) Letrozole 5 mg/day for 5 days + metformin 850 – 1700 mg/day for 6 – 8 weeks versus LOD

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.5. Comparison 4: Letrozole compared to laparoscopic ovarian drilling, Outcome 5: Multiple pregnancy rate



Footnotes

(1) Clomiphene-resistant women; 2.5 mg letrozole versus LOD

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

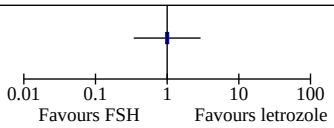
Comparison 5. Letrozole compared to FSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Live birth	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2 Ovarian hyperstimulation syndrome rate	2	236	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.08, 0.01]
5.3 Clinical pregnancy rate	2	236	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.46, 1.43]
5.4 Miscarriage rate per woman	2	236	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.19, 1.92]
5.5 Miscarriage rate per pregnancy	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.6 Multiple pregnancy rate	2	236	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.32]

Analysis 5.1. Comparison 5: Letrozole compared to FSH, Outcome 1: Live birth

Study or Subgroup	Letrozole Events	Letrozole Total	FSH Events	FSH Total	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
Shi 2019 (1)	8	48	8	48	1.00 [0.34 , 2.93]	+	?	?	?	+	+	+

Test for subgroup differences: Not applicable



Footnotes

(1) Previous treatmet unknown; 5mg Let vs 75U/d for 5 days

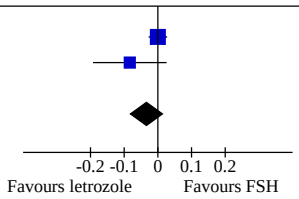
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: Letrozole compared to FSH, Outcome 2: Ovarian hyperstimulation syndrome rate

Study or Subgroup	Letrozole Events	Letrozole Total	FSH Events	FSH Total	Weight	Risk Difference M-H, Fixed, 95% CI
Hassan 2017 (1)	0	70	0	70	59.3%	0.00 [-0.03 , 0.03]
Shi 2019 (2)	2	48	6	48	40.7%	-0.08 [-0.19 , 0.03]
Total (95% CI)		**118**		**118**	**100.0%**	**-0.03 [-0.08 , 0.01]**
Total events:	2		6			

Heterogeneity: Chi² = 6.62, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



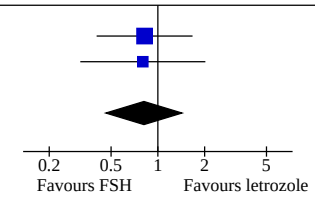
Footnotes
(1) Clomiphene-resistant women; letrozole 5 mg/day versus uFSH 75 IU
(2) Previous treatmet unknown; 5mg Let vs 75U/d for 5 days

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.3. Comparison 5: Letrozole compared to FSH, Outcome 3: Clinical pregnancy rate

Study or Subgroup	Letrozole Events	Letrozole Total	FSH Events	FSH Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hassan 2017 (1)	21	70	24	70	62.6%	0.82 [0.40 , 1.67]
Shi 2019 (2)	11	48	13	48	37.4%	0.80 [0.32 , 2.02]
Total (95% CI)		**118**		**118**	**100.0%**	**0.81 [0.46 , 1.43]**
Total events:	32		37			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



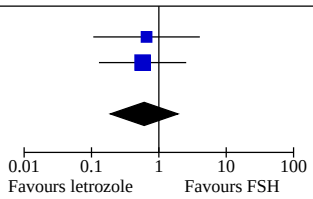
Footnotes
(1) Clomiphene-resistant women; letrozole 5 mg/day versus uFSH 75 IU
(2) Previous treatmet unknown; 5mg Let vs 75U/d for 5 days

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.4. Comparison 5: Letrozole compared to FSH, Outcome 4: Miscarriage rate per woman

Study or Subgroup	Letrozole Events	Letrozole Total	FSH Events	FSH Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hassan 2017 (1)	2	70	3	70	38.3%	0.66 [0.11 , 4.06]
Shi 2019 (2)	3	48	5	48	61.7%	0.57 [0.13 , 2.55]
Total (95% CI)		**118**		**118**	**100.0%**	**0.61 [0.19 , 1.92]**
Total events:	5		8			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable

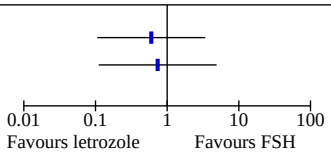


Footnotes
(1) Clomiphene-resistant women; letrozole 5 mg/day versus uFSH 75 IU
(2) Previous treatmet unknown; 5mg Let vs 75U/d for 5 days

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.5. Comparison 5: Letrozole compared to FSH, Outcome 5: Miscarriage rate per pregnancy

Study or Subgroup	Letrozole Events	Letrozole Total	FSH Events	FSH Total	Odds Ratio M-H, Fixed, 95% CI
Shi 2019 (1)	3	11	5	13	0.60 [0.11 , 3.40]
Hassan 2017 (2)	2	21	3	24	0.74 [0.11 , 4.90]



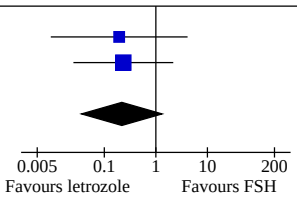
Footnotes
(1) Previous treatmet unknown; 5mg Let vs 75U/d for 5 days
(2) Clomiphene-resistant women; letrozole 5 mg/day versus uFSH 75 IU

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.6. Comparison 5: Letrozole compared to FSH, Outcome 6: Multiple pregnancy rate

Study or Subgroup	Letrozole Events	Letrozole Total	FSH Events	FSH Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hassan 2017 (1)	0	70	2	70	38.8%	0.19 [0.01 , 4.12]
Shi 2019 (2)	1	48	4	48	61.2%	0.23 [0.03 , 2.18]
Total (95% CI)		**118**		**118**	**100.0%**	**0.22 [0.04 , 1.32]**
Total events:	1		6			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Footnotes
(1) Clomiphene-resistant women; letrozole 5 mg/day versus uFSH 75 IU
(2) Previous treatmet unknown; 5mg Let vs 75U/d for 5 days

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

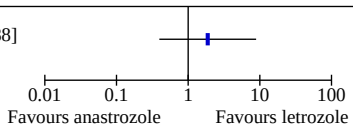
Comparison 6. Letrozole compared to anastrozole

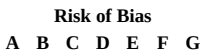
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.2 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 6.1. Comparison 6: Letrozole compared to anastrozole, Outcome 1: Clinical pregnancy rate

Study or Subgroup	Letrozole Events	Letrozole Total	Anastrozole Events	Anastrozole Total	Odds Ratio M-H, Fixed, 95% CI
Al-Omari 2004 (1)	6	22	3	18	1.88 [0.40 , 8.88]

Test for subgroup differences: Not applicable





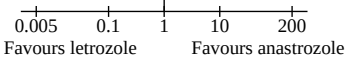
Footnotes
(1) Unknown if primary fertility treatment or CC-resistant; letrozole 2.5 mg/day versus anastrozole 1 mg/day

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.2. Comparison 6: Letrozole compared to anastrozole, Outcome 2: Multiple pregnancy rate

Study or Subgroup	Letrozole Events	Letrozole Total	Anastrozole Events	Anastrozole Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Al-Omari 2004 (1)	0	22	0	18	Not estimable		+ ? - - + + +

Test for subgroup differences: Not applicable



Footnotes

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

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

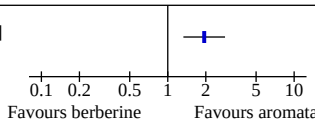
Comparison 7. Letrozole compared to berberine, followed by timed intercourse

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Live birth rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.2 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.3 Miscarriage rate per woman	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.4 Miscarriage rate per pregnancy	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.5 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 7.1. Comparison 7: Letrozole compared to berberine, followed by timed intercourse, Outcome 1: Live birth rate

Study or Subgroup	Aromatase inhibitor Events	Total	Berberine Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Wu 2016 (1)	152	430	47	214	1.94 [1.33 , 2.84]		+ ? + + + + +

Test for subgroup differences: Not applicable



Footnotes

(1) Previous subfertility treatment unknown; letrozole 2.5 mg - 5 mg/day ± berberine 1.5 g for 6 months (50%) versus berberine for 6 months

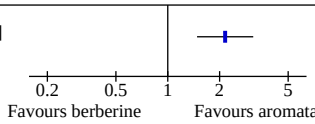
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.2. Comparison 7: Letrozole compared to berberine, followed by timed intercourse, Outcome 2: Clinical pregnancy rate

Study or Subgroup	Aromatase inhibitor Events	Total	Berberine Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Wu 2016 (1)	165	430	48	214	2.15 [1.48 , 3.13]		+ ? + + + + +

Test for subgroup differences: Not applicable



Footnotes

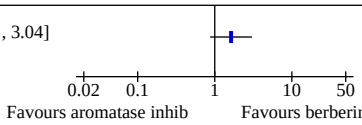
(1) Previous subfertility treatment unknown; letrozole 2.5mg - 5mg/day +/- berberine 1.5g for 6 months (50%) versus berberine 1.5g for 6 months

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.3. Comparison 7: Letrozole compared to berberine, followed by timed intercourse, Outcome 3: Miscarriage rate per woman

Study or Subgroup	Aromatase inhibitor Events	Total	Berberine Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Wu 2016 (1)	44	430	14	214	1.63 [0.87 , 3.04]		+ ? + + + + +
Test for subgroup differences: Not applicable							



Footnotes

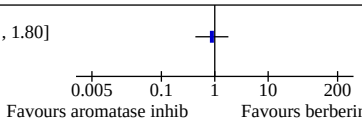
(1) Previous subfertility treatment unknown; letrozole 2.5 mg – 5 mg/day +/- berberine 1.5 g for 6 months (50%) versus berberine for 6 months

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.4. Comparison 7: Letrozole compared to berberine, followed by timed intercourse, Outcome 4: Miscarriage rate per pregnancy

Study or Subgroup	Aromatase inhibitor Events	Total	Berberine Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Wu 2016 (1)	44	165	14	48	0.88 [0.43 , 1.80]		+ ? + + + + +
Test for subgroup differences: Not applicable							



Footnotes

(1) Previous subfertility treatment unknown; letrozole 2.5 mg - 5 mg/day +/- berberine 1.5 g for 6 months (50%) versus berberine for 6 months

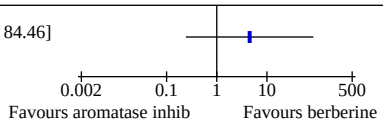
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.5. Comparison 7: Letrozole compared to berberine, followed by timed intercourse, Outcome 5: Multiple pregnancy rate

Study or Subgroup	Aromatase inhibitor Events	Total	Berberine Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Wu 2016 (1)	4	430	0	214	4.53 [0.24 , 84.46]		+ ? + + + + +

Test for subgroup differences: Not applicable



Footnotes
(1) Previous subfertility treatment unknown; letrozole 2.5 mg – 5 mg/day +/- berberine 1.5 g for 6 months (50%) versus berberine for 6 months

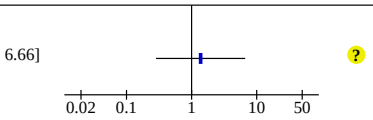
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 8. Different administration protocols of letrozole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1.1 Letrozole day 3-7 administration versus day 5-9 administration	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Different administration protocols of letrozole, Outcome 1: Clinical pregnancy rate

Study or Subgroup	5 days / Day 3 Letrozole Events	Total	10 days / Day 5 Letrozole Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
8.1.1 Letrozole day 3-7 administration versus day 5-9 administration							
Ghomian 2015 (1)	4	35	3	35	1.38 [0.28 , 6.66]		? ? ? ? + + +



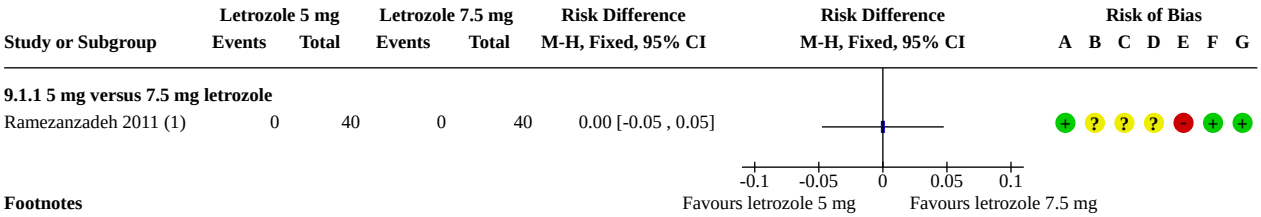
Footnotes
(1) Letrozole 5 mg/day in both groups

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 9. Dosage studies of letrozole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Ovarian hyperstimulation syndrome rate	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
9.1.1 5 mg versus 7.5 mg letrozole	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
9.2 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2.1 5 mg versus 7.5 mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3 Miscarriage rate per woman	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3.1 5 mg versus 7.5 mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.4 Miscarriage rate per pregnancy	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.4.1 5 mg versus 7.5 mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.5 Multiple pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.5.1 5 mg versus 7.5 mg letrozole	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Dosage studies of letrozole, Outcome 1: Ovarian hyperstimulation syndrome rate



Footnotes

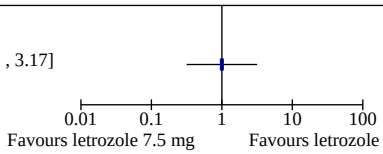
(1) No previous ovulation induction treatment

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 9.2. Comparison 9: Dosage studies of letrozole, Outcome 2: Clinical pregnancy rate

Study or Subgroup	Letrozole 5 mg Events	Total	Letrozole 7.5 mg Events	Total	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
9.2.1 5 mg versus 7.5 mg letrozole						
Ramezanzadeh 2011 (1)	7	40	7	40	1.00 [0.32 , 3.17]	+ ? ? ? - + +

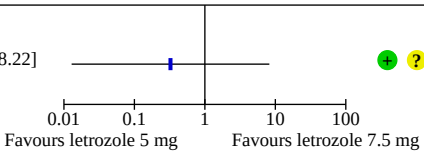


Footnotes
(1) No previous ovulation induction treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 9.3. Comparison 9: Dosage studies of letrozole, Outcome 3: Miscarriage rate per woman

Study or Subgroup	Letrozole 5 mg Events	Total	Letrozole 7.5 mg Events	Total	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
9.3.1 5 mg versus 7.5 mg letrozole						
Ramezanzadeh 2011 (1)	0	40	1	40	0.33 [0.01 , 8.22]	+ ? ? ? - + +

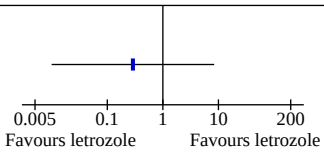


Footnotes
(1) No previous ovulation induction treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 9.4. Comparison 9: Dosage studies of letrozole, Outcome 4: Miscarriage rate per pregnancy

Study or Subgroup	Letrozole 5 mg Events	Total	Letrozole 7.5 mg Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
9.4.1 5 mg versus 7.5 mg letrozole							
Ramezanzadeh 2011 (1)	0	7	1	7	0.29 [0.01 , 8.39]		+ ? ? ? - + +

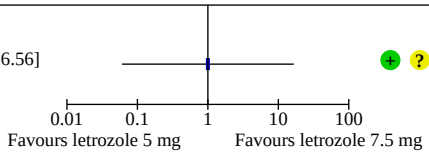


Footnotes
(1) No previous ovulation induction treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 9.5. Comparison 9: Dosage studies of letrozole, Outcome 5: Multiple pregnancy rate

Study or Subgroup	Letrozole 5 mg Events	Total	Letrozole 7.5 mg Events	Total	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
9.5.1 5 mg versus 7.5 mg letrozole							
Ramezanzadeh 2011 (1)	1	40	1	40	1.00 [0.06 , 16.56]		+ ? ? ? - + +



Footnotes
(1) No previous ovulation induction treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDICES

Appendix 1. The Cochrane Gynaecology and Fertility specialised register search strategy

ProCite platform

Searched from inception to 4 November 2021

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

(206 records)

Appendix 2. CENTRAL via the Cochrane Register of Studies Online (CRSO) search strategy

Web platform

Searched from inception to 4 November 2021

#1 MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES 1599

#2 (Polycystic Ovar*):TI,AB,KY 3955

#3 (PCOS or PCOD):TI,AB,KY 3221

#4 (stein leventh*):TI,AB,KY 33

#5 PCO:TI,AB,KY 718

#6 MESH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES 1405

#7 (ovulat* adj2 induc*):TI,AB,KY 2848

#8 superovulation:TI,AB,KY 220

#9 (ovari* adj2 hyperstimulat*):TI,AB,KY 1503

#10 (ovar* adj2 stimulat*):TI,AB,KY 2503

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 9066

#12 MESH DESCRIPTOR Aromatase Inhibitors EXPLODE ALL TREES 1460

#13 MESH DESCRIPTOR Aminoglutethimide EXPLODE ALL TREES 80

#14 MESH DESCRIPTOR Fadrozole EXPLODE ALL TREES 24

#15 (aromatase inhibitor*):TI,AB,KY 2256

#16 aminoglutethimide:TI,AB,KY 178

#17 Anastrozole:TI,AB,KY 1226

#18 Arimidex:TI,AB,KY 256

#19 Letrozole:TI,AB,KY 2187

#20 Femara:TI,AB,KY 118

#21 Exemestane:TI,AB,KY 940

#22 Aromasin:TI,AB,KY 56

#23 Vorozole:TI,AB,KY 18

#24 Rivizor:TI,AB,KY 3

#25 Formestane:TI,AB,KY 41

#26 Lentaron:TI,AB,KY 8

#27 Fadrozole:TI,AB,KY 38

#28 Afema:TI,AB,KY 0

#29 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 4782

#30 #11 AND #29 562

Appendix 3. MEDLINE search strategy

Ovid platform

Searched from 1946 to 4 November 2021

1 exp Polycystic Ovary Syndrome/ (15766)
2 Polycystic Ovar$.tw. (18537)
3 PCOS.tw. (12806)
4 PCOD.tw. (302)
5 stein leventh$.tw. (626)
6 (ovar$ adj2 sclerocystic).tw. (105)
7 (ovar$ adj2 degeneration).tw. (154)
8 PCO.tw. (4908)
9 exp ovulation induction/ or exp superovulation/ (13918)
10 (ovulat$ adj2 induc$).tw. (8049)
11 superovulation.tw. (2132)
12 (ovari$ adj2 hyperstimulat$).tw. (5435)
13 (ovari$ adj2 stimulat$).tw. (7765)
14 or/1-13 (48358)
15 exp aromatase inhibitors/ or exp aminoglutethimide/ or exp fadrozole/ (9337)
16 aromatase inhibitor$.tw. (7829)
17 aminoglutethimide.tw. (1400)
18 Anastrozole.tw. (1880)
19 Arimidex.tw. (258)
20 Letrozole.tw. (3202)
21 Femara.tw. (87)
22 Exemestane.tw. (1390)
23 Aromasin.tw. (33)
24 Vorozole.tw. (127)
25 Rivizor.tw. (5)
26 Formestane.tw. (167)
27 Lentaron.tw. (15)
28 Fadrozole.tw. (377)
29 Afema.tw. (6)
30 or/15-29 (13775)
31 14 and 30 (921)
32 randomized controlled trial.pt. (549418)
33 controlled clinical trial.pt. (94513)
34 randomized.ab. (539225)
35 placebo.tw. (228833)
36 clinical trials as topic.sh. (197987)
37 randomly.ab. (369070)
38 trial.ti. (250408)
39 (crossover or cross-over or cross over).tw. (91109)
40 or/32-39 (1437766)
41 exp animals/ not humans.sh. (4909657)
42 40 not 41 (1321608)
43 31 and 42 (265)

Appendix 4. Embase search strategy

Ovid platform

Searched from 1980 to 4 November 2021

1 exp ovary polycystic disease/ (29828)
2 Polycystic Ovar$.tw. (25622)
3 PCOS.tw. (19277)
4 PCOD.tw. (431)
5 stein leventh$.tw. (135)
6 (ovar$ adj2 sclerocystic).tw. (48)
7 (ovar$ adj2 degeneration).tw. (150)
8 PCO.tw. (4782)
9 exp ovulation induction/ (15520)
10 (ovulat$ adj2 induc$).tw. (9450)
11 (ovari$ adj2 hyperstimulat$).tw. (7977)

12 superovulation.tw. (2501)
13 (ovari$ adj2 stimulat$).tw. (12123)
14 or/1-13 (66109)
15 exp aromatase inhibitor/ (34277)
16 aromatase inhibitor$.tw. (12717)
17 aminoglutethimide.tw. (1310)
18 Anastrozole.tw. (3249)
19 Arimidex.tw. (1750)
20 Letrozole.tw. (6067)
21 Femara.tw. (1170)
22 Exemestane.tw. (2646)
23 Aromasin.tw. (546)
24 Vorozole.tw. (160)
25 Rivizor.tw. (28)
26 Formestane.tw. (210)
27 Lentaron.tw. (129)
28 Fadrozole.tw. (404)
29 Afema.tw. (28)
30 or/15-29 (35982)
31 14 and 30 (2179)
32 Clinical Trial/ (1007849)
33 Randomized Controlled Trial/ (677700)
34 exp randomization/ (92216)
35 Single Blind Procedure/ (44143)
36 Double Blind Procedure/ (186128)
37 Crossover Procedure/ (68417)
38 Placebo/ (359368)
39 Randomi?ed controlled trial$.tw. (269387)
40 Rct.tw. (43953)
41 random allocation.tw. (2228)
42 randomly allocated.tw. (39371)
43 allocated randomly.tw. (2698)
44 (allocated adj2 random).tw. (832)
45 Single blind$.tw. (27447)
46 Double blind$.tw. (217387)
47 ((treble or triple) adj blind$).tw. (1418)
48 placebo$.tw. (327421)
49 prospective study/ (721072)
50 or/32-49 (2424186)
51 case study/ (81682)
52 case report.tw. (454480)
53 abstract report/ or letter/ (1167318)
54 or/51-53 (1691117)
55 50 not 54 (2365980)
56 31 and 55 (699)

Appendix 5. PsycINFO search strategy

Ovid platform

Searched from 1806 to 4 November 2021

1 exp Endocrine Sexual Disorders/ (1855)
2 Polycystic Ovar$.tw. (468)
3 PCOS.tw. (324)
4 PCOD.tw. (8)
5 or/1-4 (2158)
6 aromatase inhibitor$.tw. (277)
7 Anastrozole.tw. (32)
8 Arimidex.tw. (3)
9 Letrozole.tw. (90)
10 Femara.tw. (0)
11 Exemestane.tw. (16)

12 or/6-11 (328)
13 5 and 12 (7)

Appendix 6. Trial registries search strategy

The ClinicalTrials database, a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home) and the World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx.

Web Platform

Searched from inception to 4 November 2021

1 polycystic ovary syndrome (490)

2 PCOS (560)

3 letrozole (438)

4 aromatase inhibitor* (897)

5 (1 OR 2) AND (3 OR 4) (26)

Appendix 7. Google Scholar search strategy

Web Platform

Searched from inception to 4 November 2021

Keywords included: polycystic ovary syndrome, PCOS, letrozole, aromatase inhibitor, anastrozole, ovulation induction

WHAT'S NEW

Date	Event	Description
4 November 2021	New search has been performed	The review has been updated. We conducted a new search in November 2021. We include 5 new studies (Ashfaq 2018; Behnoud 2019; Najafi 2020; Salazar-Ortiz 2016; Shi 2019). We added 6 new studies to awaiting classification (NCT03664050; NCT02703649; Jindal 2019; ,Ghoneim 2020; Kamel 2019; Rezk 2018). We added 5 studies as ongoing (CTRI/2018/04/013343; Cutler 2018; Huang 2020; IRCT2016030926962N2; Priest 2019). 4 studies that were included in the previous version have been excluded due to concerns about validity of the study data (study retraction or expression of concern) (Abu Hashim 2010; Badawy 2008; Badawy 2009a; Badawy 2009b). 2 studies that were included in the previous version have been moved to awaiting classification due to concerns about validity of the study data (Abdellah 2011; Abu Hashim 2010a).
4 November 2021	New citation required but conclusions have not changed	The addition of new studies has not led to a change in conclusions.

HISTORY

Protocol first published: Issue 12, 2012

Review first published: Issue 2, 2014

Date	Event	Description
6 November 2017	New search has been performed	The review has been updated. We conducted a new search on 6 November 2017. We included 16 new studies in the 2018 update (Amer 2017; Chen 2016; El-Gharib 2015; El-Khayat 2016; Ghahiri 2016; Ghomian 2015; Hassan 2017; Hendawy 2011; Ibrahim 2017; Liu 2015; Liu 2017; Moussa 2016; Seyedoshohadaei 2016; Sharief 2015; Wu 2016; Zarei 2015). We added one study as ongoing (NCT03009838).
6 November 2017	New citation required but conclusions have not changed	There is no change to the conclusions of this review.
24 September 2014	Amended	This review has been amended. A new search was conducted on 18 September 2014 and new ongoing studies added.
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.
JK and CF acted as clinical experts and commented on the protocol and full review.

SF and QL updated the 2021 version of the review.
CF, JK and LK acted as clinical expert and commented on the full review update in 2021.

DECLARATIONS OF INTEREST

SF has nothing to declare

QL has nothing to declare

JK has nothing to declare

LK has received payment for consulting/lectures from Ferring Pharmaceuticals A/S, Mithra Pharmaceuticals SA, AstraZeneca, Dr KADE/Besins, Actavis, Abvie; consulting fees from Roche, Pantarhei, Gideon Richter, Dr KADE/Besins, payment participation on a data safety monitoring board from Palleos Pharma GmbH

CF is a co-ordinating editor of CGF group and has not participated in the editorial process. CF has nothing further to declare.

SOURCES OF SUPPORT

Internal sources

- Cochrane Gynaecology and Fertility Group, New Zealand

  editorial support

External sources

- None, Other

This review was written without external support.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2021 update, we changed the title from 'Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome' to 'Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome' for clarity.

NOTES

In the 2021 update, we changed the title from 'Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome' to 'Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome' for clarity.

INDEX TERMS

Medical Subject Headings (MeSH)

*Abortion, Spontaneous [epidemiology]; *Anovulation [complications] [drug therapy]; Aromatase Inhibitors [adverse effects]; Clomiphene [adverse effects]; Fertility Agents, Female [adverse effects]; *Infertility, Female [drug therapy] [etiology]; Letrozole [therapeutic use]; Live Birth [epidemiology]; *Ovarian Hyperstimulation Syndrome; Ovulation Induction [methods]; *Polycystic Ovary Syndrome [drug therapy]; Pregnancy Rate; Selective Estrogen Receptor Modulators [therapeutic use]

MeSH check words

Female; Humans; Pregnancy