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Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation.
Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD008528.
DOI: 10.1002/14651858.CD008528.pub3.

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[Intervention Review]

Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2017.

Citation: Kamath MS, Maheshwari A, Bhattacharya S, Lor KY, Gibreel A. Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD008528. DOI: 10.1002/14651858.CD008528.pub3.

ABSTRACT

Background

Gonadotropins are the most commonly used medications for controlled ovarian stimulation in in vitro fertilisation (IVF). However, they are expensive and invasive, and are associated with the risk of ovarian hyperstimulation syndrome (OHSS). Recent calls for more patient-friendly regimens have led to growing interest in the use of clomiphene citrate (CC) and aromatase inhibitors with or without gonadotropins to reduce the burden of hormonal injections. It is currently unknown whether regimens using CC or aromatase inhibitors such as letrozole (Ltz) are as effective as gonadotropins alone.

Objectives

To determine the effectiveness and safety of regimens including oral induction medication (such as clomiphene citrate or letrozole) versus gonadotropin-only regimens for controlled ovarian stimulation in IVF or intracytoplasmic sperm injection (ICSI) treatment.

Search methods

We searched the following databases: Cochrane Gynaecology and Fertility Group Specialised Register (searched January 2017), the Cochrane Central Register of Controlled Trials (CENTRAL CRSO), MEDLINE (1946 to January 2017), Embase (1980 to January 2017), and reference lists of relevant articles. We also searched trials registries ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch/Default.aspx). We handsearched relevant conference proceedings.

Selection criteria

We included randomized controlled trials (RCTs). The primary outcomes were live-birth rate (LBR) and OHSS.

Data collection and analysis

Three review authors independently assessed trial eligibility and risk of bias. We calculated risk ratios (RR) and Peto odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MD) for continuous outcomes. We analyzed the general population of women undergoing IVF treatment and (as a separate analysis) women identified as poor responders. We assessed the overall quality of the evidence using the GRADE approach.

Main results

We included 27 studies in the updated review. Most of the new trials in the updated review included poor responders and evaluated Ltz protocols. We could perform meta-analysis with data from 22 studies including a total of 3599 participants. The quality of the evidence for different comparisons ranged from low to moderate. The main limitations in the quality of the evidence were risk of bias associated with poor reporting of study methods, and imprecision.

In the general population of women undergoing IVF, it is unclear whether CC or Ltz used with or without gonadotropins compared to use of gonadotropins along with gonadotropin-releasing hormone (GnRH) agonists or antagonists resulted in a difference in live birth (RR 0.92, 95% CI 0.66 to 1.27, 4 RCTs, n = 493, I^2 = 0%, low-quality evidence) or clinical pregnancy rate (RR 1.00, 95% CI 0.86 to 1.16, 12 RCTs, n = 1998, I^2 = 3%, moderate-quality evidence). This means that for a typical clinic with 23% LBR using a GnRH agonist regimen, switching to CC or Ltz protocols would be expected to result in LBRs between 15% and 30%. Clomiphene citrate or Ltz protocols were associated with a reduction in the incidence of OHSS (Peto OR 0.21, 95% CI 0.11 to 0.41, 5 RCTs, n = 1067, I^2 = 0%, low-quality evidence). This means that for a typical clinic with 6% prevalence of OHSS associated with a GnRH regimen, switching to CC or Ltz protocols would be expected to reduce the incidence to between 0.5% and 2.5%. We found evidence of an increase in cycle cancellation rate with the CC protocol compared to gonadotropins in GnRH protocols (RR 1.87, 95% CI 1.43 to 2.45, 9 RCTs, n = 1784, I^2 = 61%, low-quality evidence). There was moderate quality evidence of a decrease in the mean number of ampoules used,) and mean number of oocytes collected with CC with or without gonadotropins compared to the gonadotropins in GnRH agonist protocols, though data were too heterogeneous to pool.

Similarly, in the poor-responder population, it is unclear whether there was any difference in rates of live birth (RR 1.16, 95% CI 0.49 to 2.79, 2 RCTs, n = 357, I^2 = 38%, low-quality evidence) or clinical pregnancy (RR 0.85, 95% CI 0.64 to 1.12, 8 RCTs, n = 1462, I^2 = 0%, low-quality evidence) following CC or Ltz with or without gonadotropin versus gonadotropin and GnRH protocol. This means that for a typical clinic with a 5% LBR in the poor responders using a GnRH protocol, switching to CC or Ltz protocols would be expected to yield LBRs between 2% to 14%. There was low quality evidence that the CC or Ltz protocols were associated with an increase in the cycle cancellation rate (RR 1.46, 95% CI 1.18 to 1.81, 10 RCTs, n = 1601, I^2 = 64%) and moderate quality evidence of a decrease in the mean number of gonadotropin ampoules used and the mean number of oocytes collected, though data were too heterogeneous to pool. The adverse effects of these protocols were poorly reported. In addition, data on foetal abnormalities following use of CC or Ltz protocols are lacking.

Authors' conclusions

We found no conclusive evidence indicating that clomiphene citrate or letrozole with or without gonadotropins differed from gonadotropins in GnRH agonist or antagonist protocols with respect to their effects on live-birth or pregnancy rates, either in the general population of women undergoing IVF treatment or in women who were poor responders. Use of clomiphene or letrozole led to a reduction in the amount of gonadotropins required and the incidence of OHSS. However, use of clomiphene citrate or letrozole may be associated with a significant increase in the incidence of cycle cancellations, as well as reductions in the mean number of oocytes retrieved in both the general IVF population and the poor responders. Larger, high-quality randomized trials are needed to reach a firm conclusion before they are adopted into routine clinical practice.

PLAIN LANGUAGE SUMMARY

Use of clomiphene citrate or letrozole in in vitro fertilisation treatment

Review question

The aim of this review was to compare treatment with clomiphene citrate (CC) or letrozole (Ltz) versus gonadotropins alone for stimulation of the ovaries during in vitro fertilisation (IVF) treatment.

Background

Gonadotropin hormonal injections are commonly used in an IVF treatment to stimulate the ovaries to produce eggs, which can then be mixed with sperm in the laboratory to create embryos for transfer into the uterus. However, these injections are expensive, inconvenient, and are associated with side effects. Calls for patient-friendly stimulation regimens have led to the use of tablets such as clomiphene or letrozole instead of injections, but it is unclear whether these are associated with similar pregnancy rates.

Study characteristics

We included 27 studies, of which 22 studies with a total of 3599 participants had data suitable for analysis. We studied the general IVF population and those women who had fewer eggs (poor responders) during IVF separately. This is an update of a previous Cochrane Review first published in 2012. The evidence is current to 10 January 2017.

Key results

There was no clear evidence of a difference in live-birth or pregnancy rates between the groups in the general IVF population**.** Low-quality evidence suggests that for a typical clinic with 23% live-birth rate (LBR) using only gonadotropin hormonal injections, switching to CC or Ltz regimens would be expected to result in LBRs between 15% and 30%.

The risk of ovarian hyperstimulation syndrome (OHSS) was lower with CC or Ltz use compared to gonadotropins alone. Low-quality evidence suggests that for a typical clinic with 6% prevalence of OHSS associated with a gonadotropin hormonal injection, switching to CC or Ltz regimen would be expected to reduce the incidence to between 0.5% and 2.5%.

Among women designated as poor responders, there was no clear evidence of a difference between the groups in live-birth or pregnancy rates. Low-quality evidence suggests that for a typical clinic with 5% LBRs in poor responders using only gonadotropin hormonal injection, switching to CC or Ltz regimen would be expected to result in LBRs between 2% and 14%. The side effects of these drugs and data on foetal abnormalities following CC or Ltz protocols were poorly reported.

Quality of the evidence

The quality of the evidence for the different comparisons ranged from low to moderate. The main limitations were risk of bias associated with poor reporting of study methods, and imprecision.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population for controlled ovarian stimulation

Patient or population: Women undergoing controlled ovarian stimulation in IVF and ICSI cycles (general population)
Setting: Assisted reproduction clinic
Intervention: Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist)
Comparison: Gonadotropins (with GnRH agonists or midcycle antagonist)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with gonadotropins (with GnRH agonists or mid-cycle antagonist)	Risk with clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist)				
Live birth per woman	**235 per 1000**	**216 per 1000** (155 to 299)	**RR 0.92** (0.66 to 1.27)	493 (4 RCTs)	⊕⊕◯◯ **LOW**[1,2]	
Ovarian hyperstimulation syndrome per woman	**63 per 1000**	**14 per 1000** (7 to 27)	**Peto OR 0.21** (0.11 to 0.41)	1067 (5 RCTs)	⊕⊕◯◯ **LOW**[1,3]	
Clinical pregnancy rate per woman	**248 per 1000**	**248 per 1000** (213 to 288)	**RR 1.00** (0.86 to 1.16)	1998 (12 RCTs)	⊕⊕⊕◯ **MODERATE**[1]	
Cancellation rate per woman	**80 per 1000**	**150 per 1000** (114 to 196)	**RR 1.87** (1.43 to 2.45)	1784 (9 RCTs)	⊕⊕◯◯ **LOW**[1,4]	
Mean number of gonadotropin ampoules used per woman	The mean number of ampoules used in the control group ranged from 18 to 50	In all studies CC plus gonadotropins was associated with use of fewer ampoules. The mean difference	-	1098 (6 RCTs)	⊕⊕⊕◯ **MODERATE**[1,5]	

		ranged from 5.6 to 24. 6 ampoules			
Mean number of oocytes retrieved per woman	The mean number of oocytes retrieved in the control group ranged from 5 to 17	In seven studies CC plus gonadotropins was associated with retrieval of fewer oocytes, with the mean difference ranging from 1. 02 to 6.20 oocytes. The difference was statistically significant in five of these studies. The eighth study found no evidence of a difference between the groups	-	1481 (8 RCTs)	⊕⊕⊕◯ **MODERATE**[1,5]

*__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; **GnRH:** gonadotropin-releasing hormone; **ICSI:** intracytoplasmic sperm injection; **IVF:** in vitro fertilisation; **MD**: mean difference; **OR**: odds ratio; **RCT:** randomised controlled trial; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

[1]Downgraded one level (serious risk of bias). All included studies had unclear risk of bias for allocation concealment.
[2]Downgraded one level (serious imprecision). Confidence interval is wide and compatible with benefit in either group, or with no effect.
[3]Downgraded one level (serious imprecision). Small number of events.
[4]Downgraded one level (serious inconsistency). I^2 61%.
[5]Not downgraded for inconsistency. Although there was significant statistical heterogeneity, this referred to the magnitude of difference rather than direction of evidence.

BACKGROUND

Description of the condition

Controlled ovarian stimulation (COS) is an essential step in in vitro fertilisation (IVF) treatment (Arslan 2005). The goal of COS is to encourage the recruitment of a larger number of oocytes and hence maximise the number of dominant follicles that are available for retrieval (Strickler 1995). A number of different hormones, used within a variety of protocols, have been described for COS in IVF (Balasch 2001; Gregoriou 2008; Khalaf 2002; Kingsland 1992; Out 2000; Weigert 2002). Conventional regimens for ovarian stimulation are based on gonadotropins alone and are complex and expensive. In addition, they are associated with the risk of complications such as ovarian hyperstimulation syndrome and multiple pregnancies (Fauser 1999; Olivennes 1998; Verberg 2009).

Description of the intervention

Administered initially on its own (Trounson 1981), and then later in conjunction with gonadotropins (Lopata 1983; Quigley 1983), clomiphene citrate (CC) was the first drug to be used for COS in IVF (Marrs 1984). Concerns about anti-oestrogenic side effects on the whole reproductive tract, Eden 1989, Kokko 1981, Nakamura 1997, Rogers 1991, Yagel 1992, and premature luteinising hormone surge with subsequent premature ovulation and luteinisation as well as poor follicular development, Abdalla 1990, Messinis 1985, have led to a search for alternative strategies. Aromatase inhibitors have emerged as an alternative to CC as an oral ovulation induction drug (Holzer 2006). The combining of the aromatase inhibitor letrozole (Ltz) with gonadotropin during COS has been suggested as a way to reduce the total gonadotropin requirement in IVF (Goswami 2004). Gonadotropin-releasing hormone (GnRH) agonists were introduced into clinical practice for pituitary downregulation in order to achieve better control of ovarian stimulation and timing of ovulation (Porter 1984). Long protocol GnRH agonist pituitary downregulation followed by administration of gonadotropins became the norm. A number of reports suggested that its use resulted in improved follicular development, lower rates of cycle cancellation, and higher rates of fertilisation and implantation (Abdalla 1990; Macnamee 1989; Smitz 1987), as well as significantly better IVF outcomes (Hughes 1992). Later, GnRH antagonists were introduced for pituitary control. Most conventional stimulation regimens now use either GnRH agonists or antagonists along with gonadotropins. In recent years, the use of CC or Ltz along with gonadotropins has grown, particularly in women expected to respond poorly to controlled ovarian hyperstimulation (Goswami 2004; Lee 2012; Ragni 2012).

How the intervention might work

Clomiphene citrate has both oestrogenic and anti-oestrogenic effects (Glasier 1989). It acts primarily by occupying the hypothalamic oestrogen receptors for a longer period than oestrogens (weeks versus hours) (Mikkelson 1986). Consequently, it increases the release of GnRH through a negative feedback mechanism, with an ultimate increase in follicle-stimulating hormone and luteinising hormone (Dickey 1996). This increase in endogenous gonadotropin levels stimulates the ovaries and increases the number of follicles reaching ovulation (Kousta 1997). A selective aromatase inhibitor such as letrozole acts by preventing conversion of androgens to oestrogens in the ovary, thus releasing the hypothalamo-pituitary axis from the negative feedback of oestrogen. This results in an increase in follicle-stimulating hormone secretion, eventually leading to follicular development (Holzer 2006)

Why it is important to do this review

Calls for milder forms of ovarian stimulation in IVF have led to a revival of the use of CC (Edwards 1996). It has been suggested that the use of CC, alone or in combination with other drugs, is consistent with the concept of 'patient-friendly IVF' (Engel 2002; Ingerslev 2001), as it is inexpensive, readily available, safe, and can be administered orally (Lehmann 1988; Quigley 1983; Ronen 1988). The concept of patient-friendly IVF involves the use of natural cycle IVF, low-dose gonadotropins, or oral ovulation induction medications such as CC or aromatase inhibitors alone or with gonadotropins (Fauser 1999; Ingerslev 2001). While the effects of adding GnRH agonists or antagonists to gonadotropins compared to gonadotropins alone have been examined in previous systematic reviews (Al-Inany 2016; Hughes 1992), reports on the effectiveness of CC and gonadotropins compared to standard long or short protocols have demonstrated conflicting results (Dhont 1995; Grochowski 1999; Weigert 2002). Hence we decided to undertake this systematic review of randomized trials to investigate the effectiveness of oral ovulation induction medications along with gonadotropins versus gonadotropins alone (with GnRH agonists or antagonists) in controlled ovarian stimulation for IVF or intracytoplasmic sperm injection (ICSI) treatments.

OBJECTIVES

To determine the effectiveness and safety of regimens including oral induction medication (such as clomiphene citrate or letrozole) versus gonadotropin-only regimens for controlled ovarian stimulation in IVF or ICSI treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group randomized controlled trials (RCTs) if they compared oral ovarian stimulation agents, alone or in combination with gonadotropins, versus conventional gonadotropin (with GnRH agonist or antagonist) protocols in women undergoing IVF or ICSI. We excluded cross-over trials and quasi-randomised trials.

Types of participants

Women who were subfertile and undergoing fresh IVF or ICSI were eligible for inclusion.

Types of interventions

Interventions

- Clomiphene citrate with or without gonadotropins
- Aromatase inhibitors with or without gonadotropins
- Other oral induction medications with or without gonadotropins

Control

- Gonadotropins

Types of outcome measures

All outcome measures were expressed as per woman.

Primary outcomes

1. Live-birth rate per woman randomized, defined as delivery of a live foetus after 20 completed weeks of gestation
2. Ovarian hyperstimulation syndrome (OHSS) for the general IVF population only

Secondary outcomes

1. Ongoing pregnancy rate, defined as evidence of a gestational sac with foetal heart motion at 12 weeks confirmed with ultrasound
2. Clinical pregnancy rate, defined as evidence of a gestational sac confirmed with ultrasound
3. Cycle cancellation rate
4. Mean number of ampoules of gonadotropin used
5. Mean number of oocytes retrieved
6. Multiple pregnancy rate
7. Rate of miscarriage, defined as foetal loss after confirmation of a gestational sac confirmed on ultrasound, and up to 20 completed weeks of gestation
8. Rate of ectopic pregnancies
9. Rate of foetal abnormalities

Search methods for identification of studies

We sought all published and unpublished RCTs comparing oral ovulation induction medications alone or in combination with gonadotropins versus conventional gonadotropin (with GnRH agonist or antagonist) protocols in women undergoing IVF or ICSI. We used the following search strategy without language restrictions and in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist.

Electronic searches

We performed an updated search of the following electronic databases, trials registers, and websites (from inception to 10 January 2017): Cochrane Gynaecology and Fertility Group Specialised Register (Appendix 1), Cochrane Central Register of Controlled Trials (CENTRAL CRSO) (Appendix 2), MEDLINE (Appendix 3), Embase (Appendix 4), PsycINFO (Appendix 5), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) (Appendix 6). We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials, as described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We combined the Embase search with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/search-filters.html).

Other electronic sources of trials included registers for ongoing and registered trials: ClinicalTrials.gov, a service of the US National Institutes of Health (clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch/Default.aspx) (Appendix 7); conference abstracts in the Clarivate analytics Web of Science (www.wokinfo.com); LILACS (Latin American and Caribbean Health Sciences Literature) database as a source of Portuguese and Spanish trials (lilacs.bvsalud.org/en/); PubMed (www.ncbi.nlm.nih.gov/pubmed/), where the random control filter for PubMed was taken from Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*; and the OpenGrey database (www.opengrey.eu/) and Google for grey literature. We also searched PubMed and Google in order to find any published trials not yet indexed in the major databases .

Searching other resources

We handsearched the reference lists of articles retrieved by the search. Any relevant journals and conference abstracts that were not covered in the Cochrane Gynaecology and Fertility Group Specialised Register were handsearched in liaison with the Information Specialist.

Data collection and analysis

We conducted data collection and analysis in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Three review authors (AG, MSK, KY) scanned the titles and abstracts of articles retrieved by the updated search, removing those that were clearly irrelevant. We retrieved the full text of all potentially eligible studies. Three review authors (KY, AG, MSK) independently examined the full-text articles for compliance with the inclusion criteria and selected those studies that were eligible for inclusion in the review. Where required we corresponded with study investigators to clarify study eligibility (e.g. with respect to participant eligibility criteria and allocation methods). Disagreements as to study eligibility were resolved by consensus or by discussion with a fourth review author (AM).

Data extraction and management

We entered study details into the 'Characteristics of included studies' table using Review Manager software (RevMan 2014) and collected outcome data.
We extracted the following information from the included studies.

Trial methods

- Method of randomization.
- Method of allocation concealment.
- Exclusion of participants after randomization, proportion of and reasons for losses at follow-up.
- Duration, timing, and location of the trial (single-centre or multicentre trial), duration of follow-up.
- Co-interventions.
- The presence of a power calculation.

Participants

- Cause and duration of pre-existing infertility.
- Age of the women and parity.
- Investigative work-up.
- Previously administered treatment(s).

Intervention

- Type of intervention and control comparator.
- Dose and type of regimen for controlled ovarian stimulation.
- We differentiated between whether the study population included all women undergoing assisted reproductive technology or if it was limited to women who had responded poorly in a previous attempt or were expected to have a diminished response.

Outcomes

- Outcomes reported.
- How outcomes were defined.
- Timing of outcome measurement.

We extracted data were extracted from eligible studies using a data extraction form designed and pilot-tested by the authors. Where studies had multiple publications, we used the main trial report as the reference and supplemented additional details from secondary papers. Review authors corresponded with study investigators in order to resolve any data queries, as required. Three review authors (AG, MSK, KYKY) independently extracted the data. Any disagreements between these review authors were resolved by a fourth review author (SB).

Assessment of risk of bias in included studies

We assessed and reported on the risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following domains.

Sequence generation

Was sequence generation at low risk of bias (e.g. use of a random number table, a computer random number generator, or coin tossing), or unclear risk of bias (insufficient information provided about the process of sequence generation)?

Allocation concealment

Was allocation concealment at low risk of bias (e.g. use of central allocation or opaque, sealed envelopes), high risk of bias (e.g. use of an open random allocation schedule), or unclear risk of bias (insufficient information provided about the process of allocation concealment)?

Blinding of participants and assessors

There were two comparisons in this review. For the general IVF population, we considered lack of blinding as high risk since assessment of one of the primary outcomes (OHSS) may be subject to bias. For the poor responder population, the primary outcome (live birth) was objective, therefore we judged studies evaluating the poor responder population without use of blinding as low risk as it was not likely to influence the outcome.

Selective outcome reporting

Was the study free of selective reporting, that is at low risk of bias (e.g. the study protocol was available and all prespecified outcomes had been reported on, or the study protocol was not available but all prespecified outcomes had been reported); high risk of bias (e.g. not all prespecified primary outcomes had been reported); or

unclear risk of bias (insufficient information provided about the process of outcome reporting)? We tried to ascertain the risk of within-study reporting bias by seeking protocols for the original studies and checking whether the planned outcomes had been reported.

Other sources of bias

Other problems that could put a trial at high risk of bias include differences at baseline between study groups.

Two review authors (AG, MSK) assessed these domains, resolving any disagreements by consensus or by discussion with a third review author (AM). We presented the conclusions in the 'Risk of bias' table and incorporated them into the interpretation of the review findings. Where included studies failed to report the primary outcome of live birth, but did report interim outcomes such as pregnancy, we undertook informal assessment as to whether those studies reporting the primary outcome have similar values as the interim outcomes.

We presented the 'Risk of bias' assessment in the 'Characteristics of included studies' table, including commentary about each of the domains. This led to an overall assessment of the risk of bias of included studies.

Measures of treatment effect

For dichotomous data (e.g. live-birth rates), we used the numbers of events in the control and intervention groups of each study to calculate risk ratios (RR). Where events were very rare, we calculated the Peto odds ratio (OR). For continuous data (e.g. mean number of retrieved oocytes), we calculated mean differences (MD) between treatment groups. We presented the 95% confidence intervals (CI) for all outcomes.

Unit of analysis issues

We pooled data that reported outcomes per woman randomized wherever possible.

Dealing with missing data

In the case of missing data in the included studies, we contacted the original investigators by email or post to request the relevant missing information. We reported the data according to the intention-to-treat principle wherever possible. We assumed live births not to have occurred in participants without a reported outcome. For other outcomes (e.g number of oocytes retrieved and ampoules of gonadotropins used), we only analyzed the available data.

Assessment of heterogeneity

We judged whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. We assessed statistical heterogeneity by using the Chi^2 test. A low P value (or a large Chi^2 statistic relative to its degree of freedom) potentially provides evidence of heterogeneity of intervention effects and shows that results are not influenced by chance alone (Higgins 2011). We also used the I^2 statistic to assess the impact of the heterogeneity on the meta-analysis. We took an I^2 greater than 50% to indicate substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we tried to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. Whenever there was an adequate number of studies in an analysis, we used a funnel plot to explore whether a difference was due to publication or reporting bias.

Data synthesis

If studies were sufficiently similar, we performed meta-analysis whenever there were at least two trials assessing the same outcome. We performed statistical analysis in accordance with the guidelines for statistical analysis in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We combined the data from primary studies using a fixed-effect model, unless heterogeneity was considerable ($I^2 > 50\%$), in which case we used a random-effects model. This applied to the following comparisons.

1. Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle GnRH antagonist versus gonadotropins (with GnRH agonist or midcycle antagonist protocols) in IVF and ICSI cycles in the general population.
2. Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle GnRH antagonist versus gonadotropins (with GnRH agonist or midcycle antagonist protocols) in IVF and ICSI cycles in a population of poor responders.

An increase in the risk of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. OHSS), was displayed graphically in the meta-analyses to the right of the centre line, and a decrease in the risk of an outcome was displayed to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

We planned to the following subgroup analyses.

- Clomiphene citrate with or without gonadotropins in conjunction with or without antagonist versus GnRH agonist protocol.
- Clomiphene citrate with or without gonadotropins in conjunction with or without antagonist versus GnRH antagonist protocol.

- Letrozole with or without gonadotropins in conjunction with or without antagonist versus GnRH agonist protocol.
- Letrozole with or without gonadotropins in conjunction with or without antagonist versus GnRH antagonist protocol.

Sensitivity analysis

We conducted sensitivity analysis for primary outcomes (live birth and OHSS) to determine whether the conclusions were robust to decisions made during the review process. These analyses included consideration of whether the review conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias (not at high risk of bias in any domain and at low risk for randomization procedures);
2. a random-effects model had been adopted;
3. the summary effect measure was odds ratio (OR) rather than risk ratio (RR) and vice versa.

Overall quality of the body of evidence: 'Summary of findings' tables

We used the GRADE approach to summarise and interpret findings (Schünemann 2011), and GRADEpro GDT 2015 software to import data from RevMan 2014 to create 'Summary of findings' tables. These tables provide outcome-specific information concerning within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias, and the sum of available data on all outcomes rated as important to patient care and decision-making. The GRADE approach specifies four levels of quality, as follows.

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

Two review authors independently assessed the quality of the evidence, resolving any disagreements by discussion.

The main comparisons were: CC or Ltz with or without gonadotropins (with or without midcycle GnRH antagonist) versus gonadotropins (with GnRH agonist or midcycle antagonist protocols) in IVF and ICSI cycles in the general population and in poor responders. We presented 'Summary of findings' tables for the two comparisons separately.

We included the following outcomes in the 'Summary of findings' tables.

1. Live-birth rate
2. Ovarian hyperstimulation syndrome for the general IVF population only
3. Clinical pregnancy rate
4. Cycle cancellation rate
5. Mean number of ampoules of gonadotropin used
6. Mean number of oocytes retrieved.

RESULTS

Description of studies

Results of the search

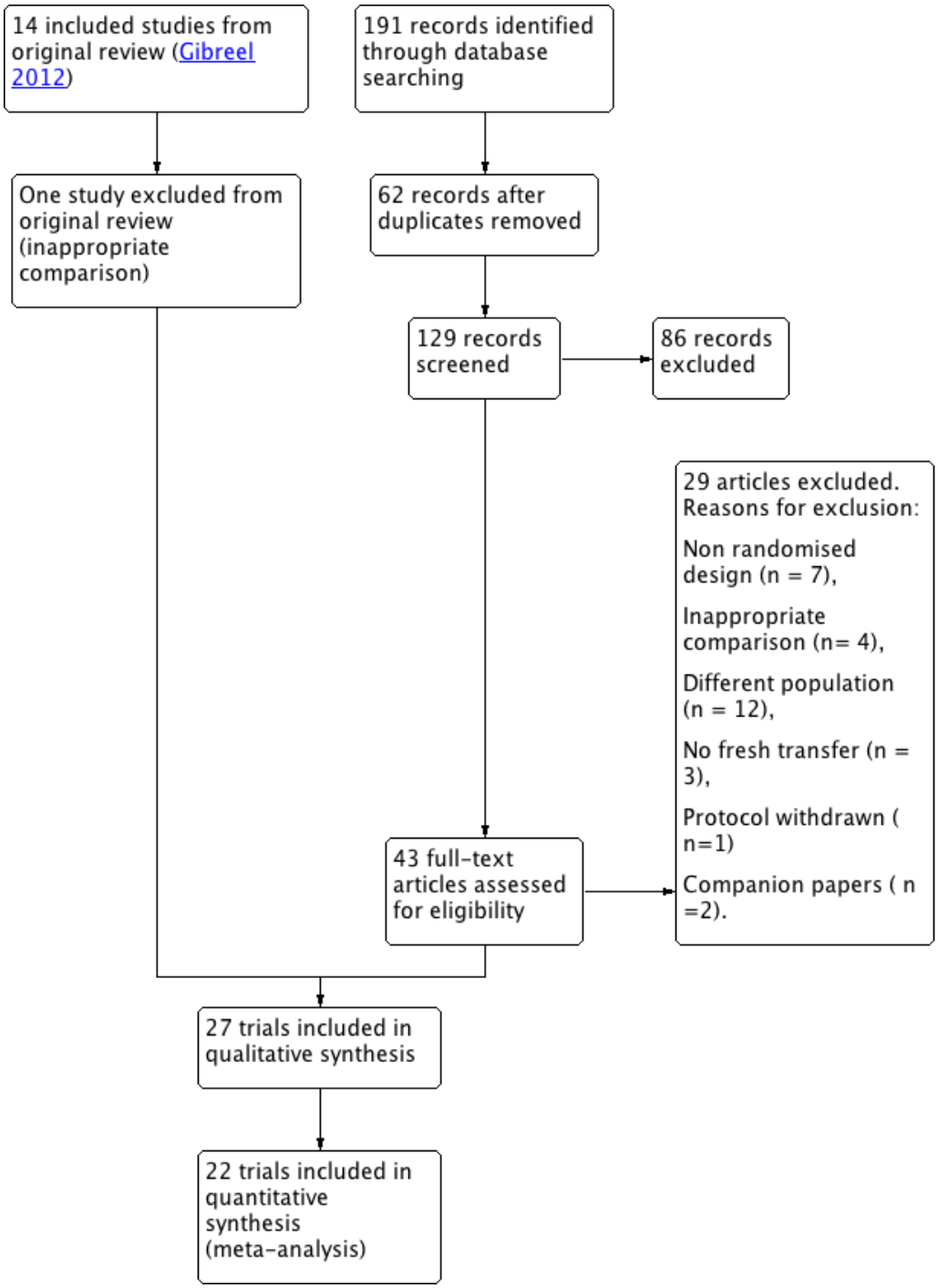
The original search strategy identified 61 records through database searching. We identified one additional record as an abstract for an ongoing trial through our search of registered trials (Youssef 2011); we contacted the corresponding author by email for more information and obtained some of the missing data. Of the 62 studies identified, five duplicates were removed, leaving 57 records. We excluded abstracts if a full article was detected for the same study, and excluded 30 abstracts that did not meet the basic inclusion criteria as identified from the study title and abstract. Where the title or abstract identified a study as 'possibly for inclusion', or if there was any doubt about the exclusion of a study, we obtained the full article for further evaluation. Of the remaining 27 studies identified as possibly for inclusion (Abdalla 1990; Ashrafi 2005; Cassidenti 1992; Dhont 1995; Engel 2002; Fenichel 1988; Ferrier 1990; Fiedler 2001; Ghosh Dastidar 2010; Gonen 1990; Grochowski 1999; Harrison 1994; Imoedemhe 1987; Jutras 1991; Karimzadeh 2010; Karimzadeh 2011; Kingsland 1992; Kubik 1990; Lin 2006; Long 1995; Macnamee 1989; Martinez 2003; Quigley 1984; Shelton 1991; Tummon 1992; Weigert 2002; Youssef 2011), 14 studies were eligible for inclusion in the final analysis of the original review (Ashrafi 2005; Fenichel 1988; Fiedler 2001; Ghosh Dastidar 2010; Grochowski 1999; Harrison 1994; Jutras 1991; Karimzadeh 2010; Kingsland 1992; Lin 2006; Long 1995; Tummon 1992; Weigert 2002; Youssef 2011).

The targeted update search resulted in 191 records. Three review authors independently examined the titles and abstracts, identifying 43 records as potentially eligible, for which full papers were obtained. We excluded 27 full texts (Ferraretti 2015; Ghanem 2013; Goldman 2014; Ibrahim 2012; Kim 2000; Legro 2012; Liu 2016; Nagulapally 2012; Nahid 2012; Nakajo 2011; NCT01577199; NCT01577472; NCT01679574; NCT01718444; NCT01791751; NCT01856062; NIH/NICHD Reproductive Medicine Network 2013; Oktem 2015; Oride 2015; Reindollar 2011; Rose 2015; Roy 2012; Sharma 2014; Siristatidis 2016; Wagman 2010; Ye 2016; Zhang 2014), and included 14 new studies (15 articles; one study had a companion paper) (Bastu 2016; Elnashar 2016; Fujimoto 2014; Galal 2012; Goswami 2004; Jindal 2013; Lee 2012; Mohsen 2013; Mukherjee 2012; Nabati

2016; Pilehvari 2016; Ragni 2012; Revelli 2014; Schimberni 2016). In addition, we identified a companion paper to one of the already included studies (Youssef 2011), but it did not provide any new data. We identified three ongoing studies (NCT 01921166; NCT 01948804; NCT 02237755). See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies for further details.

We excluded a trial that was included in original review (Fiedler 2001), since both groups included clomiphene citrate (CC) and gonadotropins. The final number of studies included in the updated review was 27 (13 studies from original review and 14 new studies from the updated search). The search result is summarized in the PRISMA figure (Figure 1).

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies for details.

Design

Our update includes 13 RCTs that were included in the original review (Ashrafi 2005; Fenichel 1988; Ghosh Dastidar 2010; Grochowski 1999; Harrison 1994; Jutras 1991; Karimzadeh 2010; Kingsland 1992; Lin 2006; Long 1995; Tummon 1992; Weigert 2002; Youssef 2011). None were multicentred. Three studies reported an a priori power calculation (Grochowski 1999; Lin 2006; Tummon 1992). None of the included trials reported financial support by any pharmaceutical company.

Following the updated search, we included 14 more RCTs in the current review (Bastu 2016; Elnashar 2016; Fujimoto 2014; Galal 2012; Ghosh Dastidar 2010; Jindal 2013; Lee 2012; Mohsen 2013; Mukherjee 2012; Nabati 2016; Pilehvari 2016; Ragni 2012; Revelli 2014; Schimberni 2016). All trials were single-centre trials, and none received financial support from any pharmaceutical company.

Participants

All of the included studies involved subfertile couples undergoing IVF treatment, but the inclusion criteria differed among the studies (Table 1). One study did not mention the total number of participants (Jutras 1991), and one study did not mention the number of participants allocated to each interventional arm (Ghosh Dastidar 2010).

We separated the trials that included the general IVF population (15 trials), Elnashar 2016, Fenichel 1988, Ghosh Dastidar 2010, Galal 2012, Grochowski 1999, Harrison 1994, Jindal 2013, Jutras 1991, Karimzadeh 2010, Kingsland 1992, Lin 2006, Long 1995, Mukherjee 2012, Tummon 1992, Weigert 2002, from those that included poor responders (12 trials) (Ashrafi 2005; Bastu 2016; Fujimoto 2014; Goswami 2004; Lee 2012; Mohsen 2013; Nabati 2016; Pilehvari 2016; Ragni 2012; Revelli 2014; Schimberni 2016; Youssef 2011), and evaluated them separately.

Interventions

Cycle characteristics of included studies have been shown in Table 1.

Among the 15 trials evaluating the intervention in the general population of women undergoing IVF, 11 compared CC with gonadotropin (with or without antagonist) versus gonadotropin in short or long protocol (Fenichel 1988; Ghosh Dastidar 2010; Grochowski 1999; Harrison 1994; Jutras 1991; Karimzadeh 2010; Kingsland 1992; Lin 2006; Long 1995; Tummon 1992; Weigert 2002). One trial compared letrozole (Ltz) with gonadotropin and antagonist versus gonadotropin in long protocol (Elnashar 2016). Two trials compared Ltz with gonadotropin and antagonist versus gonadotropin in antagonist protocol (Galal 2012; Mukherjee 2012). One trial used both CC or Ltz along with gonadotropin and antagonist versus gonadotropin in long protocol (Jindal 2013).

Among the 12 trials evaluating the intervention in poor responders, three compared CC with gonadotropin (with or without antagonist) versus gonadotropin in either short or long protocol (Ashrafi 2005; Revelli 2014; Youssef 2011). One trial compared CC versus gonadotropin in short protocol (Ragni 2012). One trial compared CC along with gonadotropins and an antagonist versus two comparator arms - short protocol and antagonist protocol (Schimberni 2016). Two trials compared CC with gonadotropin (with or without antagonist) versus antagonist protocol (Fujimoto 2014; Pilehvari 2016). The remaining five trials compared Ltz with gonadotropin (with or without antagonist) versus gonadotropin in agonist protocol, Goswami 2004, Nabati 2016, Mohsen 2013, and antagonist protocol (Bastu 2016; Lee 2012).

Outcomes

Of the trials involving the general IVF population, four trials reported the primary outcome of live birth (Harrison 1994; Kingsland 1992; Lin 2006; Long 1995), and five trials reported the primary outcome of ovarian hyperstimulation syndrome (OHSS) (Grochowski 1999; Karimzadeh 2010; Lin 2006; Mukherjee 2012; Weigert 2002).

Of the trials on poor responders, three trials reported live-birth rate (Fujimoto 2014; Lee 2012; Ragni 2012), and one trial reported cumulative live-birth rate (fresh and frozen cycles) per woman randomized (Fujimoto 2014).

Excluded studies

A list of excluded studies along with the reasons for their exclusion is provided in the Characteristics of excluded studies table. We excluded four studies that used quasi-randomisation methods (Abdalla 1990; Kubik 1990; Macnamee 1989; Siristatidis 2016). We excluded nine studies that were non-randomised trials (Engel 2002; Ferraretti 2015; Gonen 1990; Kim 2000; Oktem 2015; Oride 2015; Rose 2015; Sharma 2014; Shelton 1991). We excluded two studies in which participants may have had either gamete intrafallopian transfer (GIFT) or IVF and it was not possible to separate the outcomes of the two forms of assisted reproduction (Dhont 1995; Ferrier 1990). We excluded one study in which participants were fertile oocyte donors (Cassidenti 1992). We excluded eight trials because of an inappropriate comparison (Fiedler 2001; Goldman 2014; Imoedemhe 1987; Karimzadeh

2011; Martinez 2003; Nagulapally 2012; Nakajo 2011; Quigley 1984). We excluded seven trials in which participants were not undergoing IVF or ICSI treatment (Ghanem 2013; Ibrahim 2012; Legro 2012; Nahid 2012; Reindollar 2011; Roy 2012; Wagman 2010). We excluded three trials because participants did not undergo fresh transfers (Liu 2016; Ye 2016; Zhang 2014).

Risk of bias in included studies

We assessed the included studies for methodological quality using the Cochrane 'Risk of bias' tool (Higgins 2011). See the 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

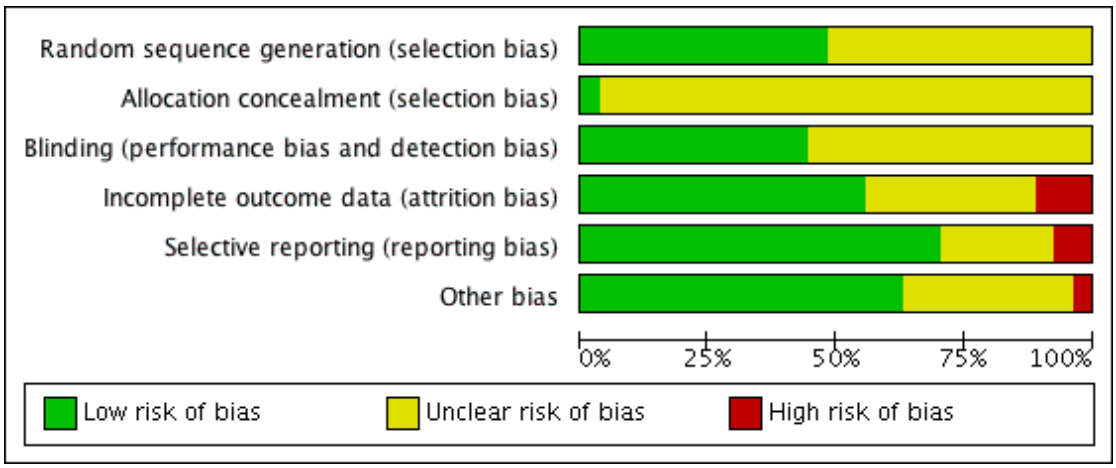
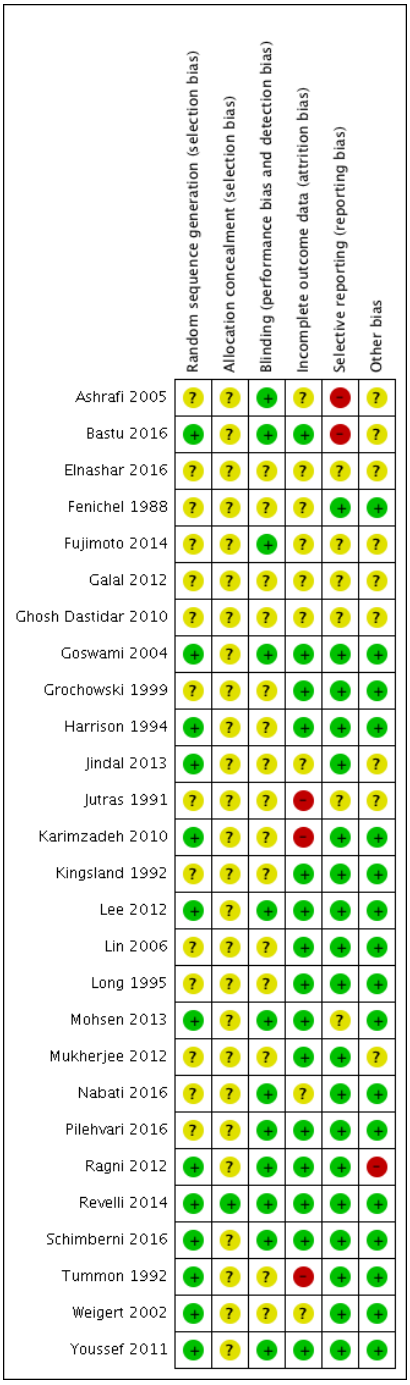


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of random sequence

The method of randomization was computer based in 11 studies (Bastu 2016; Harrison 1994; Jindal 2013; Karimzadeh 2010; Lee 2012; Mohsen 2013; Ragni 2012; Revelli 2014; Schimberni 2016; Weigert 2002; Youssef 2011). Two studies employed simple randomization using a sequence of randomized numbers (Goswami 2004; Tummon 1992). The method of randomization was not mentioned in 14 studies (Ashrafi 2005; Elnashar 2016; Fenichel 1988; Fujimoto 2014; Galal 2012; Ghosh Dastidar 2010; Grochowski 1999; Jutras 1991; Kingsland 1992; Lin 2006; Long 1995; Mukherjee 2012; Nabati 2016; Pilehvari 2016). See the 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

Allocation concealment

Thirteen studies partially described the method of allocation concealment (e.g. "sealed envelope") and were assessed as at unclear risk of bias (Ashrafi 2005; Bastu 2016; Elnashar 2016; Goswami 2004; Grochowski 1999; Karimzadeh 2010; Kingsland 1992; Lee 2012; Lin 2006; Mohsen 2013; Mukherjee 2012; Ragni 2012; Youssef 2011). In one study participant allocation was performed by an independent second party (Harrison 1994). Twelve studies did not mention the method of allocation concealment and were assessed as at unclear risk of bias (Fenichel 1988; Fujimoto 2014; Galal 2012; Jindal 2013; Jutras 1991; Long 1995; Nabati 2016; Pilehvari 2016; Schimberni 2016; Tummon 1992; Weigert 2002). Only one study stated that allocation concealment was done using consecutively numbered, opaque, sealed envelopes, which we assessed as at low risk of bias (Figure 2; Figure 3) (Revelli 2014).

Blinding

Most of the included studies did not report blinding of either clinician or participant. One trial stated that blinding was not used (Youssef 2011). Two trials described single-blinding of the clinician to the treatment allocation (Goswami 2004; Harrison 1994), while two other trials described blinding of clinicians and embryologists to the treatment allocation (Bastu 2016; Nabati 2016).

Incomplete outcome data

We assessed a total of 15 trials as at low risk of attrition bias; the majority of these reported no loss to follow-up (Goswami 2004; Grochowski 1999; Harrison 1994; Kingsland 1992; Lee 2012; Lin 2006; Long 1995; Mohsen 2013; Mukherjee 2012; Pilehvari 2016; Revelli 2014), while the few that had dropouts stated clear reasons for them, and numbers were similar in both groups (Bastu 2016; Ragni 2012; Schimberni 2016; Youssef 2011). We assessed nine trials as at unclear risk of bias due to lack of information regarding dropouts, the majority of these trials being conference abstracts (Ashrafi 2005; Elnashar 2016; Fenichel 1988; Fujimoto 2014; Galal 2012; Ghosh Dastidar 2010; Jindal 2013; Nabati 2016; Weigert 2002). We assessed three trials as at high risk of attrition bias, of which two studies had high dropout rates without clearly stated reasons (Karimzadeh 2010; Tummon 1992), and one study did not provide information regarding number of women randomized (Jutras 1991). Wherever possible, we took the denominator as the number of women randomized.

Selective reporting

None of the included studies appeared to publish or fail to publish any outcomes according to their statistical significance. Generally, few studies reported on live birth. There was a paucity of information on side effects of the CC or Ltz protocols. Most studies reported cycle cancellation due to poor response; few reported miscarriage rate and ectopic pregnancy rate; and only one trial reported foetal abnormalities. There were no data on acceptability of the adjuvant treatments.

Seven trials were published as conference abstracts (Elnashar 2016; Fujimoto 2014; Galal 2012; Ghosh Dastidar 2010; Jindal 2013; Jutras 1991; Schimberni 2016), making judgement difficult due to lack of information. Five trials had a registered protocol available (Bastu 2016; Lee 2012; Nabati 2016; Ragni 2012; Schimberni 2016).

Other potential sources of bias

One of the trial was at high risk of other bias (Ragni 2012). This study was interrupted after the scheduled two years of recruitment before reaching the sample size, leaving the study power at 60% instead of the planned 80%. One of the reasons for premature closure of the trial was slow recruitment.

We assessed studies published as conference abstracts as at unclear risk of other bias due to lack of information (Elnashar 2016; Fujimoto 2014; Galal 2012; Ghosh Dastidar 2010; Jindal 2013; Jutras 1991; Schimberni 2016). The majority of the remaining studies were at low risk for other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in

general population for controlled ovarian stimulation; **Summary of findings 2** Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonist or midcycle antagonist) in IVF and ICSI cycles in poor responders for controlled ovarian stimulation

1. Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in the general IVF population

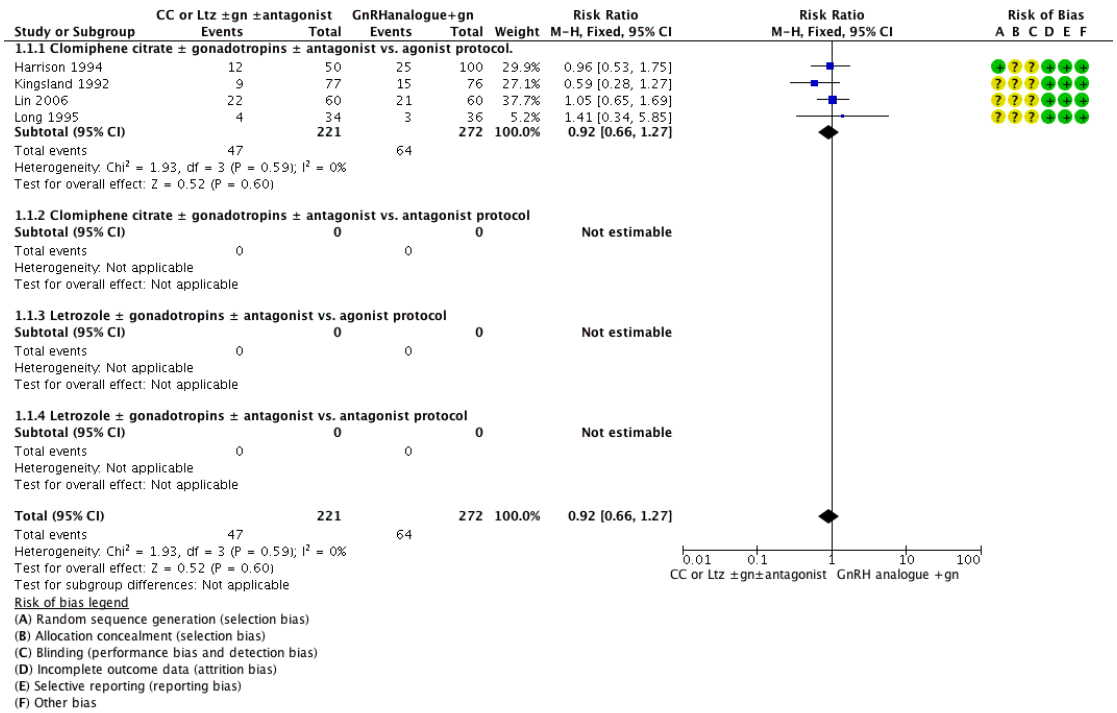
We pooled results from 12 trials (1998 women) in this comparison (Elnashar 2016; Fenichel 1988; Galal 2012; Grochowski 1999; Harrison 1994; Karimzadeh 2010; Kingsland 1992; Lin 2006; Long 1995; Mukherjee 2012; Tummon 1992; Weigert 2002). For two included trials requisite data were not available for pooling the results (Ghosh Dastidar 2010; Jutras 1991). In the intervention group of one trial, both CC or Ltz was used along with gonadotropin, hence results could not be pooled (Jindal 2013).

Primary outcomes

1.1 Live-birth rate

Four studies reported live birth. There was no clear evidence of a difference between the groups in live-birth rate (risk ratio (RR) 0.92, 95% confidence interval (CI) 0.66 to 1.27, 4 RCTs, n = 493, I^2 = 0%, low-quality evidence) (Analysis 1.1; Figure 4). This means that for a typical clinic with 23% success using a standard GnRH agonist regimen, switching to CC would be expected to result in live-birth rates between 15% and 30%. All four trials compared CC protocol versus agonist protocol. None of the included trials reported live-birth outcome for the other three subgroups. Sensitivity analysis done after removing studies without clear randomization, or by switching to odds ratio (OR), did not show any evidence of a difference in the live-birth rate.

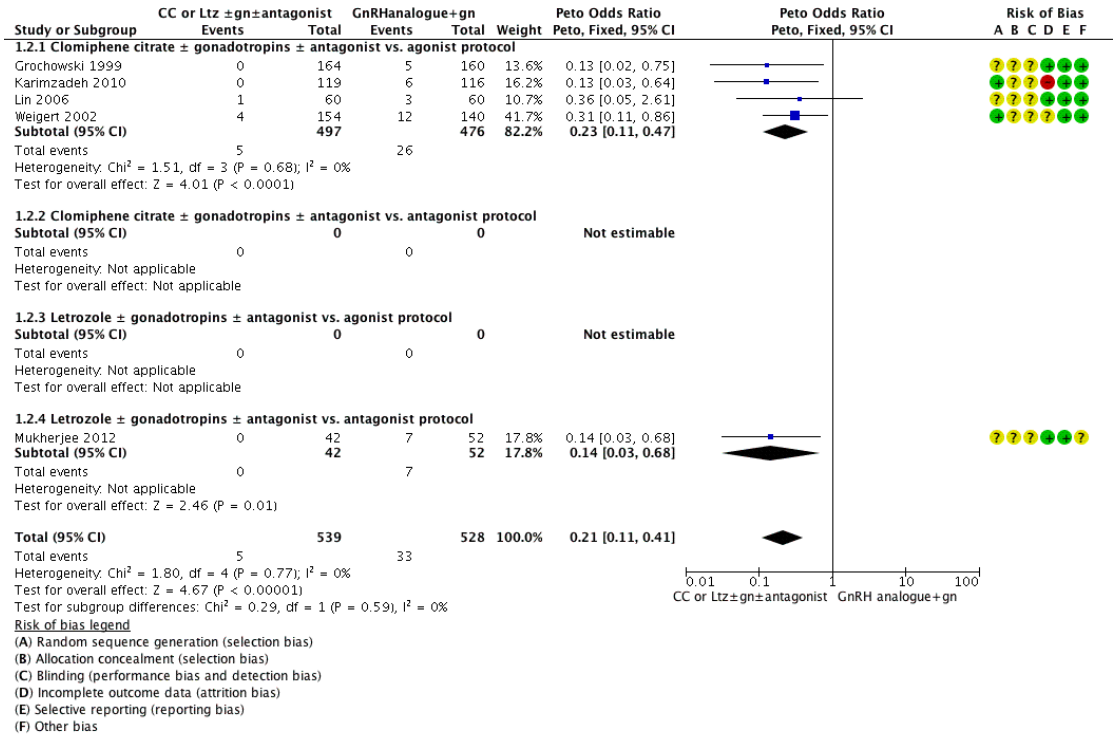
Figure 4. Forest plot of comparison: 1 Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population, outcome: 1.1 Live birth.



1.2 Ovarian hyperstimulation syndrome

Five studies reported OHSS. There was evidence of a decrease in the incidence of OHSS when CC or Ltz protocol was used (Peto OR 0.21, 95% CI 0.11 to 0.41, 5 RCTs, n = 1067, I^2 = 0%, low-quality evidence) (Analysis 1.2; Figure 5). This means that for a typical clinic with a 6% prevalence of OHSS using a standard GnRH regimen, switching to CC or Ltz protocol would be expected to reduce the incidence to between 0.5% and 2.5%. Sensitivity analysis done after removing studies without clear randomization showed a persistent decrease in the incidence of OHSS with CC or Ltz protocol.

Figure 5. Forest plot of comparison: 1 Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population, outcome: 1.2 Ovarian hyperstimulation syndrome.



Subgroup analysis according to the types of protocol compared showed no evidence of a difference between the subgroups: test for subgroup differences: Chi^2 = 0.29, df = 1 (P = 0.59), I^2 = 0%.

Secondary outcomes

1.3 Ongoing pregnancy rate

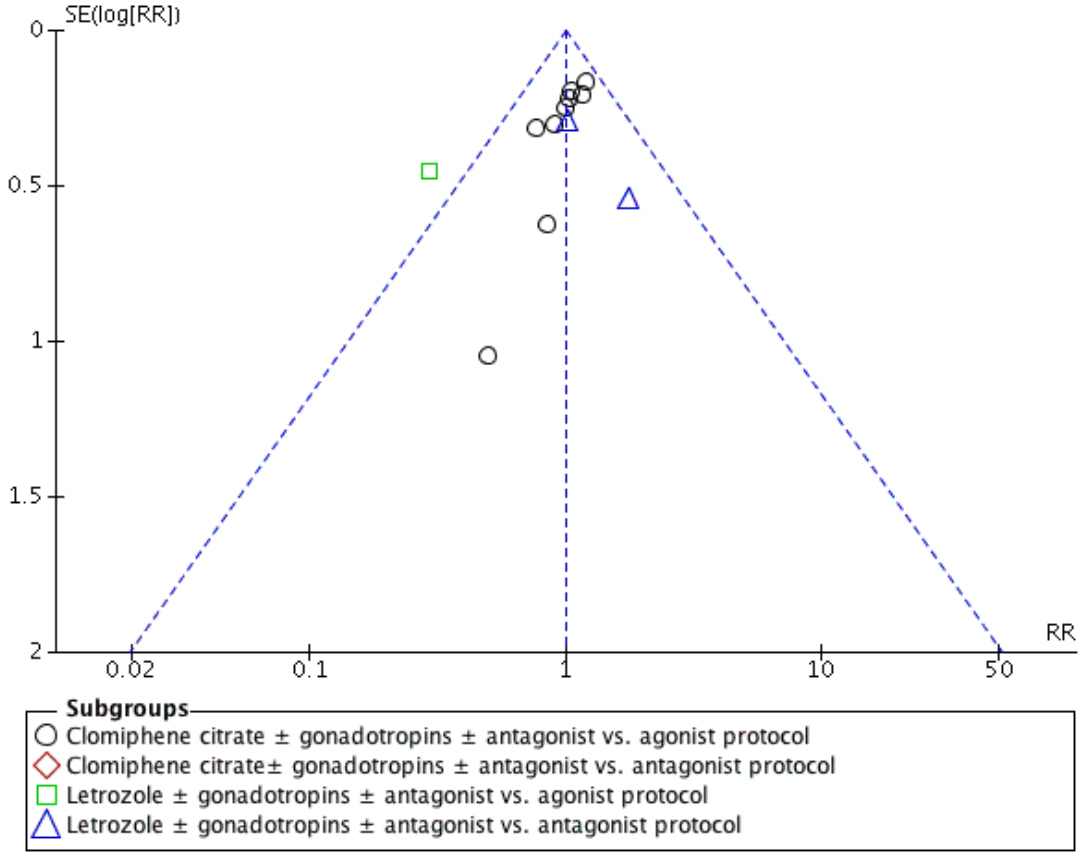
Only six studies reported the outcome of ongoing pregnancy. There was no clear evidence of a difference between the groups in ongoing pregnancy rate (RR 1.00, 95% CI 0.77 to 1.30, 6 RCTs, n = 758, I^2 = 0%) (Analysis 1.3). This means that for a typical clinic with 23% success using a standard regimen, switching to

CC protocol would be expected to result in pregnancy rates between 18% and 30%. None of the included trials reported ongoing pregnancy outcome for the other three subgroups.

1.4 Clinical pregnancy rate

Twelve studies reported clinical pregnancy rate. There was no clear evidence of a difference between the groups in clinical pregnancy rate (RR 1.00, 95% CI 0.86 to 1.16, 12 RCTs, n = 1998, I^2 = 3%, moderate-quality evidence) (Analysis 1.4). This means that for a typical clinic with 25% success using a standard regimen, switching to CC or Ltz would be expected to result in pregnancy rates between 21% and 29%. Sensitivity analysis done after removing studies without clear randomization did not show any evidence of a difference in the clinical pregnancy rate (RR 1.10, 95% CI 0.89 to 1.37). Four studies reported adequate randomization. A funnel plot for this outcome showed no evidence of publication bias (Figure 6).

Figure 6. Funnel plot of comparison: 1 Clomiphene citrate or letrozole with gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins with GnRH protocols in IVF and ICSI cycles in general population, outcome: 1.4 Clinical pregnancy rate.



Subgroup analysis according to the types of protocol compared showed evidence of a difference between the subgroups: test for subgroup differences: Chi^2 = 7.76, df = 2 (P = 0.02), I^2 = 74.2%. All the heterogeneity in this analysis was due to a single study comparing Ltz with follicle-stimulating hormone and antagonist versus long protocol with follicle-stimulating hormone (Elnashar 2016), which reported a higher clinical pregnancy rate in the inter-

vention group (RR 0.29, 95% CI 0.12 to 0.72). There was no evidence of a difference between the groups in the other subgroups.

1.5 Cycle cancellation rate

Nine studies reported on the number of cycles cancelled due to a poor response. There was evidence of an increase in cycle cancellation rate with the CC protocol compared to gonadotropins in GnRH protocol (RR 1.87, 95% CI 1.43 to 2.45, 9 RCTs, n = 1784, I^2 = 61%, low-quality evidence) (Analysis 1.5). This means that for a typical clinic with 8% prevalence of cycle cancellation using a GnRH agonist regimen, switching to CC would be expected to increase the incidence to between 11% and 20%. The increase in cycle cancellation rate persisted even after adopting a random-effects model (RR 1.74, 95% CI 1.01 to 3.00). Sensitivity analysis done after removing studies with inadequate randomization did not show any difference (RR 1.96, 95% CI 1.44 to 2.66).

1.6 Number of ampoules of gonadotropin

Six studies reported the number of ampoules of gonadotropins used along with a measure of variance. The data were too heterogeneous to pool (I^2=97%). All studies reported that CC plus gonadotropins was associated with use of fewer ampoules than gonadotropin-only regimens in agonist protocols, with the mean difference ranging from 5.6 to 24.6 ampoules (Analysis 1.6). The heterogeneity may be attributable to differences in the starting dose of gonadotropins. Sensitivity analysis, whether by removing studies with inadequate randomization or by using a random-effects model, showed persistent evidence of an increased requirement for gonadotropins in GnRH protocol.

1.7 Number of oocytes

Eight studies reported the number of oocytes retrieved, along with a measure of variance. Eight studies reported the number of oocytes retrieved, along with a measure of variance. The data were too heterogeneous to pool (I^2=92%). In seven studies CC plus gonadotropins was associated with retrieval of fewer oocytes than gonadotropin-only regimens in agonist protocols, with the mean difference ranging from 1.02 to 6.20 oocytes. The difference was statistically significant in five of these studies. The eighth study made the same comparison and found no evidence of a difference between the groups. The heterogeneity may be attributable to differences in the starting dose of gonadotropins (Analysis 1.7). Sensitivity analysis, whether by removing studies with inadequate randomization or by using a random-effects model, showed persistent evidence of a decrease in the number of oocytes retrieved with the CC with or without gonadotropins protocol compared to gonadotropins in GnRH agonist protocol.

1.8 Multiple pregnancy rate

Five trials measured multiple pregnancy rate. There was no clear evidence of a difference between the groups (RR 0.74, 95% CI 0.39 to 1.43, 5 RCTs, n = 791, I^2 = 3%) (Analysis 1.8). Subgroup analysis according to the types of protocol compared did not suggest a difference between the subgroups: test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.58), I^2 = 0%.

1.9 Miscarriage rate

Seven trials reported miscarriage rate. There was no clear evidence of a difference between the groups (RR 0.95, 95% CI 0.61 to 1.47, 7 RCTs, n = 1116, I^2 = 0%) (Analysis 1.9). Subgroup analysis according to the types of protocol compared did not suggest a difference between the subgroups: test for subgroup differences: Chi^2 = 0.39, df = 1 (P = 0.53), I^2 = 0%.

1.10 Ectopic pregnancy rate

Two trials reported ectopic pregnancy rate. There was no clear evidence of a difference between the groups (Peto OR 7.56, 95% CI 0.47 to 120.94, 2 RCTs, n = 223, I^2 = 0%) (Analysis 1.10).

1.11 Foetal abnormalities

Only one trial reported the rate of foetal abnormalities (Harrison 1994). There were no reported cases of foetal abnormalities within the two groups.

2. Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in poor responders

We could pool results from 10 trials (1601 women) in this comparison (Ashrafi 2005; Bastu 2016; Goswami 2004; Lee 2012; Mohsen 2013; Nabati 2016; Pilehvari 2016; Ragni 2012; Revelli 2014; Youssef 2011). As one trial reported only cumulative live-birth rate, we could not pool results (Fujimoto 2014). Another trial evaluated CC with gonadotropin with antagonist versus two control arms of short agonist protocol and antagonist protocol (Schimberni 2016), hence due to two different control arms we could not pool the data.

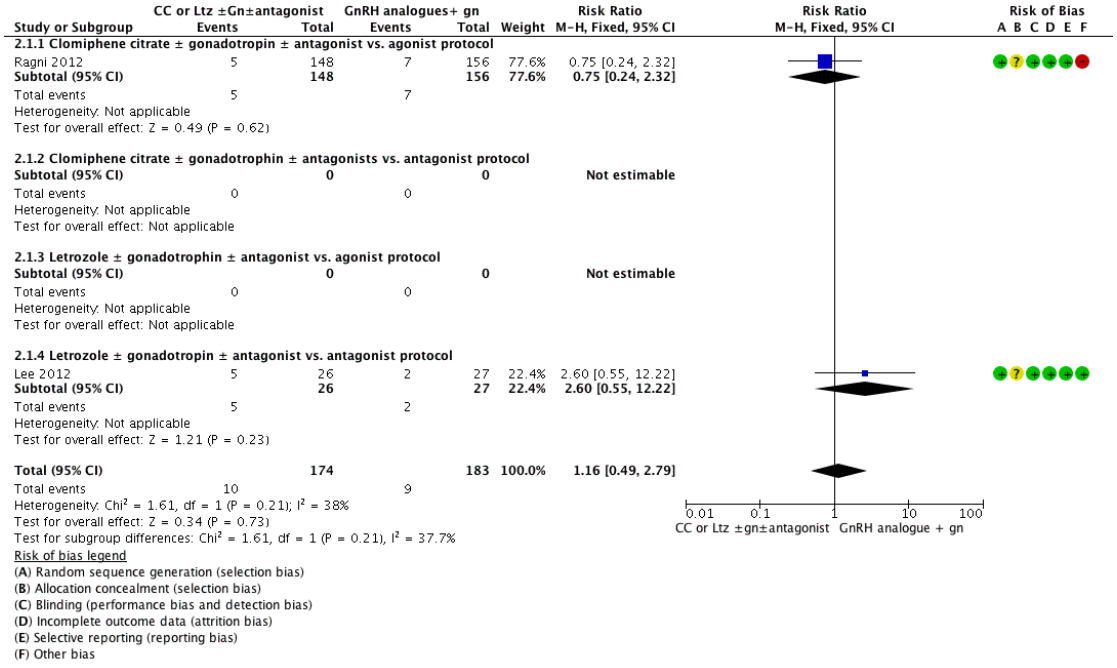
Primary outcomes

2.1 Live-birth rate

Two studies reported live-birth rate. There was no clear evidence of a difference between the groups (RR 1.16, 95% CI 0.49 to 2.79, 2 RCTs, n = 357, I^2 = 38%, low-quality evidence) (Analysis 2.1; Figure 7). This means that for a typical clinic with 5% success

using a standard GnRH analogue regimen, switching to CC or Ltz with gonadotropin would be expected to result in live-birth rates between 2% and 14%. Sensitivity analysis performed by changing summary measure effect to odds ratio or adopting a random-effects model did not show evidence of a difference in live-birth rate.

Figure 7. Forest plot of comparison: 2 Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonist or midcycle antagonist) in IVF and ICSI cycles in poor responders, outcome: 2.1 Live birth.



Subgroup analysis according to the types of protocol compared showed no evidence of a difference between the subgroups: test for subgroup differences: $Chi^2 = 1.61$, df = 1 (P = 0.21), $I^2 = 37.7\%$.

2.2 Ovarian hyperstimulation syndrome

This outcome was not applicable to this population.

Secondary outcomes

2.3 Ongoing pregnancy rate

Only two studies reported ongoing pregnancy rate. There was no clear evidence of a difference between the groups (RR 0.86 , 95% CI 0.58 to 1.28, 2 RCTs, n = 748, $I^2 = 53\%$) (Analysis 2.2). This means that for a typical clinic with 12% success using a standard regimen, switching to CC or Ltz protocol would be expected to result in pregnancy rates between 7% and 16%. Sensitivity analysis done using a random-effects model did not suggest a difference (RR 1.12, 95% CI 0.38 to 3.28).

Subgroup analysis according to the types of protocol compared did not suggest a difference between the subgroups: test for subgroup differences: $Chi^2 = 2.14$, df = 1 (P = 0.14), $I^2 = 53.4\%$.

2.4 Clinical pregnancy rate

Eight studies reported clinical pregnancy rate. There was no clear evidence of a difference between the groups (RR 0.85, 95% CI 0.64 to 1.12, 8 RCTs, n = 1462, $I^2 = 0\%$, low-quality evidence) (Analysis 2.3). This means that for a typical clinic with 13% success using a standard regimen, switching to CC or Ltz protocol

would be expected to result in pregnancy rates between 8% and 14%. Sensitivity analysis done after excluding studies without clear randomization did not show any evidence of a difference in clinical pregnancy rate (RR 0.92, 95% CI 0.68 to 1.23). Six studies had adequate randomization.

Subgroup analysis according to the types of protocol compared did not suggest a difference between the subgroups: test for subgroup differences: Chi^2 = 1.64, df = 3 (P = 0.65), I^2 = 0%.

2.5 Cycle cancellation rate

Ten studies reported on the number of cycles cancelled due to a poor response. There was evidence of an increase in cycle cancellation rate with the CC or Ltz with or without gonadotropin compared to gonadotropins in GnRH protocol (RR 1.46, 95% CI 1.18 to 1.81, 10 RCTs, n = 1601, I^2 = 64%, low-quality evidence) (Analysis 2.4). This means that for a typical clinic with 14% prevalence of cycle cancellation using a GnRH regimen, switching to CC or Ltz protocol would be expected to increase the incidence to between 17% and 26%. The increase in cycle cancellation rate did not differ after adopting a random-effects model (RR 1.35, 95% CI 0.93 to 1.98). Sensitivity analysis after removing studies with inadequate randomization revealed persistence of difference (RR 1.48, 95% CI 1.16 to 1.89).

Subgroup analysis according to the types of protocol compared did not suggest a difference between the subgroups: test for subgroup differences: Chi^2 = 5.10, df = 3 (P = 0.16), I^2 = 41.2%.

2.6 Mean number of ampoules of gonadotropin used

Three studies reported the number of ampoules of gonadotropins used along with a measure of variance.

In two studies the intervention group received CC plus gonadotropins and in the other one the intervention group received letrozole. These subgroups were too heterogeneous to pool (I^2= 96%) and the test for subgroup differences between the subgroups was statistically significant: Chi^2 = 56.37, df = 1 (P < 0.001), I^2 = 98.2%.

Compared with use of gonadotropin-only regimens in agonist protocols, there was evidence of a decrease in the mean number of ampoules used associated with the use of CC plus gonadotropins (MD -23.98, 95% CI -27.41 to -20.56; participants = 87; studies = 2; I^2 = 0%) and also with the use of letrozole plus gonadotropins (MD -46.24, 95% CI -50.93 to -41.55; participants = 49; studies = 1) (Analysis 2.5).

Sensitivity analysis done using a random-effects model showed persistent evidence of an increased requirement for gonadotropins in GnRH agonist protocols.

2.7 Mean number of oocytes retrieved

Eight studies reported the number of oocytes retrieved, along with a measure of variance.

Four of these studies compared CC plus gonadotropins versus gonadotropins in an agonist protocol. One study compared CC plus gonadotropins versus gonadotropins in an antagonist protocol, and three studies compared letrozole plus gonadotropins versus gonadotropin only in an agonist protocol. The studies were too heterogeneous to pool, either overall (I^2=83%) or within protocol subgroups (I^2=85%-88%). However, in seven of the eight studies the direction of effect was consistent and was associated with inferior findings in the intervention group. The heterogeneity may be attributable to differences in the starting dose of gonadotropins

In three studies CC plus gonadotropins was associated with retrieval of fewer oocytes than gonadotropin-only regimens in agonist protocols, with the mean difference ranging from 0.75 to 2.10 oocytes. The difference was statistically significant in two of these studies. The fourth study found no clear evidence of a difference between the groups, and the direction of effect was inconsistent with the other three studies.

The study comparing CC plus gonadotropins versus a gonadotropin-only regimen in an antagonist protocol found no clear evidence of a difference between the groups (MD -0.59, 95% CI -1.58 to 0.40; participants = 54; studies = 1). Findings were mixed in the studies comparing letrozole plus gonadotropins versus gonadotropin only in an agonist protocol: one study reported retrieval of significantly fewer oocytes in the intervention group, while the other two studies found no clear evidence of a difference between the groups. Analysis 2.6

Sensitivity analysis whether by removing the studies with inadequate randomization or by using a random-effects model for analysis showed persistent evidence of a decrease in the number of oocytes retrieved with the CC or Ltz protocol compared to GnRH protocol.

Subgroup analysis according to the types of protocol compared did not suggest a difference between the subgroups: test for subgroup differences: Chi^2 = 5.78, df = 2 (P = 0.06), I^2 = 65.4%.

2.8 Multiple pregnancy rate

Only one trial reported multiple pregnancy rate. There was no clear evidence of a difference between the groups (RR 0.53, 95% CI 0.05 to 5.75, 1 RCT, n = 304) (Analysis 2.7).

2.9 Miscarriage rate

Three trials reported miscarriage rate. There was no clear evidence of a difference between the groups (RR 0.97, 95% CI 0.45 to 2.12, 3 RCTs, n = 818, I^2 = 2%) (Analysis 2.8).

2.10 Ectopic pregnancy

No trials reported on this outcome.

2.11 Foetal abnormalities

Only one trial reported the rate of foetal abnormalities (Ragni 2012). There were no reported cases of foetal abnormalities in either group.

Other analyses

We examined publication bias in this systematic review by constructing a funnel plot. There was a paucity of trials reporting live-birth data. We considered a funnel plot for the clinical pregnancy data, using this as a surrogate endpoint. We observed symmetric distribution of studies around the vertical line, indicating no publication bias (Figure 6).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonist or midcycle antagonist) in IVF and ICSI cycles in poor responders for controlled ovarian stimulation

Patient or population: Women undergoing controlled ovarian stimulation in IVF and ICSI cycles (poor responders)
Setting: Assisted reproduction clinic
Intervention: Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist)
Comparison: Gonadotropins (with GnRH agonist or midcycle antagonist)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with gonadotropins (with GnRH agonist or mid-cycle antagonist)	Risk with clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist)				
Live birth per woman	**49 per 1000**	**57 per 1000** (24 to 137)	**RR 1.16** (0.49 to 2.79)	357 (2 RCTs)	⊕⊕◯◯ **LOW**[1,2]	
Clinical pregnancy rate per woman	**128 per 1000**	**109 per 1000** (82 to 143)	**RR 0.85** (0.64 to 1.12)	1462 (8 RCTs)	⊕⊕◯◯ **LOW**[1,2]	
Cancellation rate per woman	**145 per 1000**	**212 per 1000** (171 to 263)	**RR 1.46** (1.18 to 1.81)	1601 (10 RCTs)	⊕⊕◯◯ **LOW** [1,3]	
Mean number of gonadotropin ampoules used per woman	The mean number of ampoules used in the control group ranged from 39 to 71	There were fewer ampoules used in the intervention groups (CC plus gonadotropins: MD -23.98, 95% CI -27.41 to -20.56; participants = 87; studies = 2) ; letrozole plus go-	-	136 (3 RCTs)	⊕⊕⊕◯ **MODERATE**[1,4]	

		nadotropins: MD -46.24, 95% CI -50.93 to -41.55; participants = 49; studies = 1)			
Mean number of oocytes retrieved per woman	The mean number oocytes retrieved in the control group ranged from 2 to 5	In three of four studies CC plus gonadotropins versus gonadotropins in an agonist protocol was associated with retrieval of fewer oocytes, with the mean difference ranging from 0.75 to 2.10 oocytes. The difference was statistically significant in two of these studies. One study found no evidence of difference between CC plus gonadotropin versus gonadotropin in an antagonist protocol. Of three studies comparing letrozole plus gonadotrophins, one study reported significantly lower oocyte retrieval while the other two studies found no clear evidence of a difference	-	1203 (8 RCTs)	⊕⊕⊕◯ **MODERATE**[1,4]

*__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; **GnRH:** gonadotropin-releasing hormone; **ICSI:** intracytoplasmic sperm injection; **IVF:** in vitro fertilisation; **MD**: mean difference; **RCT:** randomised controlled trial; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

[1]Downgraded one level (serious risk of bias). Many of the included studies had unclear risk of bias for allocation concealment.
[2]Downgraded one level (serious imprecision). Confidence interval is wide and compatible with benefit in either group, or with no effect.
[3]Downgraded one level (serious inconsistency). I^2 64%.
[4]Not downgraded for inconsistency. Although there was high statistical heterogeneity, this referred to the magnitude of difference rather than direction of evidence.

DISCUSSION

Summary of main results

The main finding of this updated systematic review was that it is unclear whether the use of clomiphene citrate (CC) or letrozole (Ltz) with gonadotropins, with or without GnRH antagonist, in controlled ovarian stimulation in IVF leads to a difference in live-birth rates, ongoing pregnancy rates, or clinical pregnancy rates when compared to the use of gonadotropins with GnRH protocols in either the general population of women undergoing IVF(Summary of findings for the main comparison) or in women who are poor responders (Summary of findings 2). The use of CC or Ltz led to a significant increase in cycle cancellation rate (low-quality evidence) as well as a reduction in the incidence of OHSS (in a general IVF population) (low-quality evidence), the number of gonadotropins ampoules used (moderate-quality evidence) and number of oocytes retrieved (moderate-quality evidence) (Summary of findings for the main comparison) (Summary of findings 2). In most included studies, it was not possible to determine whether cycle cancellation was due to premature luteinising hormone surge, poor follicular development, or other reasons. Although our results showed that there may be fewer oocytes retrieved with the use of CC or Ltz protocols in both the general IVF population and poor responders, these data must be interpreted with caution as there were no differences in pregnancy or live-birth rates, which are more relevant outcomes. Some studies may have failed to count zero entries for participants with cancelled cycles, which may have affected the overall estimate of difference, particularly if cancellation was more common in the CC or Ltz arms.

Overall completeness and applicability of evidence

We performed a sample size calculation, which found that for a study to detect a 5% difference in live birth with 80% power and 0.05 significance level, when the live-birth rate in the control group is 20%, an individual trial would need to randomise over 2000 women (STATA 10.1 software)(STATA). This means that if there is truly no difference between standard gonadotropins and CC protocols, then more than 2000 patients are required to be 80% sure that the limits of a two-sided 90% confidence interval will exclude a difference between standard and new treatments of more than 5%. Unfortunately, the total number of participants in studies included in this meta-analysis was insufficient to identify this minimal effective difference. We therefore acknowledge that a type 2 (beta) statistical error cannot be excluded.

Most of the studies included in the meta-analysis suffered from an inadequate description of allocation concealment. This limits the level of confidence associated with this meta-analysis. None of the trials addressed the potential value of any surplus embryos that could have been frozen for later use. Most of the included trials did not assess cumulative live birth after pooling results from fresh and cryo-thawed cycles. One included trial reported comparable cumulative live-birth rates following CC and GnRH antagonist protocol in poor responders (Fujimoto 2014). Comparative non-randomised studies have shown inconsistent results (Demoulin 1991; Fugger 1991; Van der Elst 1996). There are no data on the acceptability of CC- or Ltz-included protocols. The adverse effects of these protocols have been poorly reported. Data on foetal abnormalities following the use of CC or Ltz protocols are also lacking.

The primary outcome of this review was live-birth rate per woman. The lack of adequately powered trials and possible clinical heterogeneity among the included trials suggest that the evidence is insufficient to effectively draw conclusions on the value of CC or Ltz alone or in combination with gonadotropins, with or without GnRH antagonist, compared to conventionally used gonadotropins and GnRH agonist protocols in the general IVF population. In the poor responder group, the different criteria used to define inclusion limits the overall applicability of evidence even within this population.

Heterogeneity

We observed the presence of variations in criteria among individual trials in terms of the definition of pregnancy, the types and doses of gonadotropins, GnRH agonist used, age, method of monitoring follicular response, type of intervention (IVF or ICSI), luteal support, starting doses of gonadotropins, causes of cycle cancellation, and type of GnRH protocols (agonist and antagonist). In addition, there was variation in inclusion for poor responders among the included studies. The literature suggests no difference in pregnancy rates between a long intramuscular depot and different preparations of subcutaneous short-acting GnRH agonists (Albuquerque 2013; Wong 2001). Meanwhile, urinary human menopausal gonadotropin has not been demonstrated to be superior to recombinant follicle-stimulating hormone in terms of live-birth rate after IVF treatment (van Wely 2011). The long luteal GnRH agonist has been observed to have better results than short protocol (Siristatidis 2015). Clinical heterogeneity among studies was also due to variations in the trials' protocols as well as the inclusion and exclusion criteria for recruited patients.

We found high statistical heterogeneity for some of the outcomes studied in this review. The statistically significant increase in cycle cancellation rate (I^2 = 61% to 64%) whenever CC or Ltz was used, and the statistically significant reductions in number of gonadotropins ampoules used (I^2 = 96% to 97%) and suggestion of fewer oocytes retrieved (I^2 = 83% to 92%) should therefore be interpreted with caution. Differences in the starting doses of gonadotropins may affect the total number of gonadotropins ampoules used as well as the number of oocytes. Meanwhile, differences in causes for cycle cancellation like poor follicular development or premature luteinising hormone surge may be a strong

contributor to this observed statistical heterogeneity for the mentioned outcomes.

Quality of the evidence

Most studies included in the original review had suboptimal methodology. We included 27 trials in the current update, 13 of which were from the original review. We included 22 studies in the meta-analysis. There was insufficient information for some outcomes, and only six trials reported live-birth rate per woman or couple. The method of randomisation was unclear in some trials. Most studies had small sample sizes. Most studies lacked blinding. A funnel plot for the outcome of clinical pregnancy in the general IVF population showed no evidence of publication bias (Figure 6).

Some of the studies comparing CC with gonadotropins versus gonadotropins in GnRH protocol in a general population of women undergoing IVF and ICSI were very old. Only one relevant study has been published within the last 15 years (Weigert 2002). Hence no recent data have been published for this comparison, although new studies comparing Ltz plus gonadotropins versus gonadotropins only in GnRH protocols have been included (Elnashar 2016; Galal 2012; Mukherjee 2012). Most of the new trials included in this update evaluated CC or Ltz in poor responders, but only two trials reported live birth (Lee 2012; Ragni 2012).

In the general IVF population, the overall quality of evidence was low for live birth, OHSS, and cancellation rate and moderate for clinical pregnancy, gonadotropins requirement, and mean oocytes retrieved. The main limitations were risk of bias (due to unclear allocation concealment) and imprecision associated with low frequency of events. In the poor responder group, the overall quality of evidence was low for live birth, clinical pregnancy, and cancellation rate and moderate for gonadotropins requirement and numbers of oocytes retrieved. The evidence was limited by serious imprecision and risk of bias. We noted a high level of statistical heterogeneity for the outcomes of cancellation rate, gonadotropins dose, and oocytes retrieved, which was due to the use of different protocols and cancellation policies in the trials. We did not downgrade the level of evidence for inconsistency for gonadotropins usage and oocytes retrieved since the statistical heterogeneity referred to the magnitude of difference rather than direction of evidence.

Potential biases in the review process

We aimed to identify all eligible studies for this update. Whenever possible, we contacted study authors for additional information for potential inclusion in the review. However, for many conference abstracts, we had difficulty contacting authors and getting necessary information and data.

Agreements and disagreements with other studies or reviews

A recent systematic review evaluated the role of CC and Ltz during ovarian stimulation in women undergoing IVF (Bechtejew 2017). The review included 23 studies, and separate pooled results were available for women with expected poor response and women without risk of poor response. The live-birth rate (RR 0.90, 95% CI 0.6 to 1.2) and clinical pregnancy rate (RR 1.02, 95% CI 0.8 to 1.4) did not differ significantly between the groups in poor responders, and mean consumption of gonadotropins was significantly lower following CC (MD -18, 95% CI -21 to -15) and Ltz (MD -35, 95% CI -47 to -23) protocol in the same population. In women who were not at risk of poor response, the live-birth rate (RR 0.90, 95% CI 0.7 to 1.1) and clinical pregnancy rate (RR 1.00, 95% CI 0.9 to 1.2) did not differ significantly between the two groups. There was a significant difference in OHSS rate (Peto OR 0.20, 95% CI 0.1 to 0.3) and gonadotropins consumption following CC protocol. The findings of Bechtejew 2017 are in agreement with the current update for all important outcomes for a general IVF population and poor responders.

Another systematic review evaluated CC protocol versus standard GnRH protocol in poor responders and included three randomised trials and one quasi-randomised trial (Song 2016). The pooled results did not show any significant difference in live birth (OR 0.71, 95% CI 0.22 to 2.29) and clinical pregnancy (OR 1.11, 95% CI 0.80 to 1.55) rates between the two groups. These findings are in agreement with the findings of the current review.

AUTHORS' CONCLUSIONS

Implications for practice

We found no conclusive evidence indicating that clomiphene citrate or letrozole with or without gonadotropins differed from gonadotropins in gonadotropin-releasing hormone agonist or antagonist protocols in terms of their effects on live birth or pregnancy rates, either in the general population of women undergoing in vitro fertilisation (IVF) treatment or in women who were poor responders. Use of clomiphene citrate or letrozole led to a reduction in the amount of gonadotropins required and the incidence of ovarian hyperstimulation syndrome. However, use of clomiphene citrate or letrozole may be associated with a significant increase in the incidence of cycle cancellations, as well as reductions in the mean number of oocytes retrieved in the general IVF population and poor responders. Larger, high-quality randomised trials are needed to reach a firm conclusion before clomiphene citrate or letrozole are adopted into routine clinical practice.

Implications for research

There is a need for an adequately powered randomised trial com-

paring clomiphene citrate or letrozole along with gonadotropins versus gonadotropins-alone protocols for controlled ovarian stimulation in IVF treatment to assess clinical and cost-effectiveness as well as the acceptability of the regimens in both the general IVF population and in poor responders. Cumulative live birth after fresh and cryo-thawed cycles should also be investigated. Outcome measures should include cost per live birth as well as patient satisfaction.

ACKNOWLEDGEMENTS

We thank:

- Richard Kirubakaran, Cochrane South Asia, Prof. BV Moses Centre for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India;

- Marian Showell, Information Specialist for the Cochrane Gynaecology and Fertility Group;

- Editorial team of the Cochrane Gynaecology and Fertility Group for their support and assistance.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ashrafi 2005

Methods	RCT
Participants	154 poor responders who had undergone at least 1 previous IVF attempt with a poor response. Responses were assessed as poor when baseline follicle-stimulating hormone concentration was > 15 mIU/mL, oestradiol concentration on the day of hCG injection was < 500 pg/mL, or the number of pre-ovulatory follicles > 16 mm in diameter was fewer than 3
Interventions	45 women went into the hMG group, 52 women into the GnRH agonist plus hMG group, and 34 women into the CC plus hMG group
Outcomes	Premature LH surges, cycles cancelled in the follicular phase, and the number of mature oocytes retrieved
Notes	Authors were contacted for the missing data through email but they did not respond

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This is an RCT, although method of random sequence generation was not mentioned
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes (there was no mention of whether they were opaque or not or whether serially numbered or not)
Blinding (performance bias and detection bias) All outcomes	Low risk	Although blinding was not mentioned, we did not consider that blinding was likely to influence findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up and missing data information was not mentioned. Information unclear to make a judgement
Selective reporting (reporting bias)	High risk	Most of the reported outcomes were surrogate outcomes, and there was no mention of our primary and secondary outcomes (i.e. live birth and OHSS)
Other bias	Unclear risk	We contacted the authors for missing data but received no response

Bastu 2016

Methods	RCT Country: Turkey Single-centre
Participants	Included poor responders by Bologna criteria (2 out of 3) ≥ 40 years or other risk factor for POR or abnormal ovarian test or previous ≤ 3 oocytes retrieved Age 18 to 42; normal uterus by HSG or hysteroscopy; regular cycles; normal hormonal cycles; BMI 19.3 to 28.9; ejaculate sample; no endocrine abnormalities Exclusion: history of gonadotoxic therapy; ovarian surgery; natural IVF; DHEA or testosterone supplement
Interventions	Group 1 (n = 31): gonadotropins 450 (hMG + recombinant) + antagonist Group 2 (n = 31): gonadotropins 300 (hMG + recombinant) + antagonist Group 3 (n = 33): mild stimulation: letrozole 5 days, 5 mg/day + hMG 150 IU + antagonist
Outcomes	Clinical pregnancy rate; ongoing pregnancy rate; implantation rate; gonadotropins usage; mean number of oocytes; cycle cancellation rate
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation described "computer generated list".
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope used"; does not mention whether opaque or numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinician and embryologist blinded. Overall we did not consider that blinding was likely to influence findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up reported, and cancellation across groups was balanced. An intention-to-treat analysis was done
Selective reporting (reporting bias)	High risk	Even though clinical and ongoing pregnancy rates were stated outcomes, in the results these outcomes were clubbed and presented as a single outcome
Other bias	Unclear risk	Funding not mentioned.

Elnashar 2016

Methods	RCT Country: Egypt Single-centre
Participants	Included normoresponders; unexplained infertility; AFC > 5, AMH > 1 ng/mL; BMI 18 to 29; age 20 to 35 Exclusion criteria: endometriosis; azoospermia; BMI > 29.
Interventions	Group 1 (n = 40): letrozole 10 mg daily day 3 to 7 along with FSH 75 IU/day from day 5 along with antagonist Group 2 (n = 40): long protocol with FSH 150 to 225 IU/day.
Outcomes	Clinical pregnancy rate; total gonadotropins usage; mature oocytes retrieved
Notes	Conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not clearly stated.
Allocation concealment (selection bias)	Unclear risk	Used "sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not enough information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information to make a judgement. Intention-to-treat analysis or loss to follow-up was not mentioned
Selective reporting (reporting bias)	Unclear risk	Not enough information to make a judgement, event rates are not mentioned
Other bias	Unclear risk	There is not enough information to make a judgement. This is a conference abstract publication

Fenichel 1988

Methods	RCT
Participants	30 women under age of 38 years with only tubal infertility and fertile semen samples from their partners
Interventions	3-arm study: Group I: clomiphene + hMG Group II: triptorelin (Decapeptyl Depot) (3.5 mg) from day 22 of the preceding cycle

Fenichel 1988 (*Continued*)

	+ hMG after desensitisation (long protocol) Group III: both GnRHa and hMG from day 2 of the cycle until day of hCG administration (short protocol)
Outcomes	Pregnancy rate, cancellation rate, premature LH surge, mean number of hMG ampoules, mean number of oocytes
Notes	Article in French

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This an RCT, however the method of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Although the authors stated in their study that "women were not aware of their allocation", the method of concealment of allocation was not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The analysis was per cycle. Not enough information to make a judgement
Selective reporting (reporting bias)	Low risk	The protocol of the study was not available, however most outcomes of interest in this review were reported
Other bias	Low risk	We found no potential sources of within-study bias.

Fujimoto 2014

Methods	RCT Country: Japan Recruitment: poor responder patients who visited the IVF Center of University of Tokyo Hospital for the purpose of ART
Participants	99 women undergoing ART Inclusion criteria: elevated basal serum FSH levels (> 10 mIU/mL); antral follicle counts < 7 in early follicular phase; previous poor response to ART treatment (< 5 retrieved oocytes) Exclusion criteria: over the age of 45; women who underwent oocyte retrieval cycles more than 3 times

Fujimoto 2014 (*Continued*)

Interventions	Group 1 (n = 44): controlled ovarian stimulation initiated on day 3 with 5 days of clomiphene citrate (2 tabs daily) followed by hMG administration. After leading follicle diameter reached 14 mm, GnRH antagonist Ganirelix was administered in addition to hMG Group 2 (n = 45): hMG administration was started on day 3, followed by combination with Ganirelix as above
Outcomes	Cumulative live-birth rate per woman; cancellation rate Other outcomes reported in study but not entered into review: fertilisation rate; oestradiol levels on day of trigger; number of growing follicles
Notes	Number of events not reported. This was a conference absract. We could not contact the authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	There was no description of blinding participants, personnel, or outcome assessment in this conference abstract. However, we did not consider that potential lack of blinding was likely to influence findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information to make a judgement. Intention-to-treat analysis or loss to follow-up was not mentioned
Selective reporting (reporting bias)	Unclear risk	Not enough information to make a judgement, event rates are not mentioned
Other bias	Unclear risk	There is not enough information to make a judgement. This is a conference abstract publication

Galal 2012

Methods	RCT Country: Egypt Single-centre
Participants	Women with PCOS and planned for ICSI
Interventions	Mild stimulation (n = 20): letrozole 10 mg day 2 to 6 along with hMG (150 to 225 IU) Conventional stimulation (n = 20): hMG (150 to 225 IU) in antagonist protocol
Outcomes	Main outcomes were gonadotropins use, day of stimulation, mean oocytes retrieved, and clinical pregnancy rate
Notes	Number of events not reported. This was a conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no description of blinding participants, personnel, or outcome assessment in this conference abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information to make a judgement. Intention-to-treat analysis or loss to follow-up was not mentioned
Selective reporting (reporting bias)	Unclear risk	Not enough information to make a judgement, event rates are not mentioned
Other bias	Unclear risk	There is not enough information to make a judgement. This is a conference abstract publication

Ghosh Dastidar 2010

Methods	RCT
Participants	116 good-prognosis patients undergoing their first IVF cycle
Interventions	Women were randomised into 2 groups. Group A participants received clomiphene citrate from day 2 to day 6 of cycle and rFSH (100 to 150 IU) on days 3 and 5 and then daily from day 7 onwards. GnRH antagonist (0.25 mg) was administered subcutaneously daily once lead follicle measured 13 to 14 mm until day of hCG. GnRHa protocol and ovarian stimulation with rFSH (200 to 225 IU starting dose) was started in Group B

Ghosh Dastidar 2010 (*Continued*)

Outcomes	Pregnancy rate, implantation rate, number of top-quality embryos	
Notes	The abstract did not report the number of women assigned to each group	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	No available protocol
Other bias	Unclear risk	The study was published as an abstract, and the authors did not reply to our emails

Goswami 2004

Methods	RCT Country: India Single-centre	
Participants	Women who had previous 1 to 3 IVF failures due to poor response were included. Women with severe endometriosis, FSH > 12 IU, and history of previous pelvic surgery were excluded. Women were randomised in a 1:2 ratio	
Interventions	Mild stimulation (n = 13): letrozole 2.5 mg from day 3 to 7 along with recombinant FSH (75 IU) from day 3 to 8 Conventional protocol (n = 25): long agonist protocol with FSH	
Outcomes	Main outcomes were total dose of gonadotropins, oocytes retrieved, endometrial thickness, and clinical pregnancy rates	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Goswami 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomised using "random number table" by study co-ordinator
Allocation concealment (selection bias)	Unclear risk	"Sequentially number sealed envelopes were used" for allocation concealment. However, there was no mention of whether the envelopes were opaque or not
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blinding of clinician done. We did not consider that blinding was likely to influence findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were included in the analysis. No loss to follow-up or missing data reported
Selective reporting (reporting bias)	Low risk	All the outcomes mentioned in material and methods section were reported
Other bias	Low risk	We did not find any other source of bias within the study.

Grochowski 1999

Methods	RCT
Participants	324 infertile couples undergoing IVF/ICSI Inclusion criteria: women younger than 36 years of age, regularly menstruating, and cause of infertility indicates IVF/ICSI Exclusion criteria: not mentioned
Interventions	2 groups: Group A: clomiphene citrate + hMG Group B: GnRHa (long) + hMG
Outcomes	Pregnancy rate, implantation rate, cancellation rate, multiple pregnancy, OHSS rate, mean number of oocytes retrieved, mean number of gonadotropins
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This is an RCT, however the method of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Serially numbered, closed envelopes, however there was no mention of whether they were opaque or not

Grochowski 1999 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis done. No missing data or loss to follow-up reported
Selective reporting (reporting bias)	Low risk	A duplicate publication for this study was checked and the trial appears to be free from selective reporting
Other bias	Low risk	We found no other potential sources of within-study bias.

Harrison 1994

Methods	RCT
Participants	150 women undergoing IVF for the first time
Interventions	150 women were randomised into 3 groups of 50 women each. Group A: triptorelin intramuscularly from day 1 of the cycle, and hMG was given daily when down regulation occurred Group B: 100 mg clomiphene citrate from day 2 for 5 days with hMG daily from day 4 of the cycle Group C: buserelin intranasally from day 1, and hMG was added when down regulation was confirmed
Outcomes	Live-birth rate, pregnancy rates
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomised code
Allocation concealment (selection bias)	Unclear risk	Although quoted "patient allocation was performed by a second party and clinicians were blinded to patient allocation", there was no description of how allocation concealment was performed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although intention-to-treat analysis was not mentioned in the study, we easily retrieved all data required from the published material with no need to contact the authors

Harrison 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol of the study was not available, however most outcomes of interest were reported
Other bias	Low risk	We found no other potential sources of within-study bias.

Jindal 2013

Methods	RCT Country: India Single-centre
Participants	Women < 40 years, no further details
Interventions	Mild stimulation (n = 173): clomiphene citrate or aromatase inhibitor for the first 5 days of cycle followed by gonadotropins and 0.25 mg antagonist (cetrorelix) injection daily until the day of hCG Long GnRH analogue protocol (n = 173)
Outcomes	gonadotropins usage, mean number of oocytes retrieved, clinical pregnancy rate Outcomes reported but not used in review: cost of the oral ovulation induction agents
Notes	This was published as a conference abstract.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using "computer generated list".
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mention of any loss to follow-up. Information insufficient to make a judgement
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in materials and methods section were reported
Other bias	Unclear risk	The trial was not registered. Funding not mentioned.

Jutras 1991

Methods	RCT
Participants	Women undergoing their first IVF cycle
Interventions	CC + hMG versus gonadotropins in GnRH agonist short protocol
Outcomes	Number of gonadotropins ampoules and midluteal progesterone
Notes	This trial was published as an abstract. Number of participants was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	The total number of participants was not mentioned.
Selective reporting (reporting bias)	Unclear risk	No important outcomes of interest were reported. Not enough information to make a judgement
Other bias	Unclear risk	The study was published as an abstract and the authors did not reply to our emails

Karimzadeh 2010

Methods	RCT
Participants	243 women who were candidates for ART Inclusion criteria: women aged 18 to 35 years, presence of a regular and proven ovulatory menstruation cycle with a length of 26 to 35 days, basal FSH < 10 IU/L, BMI 18 to 30 kg/m^2, and first IVF attempt. Indications for IVF were unexplained infertility, male factor, tubal factor, early-stage endometriosis, and cervical factor
Interventions	Group A: GnRHa every day for menstrual cycle 21 until day of desensitisation, then ovarian stimulation would commence with rFSH. Group B: stimulated with clomiphene citrate and continuous gonadotropins stimulation with rFSH. GnRH antagonist was started daily with dominant follicle 12 mm

Karimzadeh 2010 (*Continued*)

Outcomes	Pregnancy rate, implantation rate, cancellation rate, multiple pregnancy, OHSS rate, mean number of oocytes retrieved, mean number of gonadotropins
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes, however there was no mention of whether they were opaque or not
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis, however data for number of women who started treatment were provided and so could be calculated in meta-analysis; besides percentage of dropouts was above 5%
Selective reporting (reporting bias)	Low risk	The protocol of the study was not available, however most outcomes of interest were reported
Other bias	Low risk	We found no other potential sources of within-study bias.

Kingsland 1992

Methods	RCT
Participants	308 women undergoing their first IVF cycle
Interventions	4-arm study: Group A: hMG (alone) Group B: clomiphene citrate + hMG Group C: GnRH agonist from first day of the cycle and for 3 days only, then hMG was started (ultrashort the flare-up protocol) Group D: GnRH agonist from day 21 of previous cycle and then hMG was added after desensitisation (long protocol)
Outcomes	Live birth Pregnancy (not defined) rate per woman/cycle Cancellation rate Multiple pregnancy rate Mean number of oocytes retrieved

Kingsland 1992 (*Continued*)

Notes	Inclusion criteria and exclusion criteria not described.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This is an RCT, however the method of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Sealed, serially numbered envelopes, however there was no mention of whether they were opaque or not
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors did not state that analysis was by intention-to-treat, however the outcomes were analysed for all participants. No missing data or loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	We checked a duplicate publication and there was no risk of selective reporting
Other bias	Low risk	We found no other potential sources of within-study bias.

Lee 2012

Methods	RCT Country: China Single-centre	
Participants	Women < 40 years undergoing IVF. History of < 4 oocytes retrieved in previous cycle (poor responders) or < 5 AFC	
Interventions	Mild stimulation (n = 26): letrozole 2.5 mg from day 2 to 6 with hMG (225 IU) with antagonist Conventional stimulation (n = 27): hMG (225 IU) with antagonist	
Outcomes	Main outcomes were oocytes retrieved, clinical pregnancy rate, ongoing pregnancy rate, and live-birth rate	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lee 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomised using "computer generated list".
Allocation concealment (selection bias)	Unclear risk	Allocation concealment done using "opaque sealed envelopes"; not mentioned if envelopes were numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Although blinding was not mentioned, we did not consider that blinding was likely to influence findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were included in analysis.
Selective reporting (reporting bias)	Low risk	All the specified outcomes were reported.
Other bias	Low risk	We detected no other source of bias within the study.

Lin 2006

Methods	RCT
Participants	120 women undergoing their first ICSI cycle Inclusion criteria: women aged 20 to 38 years with regular cycles, day 3 FSH < 10 mIU/mL, BMI between 18.5 and 24.9 kg/m^2, male factor infertility. Exclusion criteria: other indications for infertility including endometriosis, anovulation, PCOS, and hydrosalpinx
Interventions	Clomiphene citrate + hMG + cetrorelix (antagonist) versus GnRHa (long) + hMG
Outcomes	Live-birth rate Clinical pregnancy (ultrasound viable foetus) rate Cancellation rate Implantation rate Severe OHSS rate Mean number of oocytes Mean number of gonadotropins
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This an RCT, however the method of random sequence generation was not described

Lin 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation concealment we performed through sealed envelopes and physicians were not aware of the allocation until the patients were about to start ovarian stimulation"; however, there was no mention of whether or not the envelopes were opaque or serially numbered
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed. No missing data or loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	Although there was no available published protocol, all outcomes of interest were reported
Other bias	Low risk	We found no other potential sources of within-study bias.

Long 1995

Methods	RCT
Participants	75 patients undergoing their first IVF cycle; women were between 25 and 45 years old
Interventions	CC + hMG versus GnRHa + hMG (short protocol)
Outcomes	Pregnancy rate per couple
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This is an RCT, however the method of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned in study if allocation concealment was performed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All couples that participated in the study were analysed.

Long 1995 (*Continued*)

Selective reporting (reporting bias)	Low risk	The published protocol for this study was not available, however most outcomes of interest were reported
Other bias	Low risk	We found no other potential sources of within-study bias.

Mohsen 2013

Methods	RCT Country: Egypt Single-centre
Participants	Women undergoing IVF with previous failed IVF due to poor response were included Women with severe endometriosis, severe male factor, and history of previous pelvic or ovarian surgery were excluded
Interventions	Mild stimulation (n = 30): letrozole 2.5 mg from day 2 to 6 and hMG along with antagonist Conventional (n = 30): microdose flare protocol with 300 IU hMG
Outcomes	Clinical pregnancy rate, cancellation rates; outcomes were not clearly mentioned
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomization"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment done by sealed envelopes. No other details
Blinding (performance bias and detection bias) All outcomes	Low risk	Although blinding was not mentioned, we did not consider that blinding was likely to influence findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were included in the analysis with no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly stated, and protocol not available; not enough information to make a judgement
Other bias	Low risk	We did not find any other bias in the study.

Mukherjee 2012

Methods	RCT Country: India Single-centre
Participants	Women between 25 and 35 years of age Normogonadotropic, without PCOS or endometriosis Undergoing IVF for male factor (azoospermia)
Interventions	Group A (42 women): letrozole 5 mg from day 3 to 7 along with recombinant FSH (75 IU) and antagonist Group B (52 women): recombinant FSH (150 to 225 IU) and antagonist protocol
Outcomes	Outcomes were total gonadotropins dose, oocytes retrieved, clinical pregnancy rate
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was not described, so we are unable to judge
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment is not clearly described; only randomly divided by "sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Although trial is described as single-blinded, it was unclear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All couples that participated in the study were analysed.
Selective reporting (reporting bias)	Low risk	The published protocol for this study was not available, however most outcomes previously specified were reported
Other bias	Unclear risk	We found no other potential sources of within-study bias.

Nabati 2016

Methods	RCT Country: Iran Single-centre
Participants	Included women who were poor responders: FSH 10 to 15 IU/mL or oestradiol < 1500 pg/mL or ultrasound with 3 follicles in previous IVF or age > 40 years Women were excluded for endometriosis, sustained hyperprolactinaemia, FSH > 15 IU/mL, male azoospermia, or single ovary
Interventions	Mild stimulation (n = 62): letrozole 5 mg twice daily from day 2 to 6 with gonadotropins 450 IU until trigger versus microdose flare protocol (n = 61) with gonadotropins 300 IU
Outcomes	gonadotropins consumption, number of days stimulation, number of oocytes retrieved, and clinical pregnancy rate per woman randomised
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Design stated in title and abstract, however randomisation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Ultrasound personnel and embryologist blinded. However, we did not consider blinding to influence the primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not mentioned, however intention-to-treat analysis was done
Selective reporting (reporting bias)	Low risk	Outcomes not clearly stated in methods section, however registered trial and all stated outcomes have been reported
Other bias	Low risk	We identified no potential source of bias within the study.

Pilehvari 2016

Methods	RCT Country: Iran Single-centre

Pilehvari 2016 (*Continued*)

Participants	Poor responder according to Bologna criteria, 2 out of 3 criteria: advanced maternal age ≥ 40 years or previous poor response < 3 oocytes or AFC 5 to 7 or AMH < 0.5 -1.1 ng/mL Exclusion criteria: use of any infertility medicine in the previous 3 months and "presence of any medical history"
Interventions	Group 1 (n = 42): mild stimulation, clomiphene 100 mg from day 2 for 5 days with hMG 150 IU/day from day 5 with antagonist Group 2 (n = 35): conventional protocol, gonadotropins (hMG/recombinant FSH) 300 IU/day with antagonist
Outcomes	Clinican pregnancy rate, days of stimulation, number of oocytes, cancellation rate Other outcomes not included in review: fertilisation rate, endometrial thickness
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Although blinding was not mentioned, we did not consider that blinding was likely to influence the findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	All the outcomes mentioned in methods section were reported.
Other bias	Low risk	No funding. We identified no other potential source of bias.

Ragni 2012

Methods	RCT Country: Italy Recruitment: patients referring to 4 infertility units in Milan, Rozzano, and Monza in Italy and selected for IVF were evaluated for study entry
Participants	304 women with day 3 serum FSH > 12 IU/mL on at least 2 occasions or previous poor response to hyperstimulation.

	Inclusion criteria: 1) indication to IVF-ICSI; 2) age 18 to 42 years; 3) day 3 serum FSH > 12 IU/mL on at least 2 occasions or previous poor response (≤ 3 oocytes with a conventional stimulation protocol) in a previous IVF cycle. Exclusion criteria: 1) number of previous IVF cycles ≥ 3; and 2) cycles requiring the use of spermatozoa from MESA-TESE procedures
Interventions	Group 1 (n = 148): clomiphene citrate oral tablets 150 mg/day from day 3 to 7 of the cycle Group 2 (n = 156): daily s.c. injections of triptorelin (GnRH agonist) started on day 1 or 2 of the menstrual cycle and 450 IU of s.c. recombinant FSH from day 3 of the cycle, short protocol
Outcomes	Live birth per women randomised, clinical pregnancy rate, cycle cancellation rate, multiple pregnancy rate, rate of foetal abnormalities Other outcomes not included in review: number of follicles > 15 mm; number of follicles > 10 mm; number of oocytes retrieved; fertilisation rate; number of women who underwent embryo transfer; number of embryos transferred; implantation rate; any adverse events; costs
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomised by means of a computer-generated list into two groups"
Allocation concealment (selection bias)	Unclear risk	"Sealed opaque envelopes containing treatment allocation were opened after inclusion"; not mentioned if envelopes were numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Although this study was not blinded, we did not consider that lack of blinding was likely to influence the findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was reported and reasons given. The numbers were balanced between groups. An intention-to-treat analysis was done
Selective reporting (reporting bias)	Low risk	The proposed outcomes in the ClinicalTrials.gov registration (NCT01389713) were reported in the paper publication

Ragni 2012 (*Continued*)

Other bias	High risk	The study was interrupted after the scheduled 2 years of recruitment before reaching the sample size, leaving the study power at 60% instead of the planned 80%. One of the reasons for premature closure of the trial was slow recruitment

Revelli 2014

Methods	RCT Country: Italy Recruitment: participants were recruited from those undergoing IVF who were classified as expectant poor responders
Participants	695 women with clinical, endocrine, and ultrasound characteristics suggesting a low ovarian reserve and a poor responsiveness to COH. Each woman was included in the study for only 1 IVF cycle Inclusion criteria: 1) circulating menstrual cycle day 3 FSH between 10 and 20 IU/L in the presence of oestradiol (E2) serum level < 80 pg/mL; 2) circulating AMH between 0.14 and 1.0 ng/mL; 3) antral follicle count assessed by transvaginal ultrasound of between 4 and 10 Exclusion criteria: women with basal FSH > 20 IU/L; undetectable AMH levels; AFC < 3; and age over 43 years
Interventions	"Mild" protocol (n = 355): clomiphene citrate 100 mg/day for 5 days from the 2nd to 6th day of the menstrual cycle + low-dose 150 IU/day of subcutaneously injected gonadotropins + GnRH antagonist from the 8th day of the cycle until the day of hCG administration "Long" protocol (n = 340): 0.8 mg/day GnRH agonist given intranasally from the 21st day of the run-in cycle for 14 days and at the beginning of gonadotropins administration; the dose was reduced to 0.4 mg/day and continued during ovarian stimulation. Exogenous gonadotropins were administered at a starting daily dose of 300 IU, which was eventually increased up to a maximum of 450 IU/day after 1 week
Outcomes	Mean number of oocytes retrieved, cycle cancellation rate, total administered gonadotropins dose; length of ovarian stimulation, clinical (ultrasound-confirmed) pregnancy rate per started cycle, miscarriage rate, ongoing pregnancy rate at 12 weeks' gestational age Other outcomes reported in study but not entered into review: fertilisation rate, implantation rate, pregnancy rate per oocyte pick-up and per embryo transfer
Notes	

Risk of bias

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

Revelli 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Randomization was performed using a computerized algorithm without any restriction. No blocks were used since the size of the study group was estimated to be large enough to ensure a balanced distribution of patients between groups"
Allocation concealment (selection bias)	Low risk	"Allocation concealment was obtained using sequentially numbered dark envelopes: until they were opened at the time of allocation, both physicians and patients were blinded to the study."
Blinding (performance bias and detection bias) All outcomes	Low risk	There was no description in the trial report of blinding participants or personnel after allocation was completed. However, we did not consider that potential lack of blinding was likely to influence the findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up after randomisation was reported. The "loss to follow up" term used in the report indicated the cancelled cycle due to poor response, which is expected in poor responder population
Selective reporting (reporting bias)	Low risk	Every outcome proposed in the methods was explored. However, the study protocol was not available
Other bias	Low risk	We found no other potential sources of within-study bias.

Schimberni 2016

Methods	RCT Country: Italy Single-centre
Participants	Women meeting at least 2 of the following criteria were defined as poor responders: 1) age > 40 years; 2) basal FSH > 12 mIU/ mL; 3) 3 or fewer oocytes retrieved in the previous IVF cycle; 4) low oestradiol levels on the day of hCG administration (< 1500 pmol/mL) Exclusion criteria: women with a BMI > 30; biochemical and ultrasound evidence of polycystic ovary syndrome; stage III-IV endometriosis; inflammatory, autoimmune, or metabolic disorders; infertility medications (gonadotropins, clomiphene citrate) taken within the past 2 months

Schimberni 2016 (*Continued*)

Interventions	Group 1 (n = 78) mild stimulation: clomiphene citrate 100 mg from day 2 for 5 days and FSH 450 IU/day from day 5 with antagonist Group 2 (n = 78): FSH 450 IU/day with antagonist. Group 3 (n = 78): FSH 450 IU/day with short agonist protocol
Outcomes	Clinical pregnancy rate, implantation rate, days of stimulation, mature oocytes retrieved
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation; block randomisation done
Allocation concealment (selection bias)	Unclear risk	Study mentions blinding of study team to allotted group, but does not describe actual method used
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding not mentioned, however we did not consider that potential lack of blinding was likely to influence the findings for our primary and secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised and loss to follow-up were mentioned and appeared to be balanced. However, intention-to-treat analysis not done
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	Funding not mentioned. We identified no other potential source of bias

Tummon 1992

Methods	RCT
Participants	508 couples undergoing their first IVF cycle were randomised into 2 groups. However, only 408 couples initiated treatment Inclusion criteria: any type of infertility that indicates IVF Exclusion criteria: couples in whom the sperm count was less than 100,000 motile spermatozoa
Interventions	Group A: clomiphene citrate + hMG Group B: GnRHa + hMG (long protocol)

Tummon 1992 (*Continued*)

Outcomes	Pregnancy rate Implantation rate Cancellation rate Mean number of oocytes Mean number of gonadotropins
Notes	17% of couples assigned to Group A dropped out after randomisation and before start of treatment, while 23% of couples in Group B dropped out after randomisation and before start of treatment. Reasons were not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A sequence of randomisation numbers
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not mentioned.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis and the analysis was per cycle. Loss to follow-up and dropout rates were large and reasons were not clearly specified
Selective reporting (reporting bias)	Low risk	Although live-birth rate was not reported, most secondary outcomes were reported
Other bias	Low risk	We found no other potential sources of within-study bias.

Weigert 2002

Methods	RCT
Participants	294 infertile women undergoing IVF-embryo transfer Inclusion criteria: first IVF cycle; women between 20 and 39 years of age; normal ovulatory cycles; tubal infertility, male factor, or unexplained infertility; early stage endometriosis Exclusion criteria: women with chronic medical diseases, contraindication or allergy to the study medications, irregular cycles, low or high BMI (< 20 or > 30 kg/m^2), or baseline FSH level > 15 IU/L.
Interventions	Clomiphene citrate + rFSH + rLH + prednisolone (Group A) versus long GnRH agonist suppression + rFSH (long protocol) (Group B)

Weigert 2002 (*Continued*)

Outcomes	Pregnancy rate, cancellation rate, OHSS rate, fertilisation rate, implantation rate, mean number of gonadotropins, mean number of oocytes
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not mentioned.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not mentioned; not enough information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No intention-to-treat analysis and the analysis was per cycle. No clear mention of loss to follow-up
Selective reporting (reporting bias)	Low risk	Although live-birth rate was not reported, most secondary outcomes were reported
Other bias	Low risk	We found no other potential sources of within-study bias.

Youssef 2011

Methods	RCT
Participants	70 women undergoing IVF treatment Inclusion criteria: women aged 20 to 42 years with a history of 1- or 2-year infertility were included. Poor response was defined by the number of dominant follicles on hCG day and number of mature oocytes < 3 or cycle cancellation due to poor ovarian response
Interventions	Study group (35 women): clomiphene citrate + hMG + midcycle antagonist Control group (35 women): GnRH agonist + hMG (long protocol)
Outcomes	Pregnancy rate Cancellation rate Mean number of oocytes Mean number of gonadotropins
Notes	We have categorised this study as poor responders as mentioned in the abstract after analysing the data and outcomes (e.g. mean oocytes retrieved)

Risk of bias

Youssef 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This is an RCT in which random sequence was computer generated
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes (there was no mention of whether they were opaque or not)
Blinding (performance bias and detection bias) All outcomes	Low risk	Although blinding was not mentioned, we acknowledge that participant blinding is not possible for this type of comparison
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were analysed per woman randomised. No loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	The reported outcomes were similar to those published in the protocol
Other bias	Low risk	We found no other potential sources of within-study bias.

AFC: antral follicle count
AMH: anti-Müllerian hormone
ART: assisted reproductive technology
BMI: body mass index
CC: clomiphene citrate
COH: controlled ovarian stimulation
DHEA: dehydroepiandrosterone
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone
GnRHa: gonadotropin-releasing hormone agonist
hCG: human chorionic gonadotropin
hMG: human menopausal gonadotropin
HSG: hysterosalpingogram
LH: luteinising hormone
ICSI: intracytoplasmic sperm injection
IVF: in vitro fertilisation
MESA-TESE: microsurgical epididymal sperm aspiration-testicular excisional sperm extraction
OHSS: ovarian hyperstimulation syndrome
PCOS: polycystic ovary syndrome
POR: poor ovarian reserve
RCT: randomised controlled trial
rFSH: recombinant follicle-stimulating hormone
rLH: recombinant luteinising hormone
s.c.: subcutaneous

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

Study	Reason for exclusion
Abdalla 1990	A quasi-randomised trial, as participants were randomised into 1 of 2 groups according to the day of their first consultation
Cassidenti 1992	The population was not infertile women but women undergoing ovarian hyperstimulation for the sole purpose of oocytes donation
Dhont 1995	Participants may have had either GIFT or IVF, and it was not possible to separate the outcomes of the 2 forms of assisted reproduction
Engel 2002	Non-randomised trial
Ferraretti 2015	A cohort study
Ferrier 1990	Participants may have had either GIFT or IVF and the results were analysed per cycle, and it was not possible to obtain the results per woman randomised
Fiedler 2001	Inappropriate comparison: both arms compared CC + hMG with and without antagonist
Ghanem 2013	Participants were not undergoing IVF or ICSI.
Goldman 2014	Inappropriate comparison: included IUI versus IVF treatments
Gonen 1990	Unclear whether study had a randomised trial design
Ibrahim 2012	Participants were not undergoing IVF or ICSI.
Imoedemhe 1987	Inappropriate comparison: all 3 groups used CC initially.
Karimzadeh 2011	Control arm inappropriate.
Kim 2000	Unclear whether study had a randomised trial design. We could not contact author due to lack of contact information
Kubik 1990	A quasi-randomised method (alternating method). This study was included in a previous meta-analysis by Hughes 1992, and the author of the meta-analysis obtained information about the randomisation method from the authors of the trial
Legro 2012	Participants were not undergoing IVF or ICSI.
Liu 2016	Did not have fresh embryo transfer
Macnamee 1989	A quasi-randomised trial

(*Continued*)

Martinez 2003	Inappropriate comparison: comparing short versus antagonist protocol
Nagulapally 2012	Inappropriate comparison: study compared clomiphene with gonadotropins versus letrozole with gonadotropins
Nahid 2012	Participants were not undergoing IVF or ICSI.
Nakajo 2011	Inappropriate comparison: study compared clomiphene with gonadotropins versus letrozole with gonadotropins
NCT01577199	Protocol was withdrawn before recruitment.
NCT01577472	Participants were not undergoing IVF or ICSI.
NCT01679574	Participants were not undergoing IVF or ICSI.
NCT01718444	Participants were not undergoing IVF or ICSI.
NCT01791751	Study evaluated use of CC in luteal phase on LH levels.
NCT01856062	Participants were not undergoing IVF or ICSI.
NIH/NICHD Reproductive Medicine Network 2013	Participants were not undergoing IVF or ICSI.
Oktem 2015	Not randomised
Oride 2015	Not randomised
Quigley 1984	Inappropriate comparison: compared CC versus CC with gonadotropins
Reindollar 2011	Not all participants were undergoing IVF or ICSI.
Rose 2015	Not randomised
Roy 2012	Participants were not undergoing IVF or ICSI.
Sharma 2014	Not randomised
Shelton 1991	Non-randomised trial, as allocation was intentionally by 2 clinicians acting independently without randomisation
Siristatidis 2016	Quasi-randomised trial
Wagman 2010	Participants were not undergoing IVF or ICSI.
Ye 2016	Did not have fresh embryo transfer

(*Continued*)

Zhang 2014	Did not have fresh embryo transfer in the minimal-stimulation group

CC: clomiphene citrate
GIFT: gamete intrafallopian transfer
hMG: human menopausal gonadotropin
ICSI: intracytoplasmic sperm injection
IUI: intrauterine insemination
IVF: in vitro fertilisation
LH: luteinising hormone

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

NCT 01921166

Trial name or title	Maximal stimulation and delayed fertilization for diminished ovarian reserve: a randomized pilot study
Methods	Open-label RCT
Participants	Women with a poor prognosis due to diminished ovarian reserve Inclusion criteria: basal FSH 17 IU/mL (highest ever); basal FSH 15 to 17 (highest ever), and failed EFORT test; age > 43 at the time of expected retrieval; failure to conceive with a prior "poor prognosis" IVF stimulation protocol (microdose leuprolide flare or GnRH antagonist cycle) if administered because of evidence of diminished ovarian reserve; failure to conceive with 3 or more IVF cycles at Carolinas Medical Centre (CMC) Exclusion criteria: contraindications to IVF; contraindication to pregnancy; allergy or contraindication to medications used for IVF or embryo transfer; use for a gestational carrier; uncorrected or untreatable uterine infertility; smoking or substance abuse within 3 months of initiating stimulation for IVF
Interventions	Clomiphene plus gonadotropins Leuprolide flare
Outcomes	Number of oocytes retrieved; number of oocytes vitrified; number of embryos from vitrified oocytes per ovarian stimulation treatment protocol
Starting date	January 2011
Contact information	Brad Hurst, Director, Assisted Reproductive Therapies, Carolinas Healthcare System
Notes	The status of the study in the registry is completed. We emailed contact person; authors responded with incomplete data that could not be pooled

NCT 01948804

Trial name or title	The comparison of effect of four different treatment protocols on IVF outcomes in poor responders undergoing in vitro fertilization
Methods	Double-blind RCT
Participants	Poor responders undergoing in vitro fertilisation Inclusion criteria: at least 1 of the following: • anti-Müllerian hormone < 1.1 ng/mL or a previous poor ovarian response (≤ 3 oocytes with a conventional stimulation protocol), or both; • primary infertile patients; • BMI ≤ 30 kg/m^2.
Interventions	GnRH antagonist/letrozole protocol Microdose flare-up protocol Antagonist/clomiphene protocol GnRH antagonist protocol
Outcomes	Clinical pregnancy rates; total number of oocytes retrieved
Starting date	January 2014
Contact information	Pı nar Özcan Cenksoy, Medical Doctor, Yeditepe University Hospital
Notes	We emailed contact person, have as yet received no response.

NCT 02237755

Trial name or title	Clomiphene citrate in combination with gonadotropins for ovarian stimulation in women with poor ovarian response
Methods	Single-blind RCT
Participants	Women with poor response to ovarian stimulation. The definition of poor response was based on the presence of at least 1 of the following criteria: • age > 40 years; • day 2 FSH > 9.5 mIU/mL; • AMH < 2 ng/mL; • at least 1 previous COH with < 3 oocytes retrieved; • at least 1 cancelled attempt due to poor response; • oestradiol less than 500 pg/mL on the day of hCG.
Interventions	Clomiphene citrate: clomiphene citrate (100 mg/day) in combination with gonadotropins according to a short stimulation GnRH antagonists protocol Gonadotropins: short stimulation protocol with gonadotropins and GnRH antagonists All women will be stimulated with a fixed GnRH antagonist protocol. Ovarian stimulation will be initiated with 450 IU of gonadotropins either in the form of a combination of highly purified urinary FSH and LH or with a combination of rFSH and rLH

NCT 02237755 (*Continued*)

Outcomes	Clinical pregnancy
Starting date	October 2014
Contact information	Nikos Vlahos, MD, University of Athens, 2nd Department of Obstetrics and Gynecology, nikosvlahos@med.uoa.gr
Notes	We contacted the author but have received no response.

NCT 02912988

Trial name or title	Letrozole in stimulated IVF cycles (A randomized trial of letrozole as an adjunct to follicle stimulating hormone in stimulated in vitro fertilization cycles)
Methods	RCT
Participants	900
Interventions	Experimental: Letrozole group: letrozole + standard treatment: daily 150 to 300 IU hMG/FSH from cycle day 2 to 4 (at least 5 days after stopping the oral contraceptive pill) and cotreatment with letrozole 2.5 mg daily from stimulation day 5 until the day before hCG administration. GnRH antagonist (cetrorelix (Cetrotide) or ganirelix (Orgalutran)) 0.25 mg daily from stimulation day 5 until the day of hCG administration Control group: Standard treatment: daily 150 to 300 IU hMG/FSH cycle day 2 to 4 (at least 5 days after stopping the oral contraceptive pill) until the day before hCG administration. GnRH antagonist 0.25 mg daily from stimulation day 5 until the day of hCG administration
Outcomes	• Miscarriage rate • Clinical and ongoing pregnancy rates • Ovarian hyperstimulation rate • Total IU of FSH used per cycle • Number of follicles > 12 mm on day of hCG (or the day before) • Number of oocytes obtained • Number of oocytes obtained during the operation of transvaginal ultrasound-guided oocyte retrieval • Oocyte fertilisation rate • Number and quality of embryos obtained • Endometrial thickness on day of hCG (or the day before) • Serum oestradiol level on day of hCG administration (or the day before) • Hormonal profile on day of hCG administration (or the day before): serum oestradiol level • Serum progesterone levels on day of hCG administration (or the day before) • Serum testosterone levels on day of hCG administration (or the day before) • Hormonal profile on day of hCG administration (or the day before): serum testosterone level • Follicular fluid hormonal profile: inhibin B level, testosterone and AMH level • Complications of pregnancy: small for gestational age, low birth weight, preterm delivery, pre-eclampsia, antepartum haemorrhage, congenital anomaly, perinatal mortality, multiple pregnancy
Starting date	November 2016

NCT 02912988 (*Continued*)

Contact information	Ernest HY Ng, MD, nghye@hku.hk
Notes	Multicentre trial: • The University of Hong Kong • University of Southampton • Peking University Third Hospital • Chinese PLA General Hospital

AMH: anti-Müllerian hormone
BMI: body mass index
COH: controlled ovarian stimulation
EFORT: exogenous follicle-stimulating hormone ovarian reserve
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone
hCG: human chorionic gonadotropin
hMG: human menopausal gonadotropin
IVF: in vitro fertilisation
LH: luteinising hormone
RCT: randomised controlled trial
rFSH: recombinant follicle-stimulating hormone
rLH: recombinant luteinising hormone

DATA AND ANALYSES

Comparison 1. Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	4	493	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.66, 1.27]
1.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	4	493	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.66, 1.27]
1.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Ovarian hyperstimulation syndrome	5	1067	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.11, 0.41]
2.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	4	973	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.11, 0.47]
2.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.03, 0.68]
3 Ongoing pregnancy rate	6	758	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.77, 1.30]
3.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	6	758	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.77, 1.30]
3.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

4 Clinical pregnancy rate	12	1998	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.16]
4.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	9	1784	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.88, 1.23]
4.2 Clomiphene citrate± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.72]
4.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	2	134	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.71, 1.94]
5 Cancellation rate	9	1784	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.43, 2.45]
5.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	9	1784	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.43, 2.45]
5.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Mean number of ampoules used	6		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	6		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Letrozole ± gonadotropins ± antagonists vs. antagonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean number of oocytes retrieved	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	8		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Letrozole ± gonadotropins ± antagonists vs agonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

7.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Multiple pregnancy rate	5	791	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.39, 1.43]
8.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	4	697	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.57]
8.2 Clomiphene citrate ± gonadotropins ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Letrozole ± gonadotropins ± antagonist vs. antagonist protocol	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.04, 3.82]
9 Rate of miscarriage	7	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
9.1 Clomiphene citrate ± gonadotropins ± antagonists vs. agonist protocol	6	1022	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.61, 1.75]
9.2 Clomiphene citrate ± gonadotropins ± antagonists vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Letrozole ± gonadotropins ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Letrozole ± gonadotropins ± antagonists vs. antagonists protocol	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.35, 1.66]
10 Rate of ectopic pregnancy	2	223	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.56 [0.47, 120.94]
10.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	2	223	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.56 [0.47, 120.94]
10.2 Clomiphene citrate ± gonadotrophins ± antagonists vs. antagonist protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Letrozole ± gonadotropins ± antagonists vs. agonists protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Letrozole ± gonadotropins ± antagonists vs. antagonist protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Rate of foetal abnormalities	1	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.1 Clomiphene citrate ± gonadotropins ± antagonists vs. GnRHagonists or antagonist protocol	1	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Letrozole ± gonadotropins ± antagonists vs. GnRH agonist or antagonist protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Clomiphene citrate or letrozole with or without gonadotropins in conjunction with or without midcycle antagonist versus gonadotropins (with GnRH agonist or midcycle antagonist) in IVF and ICSI cycles in poor responders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2	357	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.49, 2.79]
1.1 Clomiphene citrate ± gonadotropin ± antagonist vs. agonist protocol	1	304	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.24, 2.32]
1.2 Clomiphene citrate ± gonadotrophin ± antagonists vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Letrozole ± gonadotrophin ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Letrozole ± gonadotropin ± antagonist vs. antagonist protocol	1	53	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [0.55, 12.22]
2 Ongoing pregnancy rate	2	748	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.28]
2.1 Clomiphene citrate ± gonadotropin ± antagonist vs. agonist protocol	1	695	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.52, 1.19]
2.2 Clomiphene citrate ± gonadotrophin ± antagonists vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Letrozole ± gonadotrophin ± antagonists vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Letrozole ± gonadotropin ± antagonists vs. antagonist protocol	1	53	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [0.55, 12.22]
3 Clinical pregnancy rate	8	1462	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.64, 1.12]
3.1 Clomiphene citrate ± gonadotropins ± antagonist vs. agonist protocol	3	1069	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.66, 1.27]
3.2 Clomiphene citrate ± gonadotrophin ± antagonists vs. antagonists protocol	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.05, 12.84]
3.3 Letrozole ± gonadotropin ± antagonists vs. agonists protocol	3	221	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.29, 1.13]
3.4 Letrozole ± gonadotropin ± antagonists vs. antagonists protocol	1	95	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.38, 2.86]
4 Cancellation rate	10	1601	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.18, 1.81]
4.1 Clomiphene citrate ± gonadotropin ± antagonist vs. agonist protocol	4	1155	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.20, 2.10]

4.2 Clomiphene citrate ± gonadotropin ± antagonists vs. antagonists protocol	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.39, 1.53]
4.3 Letrozole ± gonadotropin ± antagonist vs. agonists protocol	3	221	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.10, 3.13]
4.4 Letrozole ± gonadotropin ± antagonists vs. antagonists protocol	2	148	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.67, 2.01]
5 Mean number of ampoules used	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Clomiphene citrate ± gonadotropin ± antagonists vs. agonist protocol	2	87	Mean Difference (IV, Fixed, 95% CI)	-23.98 [-27.41, -20.56]
5.2 Clomiphene citrate ± gonadotrophin ± antagonist vs. antagonist protocol	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Letrozole ± gonadotropin ± antagonist vs. agonist protocol	1	49	Mean Difference (IV, Fixed, 95% CI)	-46.24 [-50.93, -41.55]
5.4 Letrozole ± gonadotrophin ± antagonist vs. antagonist protocol	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Mean number of oocytes retrieved.	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Clomiphene citrate ± gonadotropin ± antagonists vs. agonist protocol	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Clomiphene citrate ± gonadotropin ± antagonist vs. antagonist protocol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Letrozole ± gonadotropin ± antagonists vs. agonist protocol	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Letrozole ± gonadotropin ± antagonists vs. antagonist protocol	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Multiple pregnancy rate	1	304	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.05, 5.75]
7.1 Clomiphene citrate ± gonadotropin ± antagonist vs. agonist protocol	1	304	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.05, 5.75]
7.2 Clomiphene citrate ± gonadotrophin ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Letrozole ± gonadotrophin ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Letrozole ± gonadotrophin ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Rate of miscarriage	3	818	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.45, 2.12]

8.1 Clomiphene citrate ± gonadotropin ± antagonists vs. agonist protocol	2	765	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.55, 3.01]
8.2 Clomiphene citrate ± gonadotrophin ± antagonist vs. antagonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Letrozole ± gonadotrophin ± antagonist vs. agonist protocol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Letrozole ± gonadotropin ± antagonists vs. antagonist protocol	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.73]

ADDITIONAL TABLES

Table 1. Cycle characteristics of the included trials

Study ID	Downregulation used	Type of FSH used	Starting dose of FSH	Dose of clomiphene citrateor letrozole	Cycle monitoring	Luteal support	Timing of hCG
Ashrafi 2005	Buserelin	hMG	150 to 225 IU/day	100 mg CC	Ultrasound	Progesterone	Leading follicle 17 mm
Bastu 2016	Antagonist (cetrorelix subcutaneous)	hMG and recombinant FSH	hMG and recombinant FSH but in different doses: Group 1: 225 IU hMG + 225 IU rFSH Group 2: 150 IU hMG + 150 IU rFSH Group 3: 5mg Ltz + 150 IU rFSH	5 mg Ltz	Ultrasound	Progesterone	Leading follicle > 17 mm
Elnashar 2016	Antagonist (ganirelix (Orgalutran) subcutaneous) for the Ltz group and triptorelin subcutaneous in the agonist control group	FSH	75 IU for the Ltz group versus 150 to 225 IU for the control FSH/agonist group	10 mg Ltz	Not mentioned	Not mentioned	Not mentioned

Table 1. Cycle characteristics of the included trials (*Continued*)

Fenichel 1988	Triptorelin intramuscular	hMG	hMG 125 to 300 IU/day	200 mg CC	Ultrasound and oestradiol	hCG	Leading follicle 17 mm
Fujimoto 2014	Ganirelix	hMG	Not mentioned	100 mg CC	Not mentioned	Not mentioned	Not mentioned
Galal 2012	Not mentioned	hMG	150 to 225 IU	10 mg Ltz	Not mentioned	Not mentioned	Not mentioned
Ghosh Dastidar 2010	Not mentioned	Recombinant FSH	100 to 150 IU in the CC + gonadotropins group; 200 to 225 IU in the gonadotropins + GnRH agonist group)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Grochowski 1999	Triptorelin intramuscular depot	hMG	150 to 225 IU/day	100 mg CC	Ultrasound and oestradiol	Progesterone	Leading follicle 18 mm
Harrison 1994	Triptorelin intramuscular and buserelin intranasal	hMG	150 IU/day	100 mg CC	Ultrasound and oestradiol	Progesterone	Leading follicle 17 mm
Jindal 2013	Antagonist (cetrorelix subcutaneous) for the Ltz or CC group and GnRH agonist for the control group, type not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Jutras 1991	Leuprorelin	hMG	150 IU/day	50 mg CC	Ultrasound and oestradiol	Not mentioned	Leading follicle 15 mm
Karimzadeh 2010	Buserelin	Recombinant FSH	150 to 225 IU/day	100 mg CC	Ultrasound	Progesterone	Leading follicle 18 mm
Kingsland 1992	Buserelin nasal spray	hMG	According to age (225 IU for women <	100 mg CC	Ultrasound and oestradiol	hCG	Leading follicle 17 mm

Table 1. Cycle characteristics of the included trials (*Continued*)

			35 years and 300 IU for women > 35 years)				
Lee 2012	Antagonist (cetrorelix subcutaneous)	hMG	225 IU	2.5 mg Ltz	Ultrasound and oestradiol	Progesterone	Leading follicle 18 mm
Lin 2006	Antagonist (cetrorelix subcutaneous)	hMG	150 to 300 IU/day	100 mg CC	Ultrasound, serum oestradiol, LH, and progesterone	Progesterone	Leading follicle 18 mm
Long 1995	Leuprorelin (Lupron)	hMG	150 IU/day	50 mg CC	Ultrasound and oestradiol	None	Leading follicle 15 mm
Mohsen 2013	Antagonist (cetrorelix subcutaneous) for the Ltz group and agonist (leuprorelin) for the conventional agonist group	hMG	150 IU for the Ltz group versus 300 IU for the control hMG/agonist group	2.5 mg Ltz	Ultrasound and oestradiol	Progesterone	18 mm
Mukherjee 2012	Antagonist (ganirelix (Orgalutran) subcutaneous)	Recombinant FSH	75 IU for the Ltz group versus 150 to 225 IU for the control FSH/antagonist group	5 mg Ltz	Ultrasound and oestradiol	Progesterone	18 mm
Nabati 2016	The type of antagonist used was not mentioned in the study while the agonist used in the control group was buserelin	Recombinant FSH	300 IU for the Ltz group versus 450 IU for the control FSH/agonist group	5 mg Ltz	Ultrasound	Progesterone	17 mm

Table 1. Cycle characteristics of the included trials (*Continued*)

Pilehvari 2016	Antagonist (cetrorelix subcutaneous)	hMG	150 IU for the CC group versus 300 IU for the control hMG/antagonist group	100 mg CC	Ultrasound	Progesterone	17 to 18 mm
Ragni 2012	Buserelin	Recombinant FSH	450 IU	150 mg CC	Ultrasound and oestradiol	Progesterone	18 to 20 mm
Revelli 2014	Antagonist (cetrorelix or ganirelix (Orgalutran) subcutaneous); agonist was leuprorelin	hMG	150 IU for the CC group versus 300 to 450 IU for the control hMG/antagonist group	100 mg CC	Ultrasound and oestradiol	Progesterone	18 to 20 mm
Schimberni 2016	Antagonist (cetrorelix subcutaneous)	Recombinant FSH	450 IU for both groups	100 mg CC	Ultrasound and oestradiol	Progesterone	18 mm
Tummon 1992	Leuprorelin subcutaneous	hMG	According to body weight (less than 52 kg would start with 75 IU/day, 52 to 75 kg would start with 112.5 IU/day, and 150 IU/day for women who weighed more than 75 kg)	100 mg CC	Ultrasound and oestradiol	Progesterone	Leading follicle 16 mm
Weigert 2002	Buserelin	Recombinant FSH	150 IU/day	100 mg	Ultrasound	Progesterone	Leading follicle 18 mm
Youssef 2011	Buserelin	hMG	225 to 300 IU/day	100 mg	Ultrasound	Progesterone	Not mentioned

CC: clomiphene citrate
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone
hCG: human chorionic gonadotropin
hMG: human menopausal gonadotropin
LH: luteinising hormone

Ltz: letrozole
rFSH: recombinant follicle-stimulating hormone

WHAT'S NEW

Last assessed as up-to-date: 10 January 2017.

Date	Event	Description
11 October 2017	New search has been performed	We have included 14 new trials in the update (Bastu 2016; Elnashar 2016; Fujimoto 2014; Galal 2012; Ghosh Dastidar 2010; Jindal 2013; Lee 2012; Mohsen 2013; Mukherjee 2012; Nabati 2016; Pilehvari 2016; Ragni 2012; Revelli 2014; Schimberni 2016). We amended the review title to include other oral ovulation induction medications such as letrozole, and have evaluated interventions in the general in vitro fertilisation population and poor responders separately
11 October 2017	New citation required and conclusions have changed	The scope of this review has been widened, and 14 new studies added

CONTRIBUTIONS OF AUTHORS

For the 2017 update:

MSK: data searching, selection of studies, data extraction, drafting of update, assessment of studies for inclusion, interpretation and analysis of the data, and final editing of the review.

AM: input in selection of studies, and editing the final draft of the review.

SB: overall supervision, input in selection of studies, and editing the final draft of the review.

KYL: data searching, selection of studies, data extraction.

AG: data searching, selection of studies, data extraction, assessment of studies for inclusion, and contributed to final writing of the manuscript.

DECLARATIONS OF INTEREST

MSK: no conflicts of interest to declare.

AM: no conflicts of interest to declare.

SB: no conflicts of interest to declare.

KYL: no conflicts of interest to declare.

AG: no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Reproductive Medicine Unit, Christian Medical College, Vellore, India.

MSK is working in Christian Medical College, Vellore

- University of Aberdeen, UK.

AM and SB are currently working for the University of Aberdeen

- Mansoura University, Egypt.

AG is currently working for Mansoura University

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the title of the review from 'Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization' to 'Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation'.

There has been a change of authors and contact author.

We have widened the scope of the current update by including other oral medications such as aromatase inhibitors for controlled ovarian stimulation. This resulted in the following changes.

- Type of intervention: Clomiphene citrate with or without gonadotropins (original) and aromatase inhibitors with or without gonadotropins (addition in update).

- Type of participants: We added the word 'fresh' IVF. This was done to clearly indicate inclusion of only those women who had oocyte retrieval and embryo transfer in the same cycle and not those women who had all embryos frozen and transferred in subsequent cycles.

- Primary outcomes: We included ovarian hyperstimulation syndrome as a primary outcome (adverse) along with live birth.

- Risk of bias: We considered lack of blinding as low risk for performance and detection bias for the original review. However, with ovarian hyperstimulation syndrome being added as a primary outcome for the general IVF population, we no longer considered lack of blinding as low risk for this domain.

- Measures of treatment effect: We used risk ratio instead of odds ratio for dichotomous outcomes as it is more intuitive and easier to understand. However, we used Peto odds ratio for dichotomous outcomes that were associated with low event rates.

- Data synthesis: In the original protocol, the main comparison group was clomiphene citrate with gonadotropins (with or without gonadotropin-releasing hormone (GnRH) antagonist) versus gonadotropin in GnRH agonist protocol in IVF. However, with

the advent of newer drugs and protocol, we changed this comparison. Also, due to wider use of oral medications in poor responders, we evaluated the general population and poor responders in separate comparisons:

- clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle GnRH antagonist) versus gonadotropins (with GnRH agonist or midcycle antagonist protocols) in IVF and intracytoplasmic sperm injection cycles in the general population;

- clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle GnRH antagonist) versus gonadotropins (with GnRH agonist or midcycle antagonist protocols) in IVF and intracytoplasmic sperm injection cycles in a population of poor responders.

- Effects of interventions: Given the two different comparisons, we also presented the Effects of interventions separately for the general population and poor responders.

- 'Summary of findings' table: Given the two different comparisons, we also presented separate 'Summary of findings' tables for the general population and poor responders.

INDEX TERMS

Medical Subject Headings (MeSH)

Clomiphene [*administration & dosage]; Drug Therapy, Combination [methods]; Fertility Agents, Female [*administration & dosage]; Fertilization in Vitro [*methods]; Gonadotropin-Releasing Hormone [antagonists & inhibitors]; Gonadotropins [*administration & dosage]; Live Birth [epidemiology]; Nitriles [*administration & dosage]; Oocyte Retrieval [statistics & numerical data]; Ovarian Hyperstimulation Syndrome [chemically induced; epidemiology]; Ovulation Induction [*methods]; Pregnancy Rate; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic; Triazoles [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy