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[Intervention Review]

Double versus single intrauterine insemination (IUI) in stimulated cycles for subfertile couples

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ABSTRACT

Background

In subfertile couples, couples who have tried to conceive for at least one year, intrauterine insemination (IUI) with ovarian hyperstimulation (OH) is one of the treatment modalities that can be offered. When IUI is performed a second IUI in the same cycle might add to the chances of conceiving. In a previous update of this review in 2010 it was shown that double IUI increases pregnancy rates when compared to single IUI. Since 2010, different clinical trials have been published with differing conclusions about whether double IUI increases pregnancy rates compared to single IUI.

Objectives

To determine the effectiveness and safety of double intrauterine insemination (IUI) compared to single IUI in stimulated cycles for subfertile couples.

Search methods

We searched the Cochrane Gynaecology and Fertility (CGF) Group trials register, CENTRAL, MEDLINE, Embase and CINAHL in July 2020 and LILACS, Google scholar and Epistemonikos in February 2021, together with reference checking and contact with study authors and experts in the field to identify additional studies.

Selection criteria

We included randomised controlled, parallel trials of double versus single IUIs in stimulated cycles in subfertile couples.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted study authors for additional information.

Main results

We identified in nine studies involving subfertile women. The evidence was of low quality; the main limitations were unclear risk of bias, inconsistent results for some outcomes and imprecision, due to small trials with imprecise results.

We are uncertain whether double IUI improves live birth rate compared to single IUI (odds ratio (OR) 1.15, 95% confidence interval (CI) 0.71 to 1.88; I^2 = 29%; studies = 3, participants = 468; low quality evidence). The evidence suggests that if the chance of live birth following single IUI is 16%, the chance of live birth following double IUI would be between 12% and 27%. Performing a sensitivity analysis restricted to only randomised controlled trials (RCTs) with low risk of selection bias showed similar results.

We are uncertain whether double IUI reduces miscarriage rate compared to single IUI (OR 1.78, 95% CI 0.98 to 3.24; I^2 = 0%; studies = 6, participants = 2363; low quality evidence). The evidence suggests that chance of miscarriage following single IUI is 1.5% and the chance following double IUI would be between 1.5% and 5%.

The reported clinical pregnancy rate per woman randomised may increase with double IUI group (OR 1.51, 95% CI 1.23 to 1.86; I^2 = 34%; studies = 9, participants = 2716; low quality evidence). This result should be interpreted with caution due to the low quality of the evidence and the moderate inconsistency. The evidence suggests that the chance of a pregnancy following single IUI is 14% and the chance following double IUI would be between 16% and 23%.

We are uncertain whether double IUI affects multiple pregnancy rate compared to single IUI (OR 2.04, 95% CI 0.91 to 4.56; I^2 = 8%; studies = 5; participants = 2203; low quality evidence). The evidence suggests that chance of multiple pregnancy following single IUI is 0.7% and the chance following double IUI would be between 0.85% and 3.7%.

We are uncertain whether double IUI has an effect on ectopic pregnancy rate compared to single IUI (OR 1.22, 95% CI 0.35 to 4.28; I^2 = 0%; studies = 4, participants = 1048; low quality evidence). The evidence suggests that the chance of an ectopic pregnancy following single IUI is 0.8% and the chance following double IUI would be between 0.3% and 3.2%.

Authors' conclusions

Our main analysis, of which the evidence is low quality, shows that we are uncertain if double IUI improves live birth and reduces miscarriage compared to single IUI. Our sensitivity analysis restricted to studies of low risk of selection bias for both outcomes is consistent with the main analysis. Clinical pregnancy rate may increase in the double IUI group, but this should be interpreted with caution due to the low quality evidence. We are uncertain whether double IUI has an effect on multiple pregnancy rate and ectopic pregnancy rate compared to single IUI.

PLAIN LANGUAGE SUMMARY

Double versus single intrauterine insemination for subfertile couples

Review question: Cochrane authors reviewed the evidence about the effect of double intrauterine insemination (IUI) versus single IUI in subfertile couples (couples who have tried to conceive for at least one year).

Background: for couples who have tried to conceive for at least one year a common way to induce pregnancy is placement of the sperm directly into the uterus and therefore close to any eggs. This is combined with fertility medicines to stimulate the release of eggs (IUI with ovarian stimulation). The insemination is less stressful, invasive and expensive compared to in vitro fertilisation (where an egg is combined with sperm outside the body) and similar procedures. It is often used when a male partner is subfertile, or when the reason for not becoming pregnant is unknown. Generally, IUI is carried out once in a menstrual cycle, but it is sometimes attempted twice (double IUI). Different clinical trials reached differing conclusions whether double IUI resulted in more pregnancies than single IUI.

Study characteristics: we found nine randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) comparing double IUI with single IUI with 2751 woman. The evidence is current to July 2020.

Key results *:* our main analysis, of which the evidence is rated as low quality, shows that we are uncertain if double IUI improves live birth and reduces miscarriage compared to single IUI. The evidence suggests that if the chance of live birth following single IUI is 16%, then the chance following double IUI would be between 12% and 27%. The evidence suggests that if chance of miscarriage following single IUI is 1.5%, the chance following double IUI would be between 1.5% and 5%. Performing analysis with the highest quality trials showed similar results for both outcomes. Pregnancy rate may increase with double IUI. This result should be interpreted with caution due to low quality of the evidence. The evidence suggests that chance of pregnancy following single IUI is 14% and the chance following double IUI would be between 16% and 23%. However, when we analysed only with the high quality studies, the positive effect of double IUI was lost and we no longer saw the improvement anymore.

We are uncertain whether double IUI reduces multiple- (two or more fetuses) and ectopic pregnancy rate (where a fertilised egg implants itself outside of the womb, usually in one of the tubes connecting the ovary and womb) compared to single IUI. The evidence suggests that if the chance of multiple pregnancy following single IUI is 0.7%, then the chance following double IUI would be between 0.7% and 3.2%. The evidence suggests that if the chance of ectopic pregnancy following single IUI is 0.8% and the chance following double IUI would be between 0.3% and 3.2%.

Quality of the evidence: the evidence was of low quality. The main limitations in the evidence were unclear risk of bias and small trials with imprecise results.

SUMMARY OF FINDINGS

Summary of findings 1. Double intrauterine insemination (IUI) compared to single IUI in stimulated cycles for subfertile couples

Double IUI compared to single IUI in COH cycles for stimulated cycles for subfertile couples

Patient or population: stimulated cycles for subfertile couples

Setting: fertility clinics/hospitals

Intervention: double IUI

Comparison: single IUI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with single IUI in COH cycles	Risk with double IUI				
Live birth rate [a]	162 per 1000	182 per 1000 (121 to 267)	**OR 1.15** (0.71 to 1.88)	468 (3 RCTs)	⊕⊕⊖⊖ **Low** [b,c]	—
Miscarriage rate [a]	15 per 1000	27 per 1000 (15 to 48)	**OR 1.78** (0.98 to 3.24)	2363 (6 RCTs)	⊕⊕⊖⊖ **Low** [b,c]	—
Clinical pregnancy rate [a]	136 per 1000	192 per 1000 (161 to 226)	**OR 1.51** (1.23 to 1.86)	2716 (9 RCTs)	⊕⊕⊖⊖ **Low** [b,d]	—
Multiple pregnancy rate [a]	7 per 1000	15 per 1000 (7 to 32)	**OR 2.04** (0.91 to 4.56)	2203 (5 RCTs)	⊕⊕⊖⊖ **Low** [b,c]	—
Ectopic pregnancy rate [a]	8 per 1000	9 per 1000 (3 to 32)	**OR 1.22** (0.35 to 4.28)	1048 (4 RCTs)	⊕⊕⊖⊖ **Low** [b,c]	—

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

CI: confidence interval; **COH:** controlled ovarian hyperstimulation; **IUI:** intrauterine insemination; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]per woman randomised.
[b]Downgraded once for risk of bias (most domains were at unclear risk of bias).
[c]Downgraded once for imprecision (fewer than 300 events and wide confidence interval).
[d]Downgraded once for indirectness; the effect is seen in one subgroup only (only one study Liu 2006 showed an effect).

BACKGROUND

Description of the condition

Subfertility is the inability to conceive naturally. About 10% of the couples are moderate to seriously subfertile, defined by 12 unsuccessful cycles (Gnoth 2005). Subfertility can be caused by male factor, mild endometriosis, ovulatory dysfunction, cervical factor or be unexplained.

Subfertility is considered unexplained when semen analysis, assessment of ovulation and tubal patency test show no abnormality. Mild male factor infertility is defined as when two or more semen analyses have one or more variables below the 5th percentile (NICE 2013). This is the case is approximately 15% to 30% of the couples (Gelbaya 2014). Intrauterine insemination (IUI) is not routinely offered but can be considered for couples with unexplained infertility, mild endometriosis, mild male factor infertility or female cervical factor (Cohlen 2018; NICE 2013).

Description of the intervention

IUI, with or without ovarian hyperstimulation (OH), is one of the treatment modalities offered most often to subfertile couples because it is less stressful, invasive and expensive than interventions such as in vitro fertilisation (Tjon-Kon-Fat 2017). IUI is a procedure in which a fine catheter is inserted through the cervix into the uterus to deposit the processed sperm directly into the uterus. With double IUI this procedure is performed twice in the same cycle with a certain time-interval to improve the timing of the IUI around ovulation. Ovarian stimulation improves the probability of conception by increasing the number of available oocytes and enhances the accurate timing (Ayeleke 2020; Cohlen 2005). In IUI, motile spermatozoa are directly transferred into the uterine cavity, after sperm preparation and concentration in a small volume of medium. Treatment with OH and IUI for subfertile couples is a more effective treatment for infertility than OH or IUI alone (Ayeleke 2020). This treatment may be considered one of the first treatments for this population (Ayeleke 2020; Goverde 2000).

How the intervention might work

Timing of insemination is one of the most important factors influencing treatment outcome (Cantineau 2014). Increasing the frequency of the IUI may increase the chance that the semen is inseminated at the most optimal moment. The optimal synchronisation method is evaluated in a separate systematic review (Cantineau 2014). There is no consensus in the literature about the number of inseminations per cycle (Ragni 1999a). The previous update of this review in 2010 showed that double IUI increased pregnancy rates when compared to single IUI. Since 2010, further clinical trials have been published with differing conclusions whether double IUI increases pregnancy rates compared to single IUI.

Why it is important to do this review

Compared with a single IUI, a second consecutive IUI adds significantly to the cost and psychological burden, making it important to confirm its beneficial effect before recommending this procedure on a large scale (Ragni 1999a; Ragni 1999b; Tjon-Kon-Fat 2017). It is important to summarise the available results from randomised clinical trials (RCT) on this topic.

OBJECTIVES

To determine the effectiveness and safety of double intrauterine insemination (IUI) compared to single IUI in stimulated cycles for subfertile couples.

METHODS

Criteria for considering studies for this review

Types of studies

We considered RCT for inclusion. We excluded cross-over trials.

Types of participants

Subfertile couples undergoing IUI in stimulated cycles were eligible for inclusion.

Types of interventions

Included studies had to compare double versus single IUI. OH with administration of human chorionic gonadotrophin (hCG) in combination with IUI procedure had to be carried out. The sperm used could be from woman's partner or donor sperm.

Types of outcome measures

Primary outcomes

Effectiveness

- Live birth rate, defined as delivery of a live fetus per woman randomised; achieving a live birth divided by the number of women randomised.

Adverse effects

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

Secondary outcomes

- Clinical pregnancy rate per woman randomised, confirmed by ultrasound, divided by the number of women randomised.
- Multiple pregnancy rate per woman randomised defined as more than one intrauterine pregnancy, confirmed by ultrasound or delivery.
- Ectopic pregnancy rate per woman randomised defined as pregnancy in which a fetus develops outside of the uterus, confirmed by ultrasound.

Search methods for identification of studies

We searched for all published and unpublished RCTs of comparison of double versus single IUIs in infertile couples, without date restriction. We consulted the Cochrane Gynaecology and Fertility Group (CGFG) Information Specialist.

Electronic searches

We searched the following electronic databases:

- CGFG Specialised Register, ProCite platform, searched 15 July 2020 (Appendix 1);

- The Cochrane Central Register of Controlled Trials (CENTRAL) (now containing output from two trials registers and CINAHL), via the Cochrane Register of Studies Online (CRSO), Web platform, searched 15 July 2020 (Appendix 2);
- MEDLINE, Ovid platform, searched from 1946 to 15 July 2020 (Appendix 3);
- Embase, Ovid platform, searched from 1980 to 15 July 2020 (Appendix 4);
- CINAHL, Ebsco platform, searched from 1961 to 4 March 2019 (Appendix 5), more recent CINAHL output was captured in the CENTRAL search 15 July 2020.

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in the *Cochrane Handbook of Systematic Reviews of Interventions* (Section 6.4.11; Higgins 2011). The Embase and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) *(* www.sign.ac.uk/what-we-do/methodology/search-filters/).

Other electronic sources of trials included:

- LILACS and other Spanish and Portuguese regional databases (Latin American and Caribbean Health Science Information database found in the Virtual Health Library Regional Portal (VHL) pesquisa.bvsalud.org/portal/ Web platform, searched on 28 February 2021) (Appendix 6);
- Google Scholar, Web platform, searched on 28 February 2021 (Appendix 7);
- Epistemonikos database; www.epistemonikos.org/, a multilingual database of health evidence, Web platform, searched on 28 February 2021 (Appendix 8).

Searching other resources

We handsearched reference lists of relevant trials and systematic reviews retrieved by the search and contacted experts in the field to obtain additional trials. We have also handsearched relevant journals and conference abstracts that are not covered in the CGFG register, in liaison with the Information Specialist.

Data collection and analysis

Selection of studies

Two review authors (LR and EK) independently conducted an initial screening of titles and abstracts retrieved by the search. We retrieved the full texts of all potentially eligible studies. Two review authors (LR and EK) independently examined these full-text articles for compliance with the inclusion criteria and selected eligible studies. We resolved disagreements by discussion with a third author (AEPC). We documented the selection process with a PRISMA flow chart (Figure 1). We also provided a list of excluded studies (Excluded studies).

Figure 1. Study flow diagram.

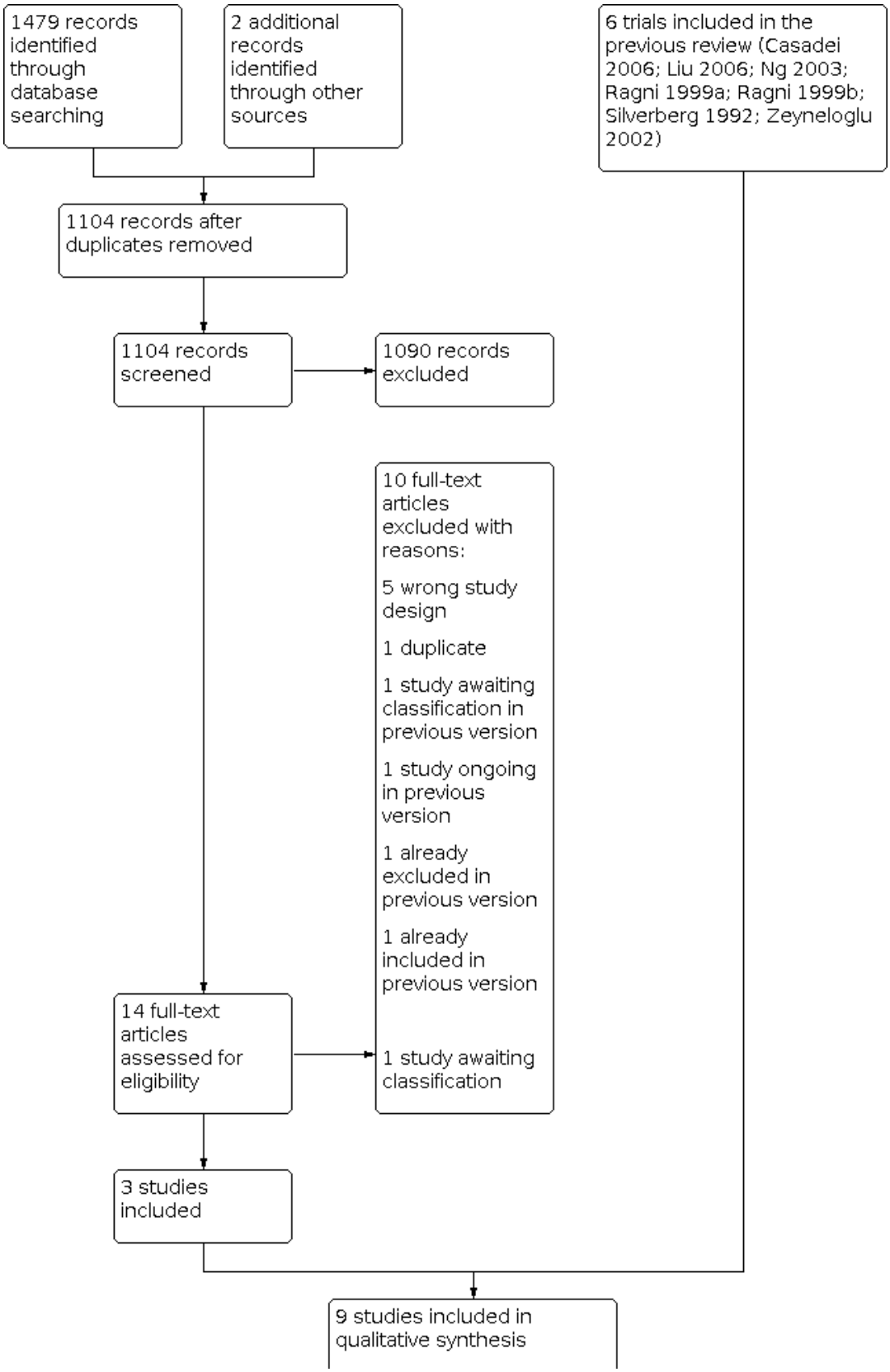
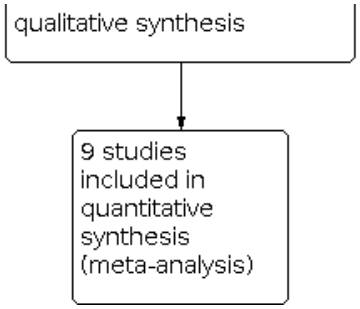


Figure 1. (Continued)



Data extraction and management

Two review authors (LR and EK) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. We resolved disagreements by discussion. Data extracted included study characteristics and outcome data, see Characteristics of included studies table for details. Where studies had multiple publications, we collated multiple reports of the same under a single study ID with multiple references. We corresponded with study investigators for further data on methods or results, or both, as required.

Assessment of risk of bias in included studies

Two review authors (LR and EK) independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool to assess (Higgins 2011): selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting) and other bias. Judgements were assigned as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Section 8.5; Higgins 2011). We resolved disagreements by discussion with a third review author (AEPC). We described all judgements fully and presented the conclusions in the risk of bias table, which was incorporated into the interpretation of the review findings by means of sensitivity analyses (Figure 2; Figure 3).

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

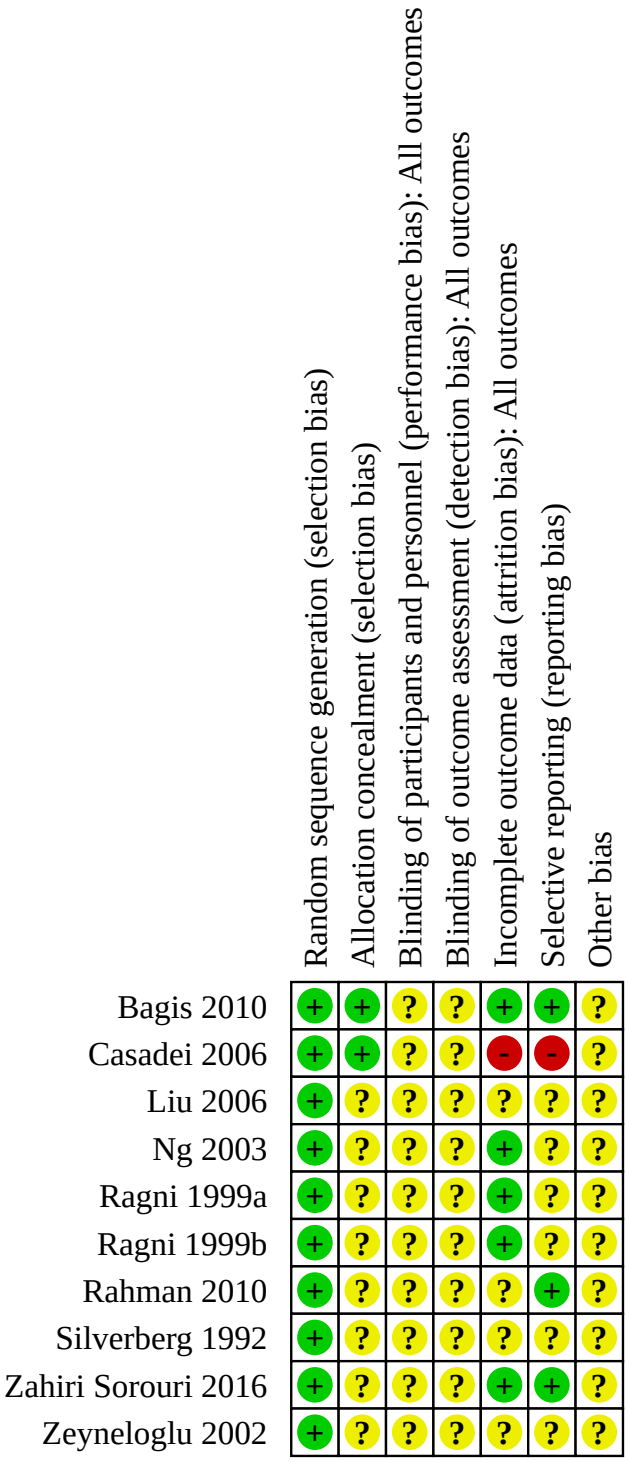
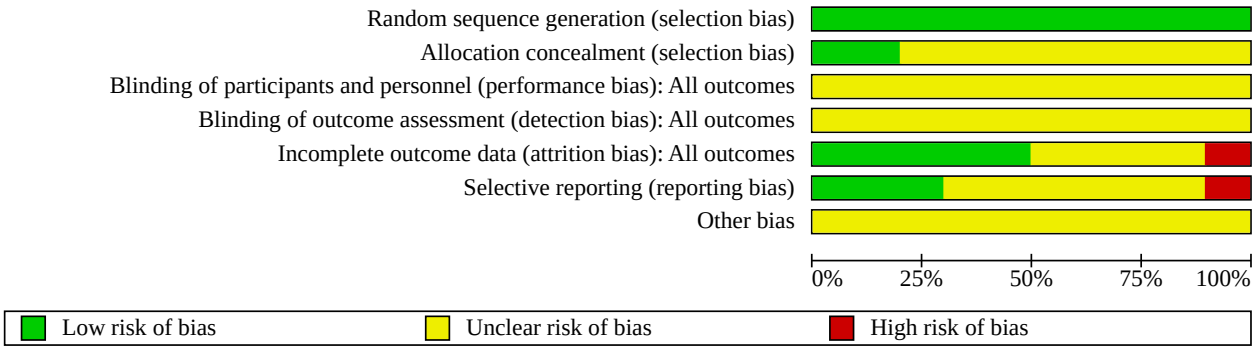


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Measures of treatment effect

All data were dichotomous. We used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). We have presented 95% confidence intervals (CI) for all outcomes. We assessed whether the estimates calculated in the review for individual studies were compatible in each case with the estimates reported in the study publications.

We performed statistical analyses in accordance with the guidelines developed by the the Cochrane Gynaecology and Fertility Group.

Where there were multiple arms in a study with a common placebo, we divided the placebo numbers equally between the arms. If the control group consisted of an uneven number (as was the case with Ragni 1999a) so that the numbers could not be equally divided, we conducted the analysis both ways to detect possible differences in the results caused by unequal division of the numerator and denominator.

When studies had follow-up for more than one cycle, we combined them in a meta-analysis resulting in higher pregnancy rates per women due to more cycles. This was not corrected since that would result in a loss of many cycle data, and cumulative cycle data is more realistic since daily practice is to offer more than one IUI cycle in general.

Unit of analysis issues

The primary analysis was calculated per woman randomised; per pregnancy data were also included for miscarriages and multiple pregnancies. Multiple births were counted as one live birth event.

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible (i.e. including all randomised participants in the analysis, in the groups to which they were randomised). We attempted to obtain missing data from the original trialists. Where these were unobtainable, we undertook imputation of individual values for the primary outcome of live birth only. Live birth was assumed not to have occurred in participants without a reported outcome. For other outcomes, we analysed only the available data.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity using the I^2 statistic. An I^2 statistic measurement greater than 50% was taken to indicate substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. When there were 10 or more studies in an analysis, we would have used a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies). We could not perform the analysis as we had no more than nine studies.

Data synthesis

We used a fixed-effect model to combine the data from the primary studies when they were sufficiently similar. We conducted statistical analysis with Review Manager 5, in accordance with the guidelines for statistical analysis developed by Cochrane (Higgins 2011).

Our comparison was double IUI versus single IUI in ovarian stimulation cycles. Increase in the odds of an outcome were shown in the forest plots of the meta-analysis to the right of the centre line (the point was to ensure consistency across plots).

Subgroup analysis and investigation of heterogeneity

A priori, we had planned to perform separate subgroup analyses for trials comparing double versus single IUI using different timing protocols and trials that used donor insemination. Nevertheless a subgroup in different timing protocols is difficult since all studies have slightly different timing protocols and there is a Cochrane Review on this topic (Cantineau 2014). The background on subgroup analysis on donor sperm is based on the fact that most woman using donor sperm are not subfertile; which is a different group. Since the study, Liu 2006 revealed a significant effect of double insemination with male factor – and not with unexplained

infertility we have performed a post-hoc subgroup analysis on this classification of subfertility.

Sensitivity analysis

We performed a sensitivity analysis on both primary outcomes, live birth and miscarriage, and clinical pregnancy to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if eligibility had been restricted to studies at low risk of bias, defined as studies at low risk of selection bias.

Summary of findings and assessment of the certainty of the evidence

We updated the summary of findings table using GRADEpro GDT and Cochrane methods (GRADEpro GDT 2015; Higgins 2011). The table presents the overall quality of the body of evidence for the main review outcomes (live birth rate, miscarriage rate, clinical pregnancy rate, multiple pregnancy rate and ectopic pregnancy rate) for the review comparison. We evaluated the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias. One review author (LR) made judgements about the evidence quality (high, moderate, low or very low) and a second review author (EK) check them. We resolved disagreements by discussion. The judgements were justified, documented and incorporated into the reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The previous version of this review included six trials (Casadei 2006; Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Silverberg 1992; Zeyneloglu 2002). We listed one trial twice. Ragni 1999a and Ragni 1999b are the same trial but Ragni 1999a performed double IUI after 12 and 34 hours and Ragni 1999b performed double IUI after 34 and 60 hours. To each treatment group, we assigned half of the control single IUI group (34h after hCG) to allow both treatment arms of the study to be included in the meta-analysis. The searches for this update in 2020 resulted in retrieval of 12 full-text papers of which three were eligible for inclusion (Bagis 2010; Rahman 2010; Zahiri Sorouri 2016).

We excluded 19 studies for different reasons (Alborzi 2003; Calderon 2000; Centola 1990; Deary 1997; Gezginç 2008; Ghanem 2011; Karlström 2000; Kemmann 1985; Khalifa 1995; Kovacs 1988; Liu 2005; Malhotra 2007; Matilsky 1998; Peddie 1997; Ransom 1994; Rawal 2003; Ruiz Anguas 2005; Tonguc 2010; Yang 1998; see Characteristics of excluded studies table). In the previous version, there was one ongoing study (Rawal 2003), which we now excluded since there is still no article available. Karlström 2000 was labelled as awaiting assessment in the previous version of the review; we excluded this study since there was still insufficient information available to determine eligibility. See PRISMA flowchart (Figure 1).

One study is awaiting classification (Jindal 2018). This study was published in the ESHRE (European Society of Human Reproduction and Embryology) 2018's conference abstract book but the complete results were not published. We attempted to contact the authors for further information and data to determine its eligibility, but received no reply.

Included studies

Study design and setting

We included nine parallel-designed RCTs in this update. Three studies were new to this update (Bagis 2010; Rahman 2010; Zahiri Sorouri 2016 ; see Characteristics of included studies table). The previous review included Casadei 2006; Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Silverberg 1992; and Zeyneloglu 2002. Most studies were single centre (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Silverberg 1992; Zahiri Sorouri 2016), one was multicentre (Rahman 2010), and one was unclear about this (Zeyneloglu 2002). Studies were set in Turkey (Bagis 2010; Zeyneloglu 2002), Iran (Zahiri Sorouri 2016), India (Rahman 2010), Italy (Casadei 2006; Ragni 1999a; Ragni 1999b), Hong Kong (Ng 2003), the USA (Silverberg 1992), and China (Liu 2006).

Participants

The nine studies included 2751 subfertile couples undergoing IUI with controlled ovarian hyperstimulation. The trials included participants with unexplained subfertility or with male subfertility. Three studies included other types of subfertility (ovulatory dysfunction, endometriosis and cervical factor, tubal factor) (Casadei 2006; Silverberg 1992; Zahiri Sorouri 2016). Zeyneloglu 2002 did not explain the type of infertility. All trials but Zeyneloglu 2002 reported age of female participants and Liu 2006 provided age per type of subfertility instead of per treatment group. The mean age was not different between the groups within the trials. None of the studies reported ages of male partners. Three studies reported mean duration of subfertility, which was comparable (Casadei 2006; Liu 2006; Ng 2003). None of the studies mentioned previous fertility treatment.

Interventions

All studies compared double IUI with single IUI. Casadei 2006 had a third arm that compared single IUI and timed intercourse; this was not used for meta-analysis. We extracted the data of one study under two references, Ragni 1999a and Ragni 1999b. Ragni 1999a performed double IUI 12 and 34 hours after hCG and Ragni 1999b performed double IUI 34 and 60 hours after hCG. To each treatment group, half of the control single IUI group (34h after hCG) was assigned in order to allow both treatment arms of the study to be included in the meta-analysis. This made it possible to detect the results of each treatment group separately, as well as the overall result by pooling them. In Ragni 1999a and Ragni 1999b the analysis used the group of single IUI for both double IUI groups equally. Three studies used gonadotropins (recombinant follicle-stimulating hormone or human menopausal gonadotropin) for OH (Casadei 2006; Ragni 1999a; Ragni 1999b; Silverberg 1992), while other studies used clomiphene citrate (CC) alone (Rahman 2010; Zeyneloglu 2002) or combined with gonadotropins (Bagis 2010; Liu 2006; Ng 2003; Zahiri Sorouri 2016). In all studies, hCG injection followed OH.

Most studies used partners' semen, for some studies it was unclear if the sperm used was from the partner (Bagis 2010; Rahman 2010), although the study by Silverberg 1992 also used cryopreserved donor semen in a small number of cycles. Nine of the total 49 cycles used cryopreserved donor semen, of which four were randomly

assigned to single IUI treatment and five to double IUI treatment. All three pregnancies resulting from the use of cryopreserved sperm occurred in cycles in which two inseminations had been performed.

Four studies used the swim-up technique to prepare the sperm (Bagis 2010; Casadei 2006; Zahiri Sorouri 2016; Zeyneloglu 2002), and five studies used a two-layer density gradient technique (Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Rahman 2010; Zeyneloglu 2002). The injected sperm volume during the insemination was between 0.3 mL and 0.7 mL suspension, although some studies did not mention this (Silverberg 1992; Zeyneloglu 2002). After the insemination, the woman remained supine for 10 to 20 minutes (Bagis 2010; Ng 2003; Rahman 2010; Zahiri Sorouri 2016;); or 30 to 60 minutes (Liu 2006).

The timing of single insemination varied; five studies performed single IUI 36 hours after hCG (Bagis 2010; Casadei 2006; Zahiri Sorouri 2016; Zeyneloglu 2002) and the others 34 hours after hCG (Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Rahman 2010; Silverberg 1992). Two research groups inseminated the first time between 18 and 24 hours after hCG and the second time between 36 and 48 hours after hCG (Liu 2006; Ng 2003). Two others inseminated 18 and 42 hours after hCG (Silverberg 1992; Zeyneloglu 2002). In Casadei 2006, Ragni 1999a, Ragni 1999b, and Rahman 2010, the first insemination was after 12 hours and the second insemination 34 to 36 hours after hCG. Bagis 2010 performed double IUI 18 and 40 hours after hCG.

Outcomes

- Three studies reported the primary outcome of live birth per woman randomised (Bagis 2010; Casadei 2006; Rahman 2010).
- Six studies reported the primary outcome of miscarriage rate per woman randomised (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003; Rahman 2010; Zahiri Sorouri 2016).
- Eight studies reported the secondary outcome of clinical pregnancy rate per woman randomised (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Rahman 2010; Zahiri Sorouri 2016; Zeyneloglu 2002); Silverberg 1992 reported pregnancy per cycle. All studies detected pregnancy with ultrasound.
- Five studies reported the secondary outcome of multiple pregnancy rate per woman randomised (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003; Zahiri Sorouri 2016).
- Four studies reported the secondary outcome of ectopic pregnancy per woman randomised (Bagis 2010; Casadei 2006; Rahman 2010; Zahiri Sorouri 2016).

Excluded studies

In this update, we excluded eight studies with reasons outlined in the Characteristics of excluded studies table (Gezginç 2008; Ghanem 2011; Karlström 2000; Malhotra 2007; Peddie 1997; Rawal 2003; Ruiz Anguas 2005; Tonguc 2010).

Furthermore, one study was excluded as it was included in the previous version (Casadei 2006), and one excluded study was already excluded previously (Alborzi 2003) (Figure 1).

In the previous version of this review 11 studies were excluded (Alborzi 2003; Calderon 2000; Centola 1990; Deary 1997; Kemmann 1985; Khalifa 1995; Kovacs 1988; Liu 2005; Matilsky 1998; Ransom 1994; Yang 1998).

Studies awaiting classification

One study is awaiting classification (Jindal 2018). This study was published in the ESHRE 2018's conference abstract book but the complete results were not published. We attempted to contact the authors for further information and data to determine its eligibility, but received no reply (see Characteristics of studies awaiting classification table).

Ongoing studies

There were no ongoing studies.

Risk of bias in included studies

See Figure 2, Figure 3, and the Characteristics of included studies table.

Allocation

All studies were at low risk of random sequence generation as they used a random number table, computer randomisation, a random number table or block randomisation method. Two studies were at low risk for allocation concealment as they used sealed opaque envelopes (Bagis 2010; Casadei 2006); allocation concealment was unclear in seven studies.

Blinding

None of the studies mentioned the blinding of participants and personnel, so the risk of bias was unclear.

Incomplete outcome data

Four studies analysed all or most (more than 95%) of the woman randomised and had low dropout rates (Bagis 2010; Ng 2003; Ragni 1999a; Ragni 1999b; Zahiri Sorouri 2016). One study was at high risk bias because of high dropout, 64/94 woman dropped out at some point (Casadei 2006). In four studies, the bias was unclear because of insufficient information to mark the bias as low or high (Liu 2006; Rahman 2010; Silverberg 1992; Zeyneloglu 2002).

Selective reporting

Although the studies had no published protocols, reporting bias was low for three studies because the outcomes mentioned in the methods sections were reported in the result sections (Bagis 2010; Rahman 2010; Zahiri Sorouri 2016). Most studies were at unclear risk because of insufficient information to permit judgment of low or high risk (Liu 2006; Ng 2003; Ragni 1999a; Ragni 1999b; Silverberg 1992; Zeyneloglu 2002). Casadei 2006 was at high risk of bias because there were no specific prespecified outcomes mentioned.

Other potential sources of bias

All studies were at unclear risk of other bias. Casadei 2006 and Silverberg 1992 merged different types of infertility. For Rahman 2010, there was a significant fall of sperm count between the two time intervals.

Effects of interventions

See: **Summary of findings 1** Double intrauterine insemination (IUI) compared to single IUI in stimulated cycles for subfertile couples

See Summary of findings 1 for comparison of double versus single IUI in stimulated cycles for subfertile couples. See Analysis 1.1;

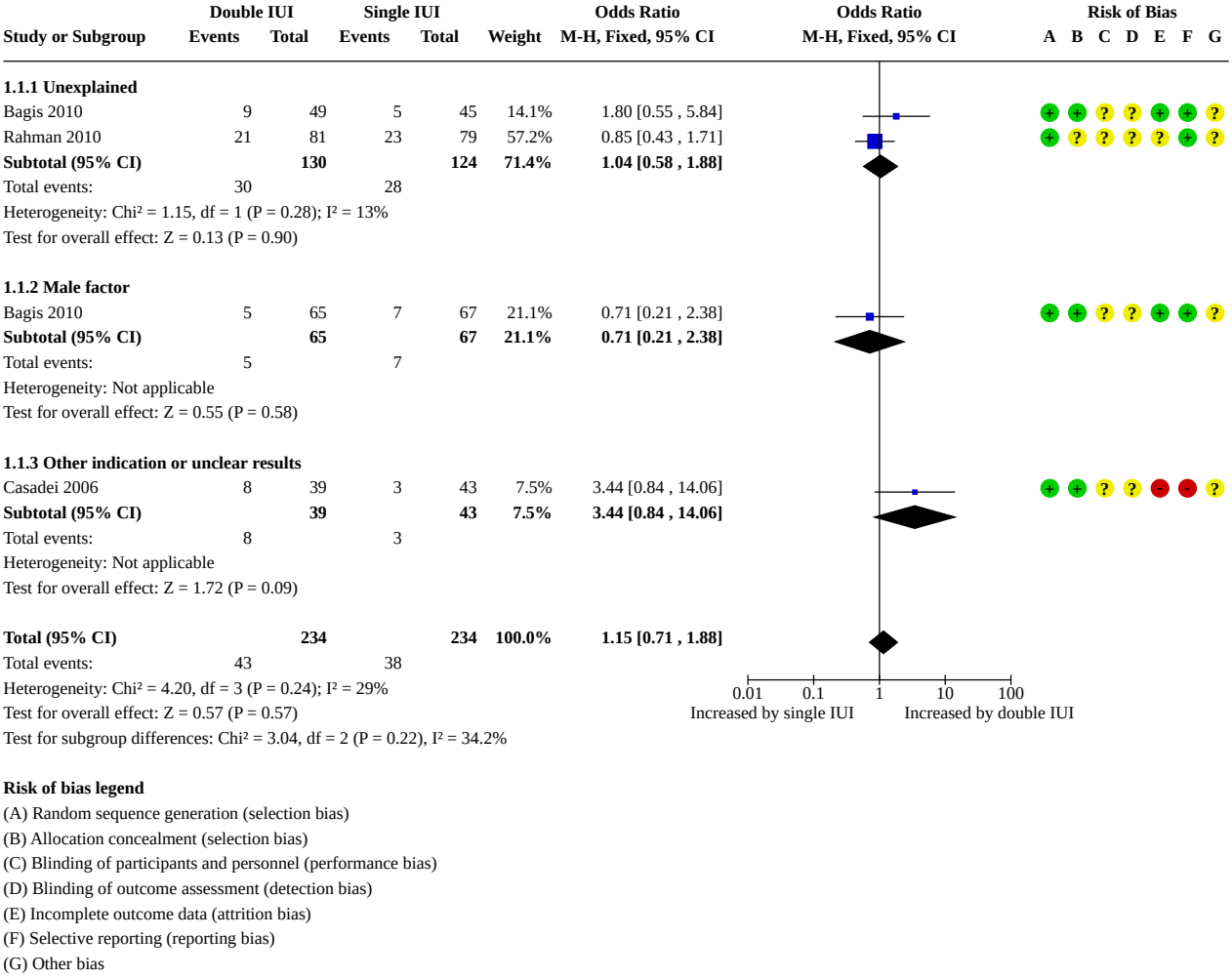
Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; for all individual meta-analysis.

Primary outcomes

1.1 Live birth rate per woman randomised

Three studies including 468 participants reported live birth rate (Bagis 2010; Casadei 2006; Rahman 2010). We are uncertain if double IUI improves live birth rate compared to single IUI (OR 1.15, 95% CI 0.71 to 1.88; I^2 = 29%; studies = 3, participants = 468; low quality evidence; Analysis 1.1; Figure 4). This suggests that if the chance of live birth following single IUI is 16% the chance following double IUI would be between 12% and 27%. Subgroup analysis for live birth based on indications (male factor, unexplained and other indications) did not suggest differences based on indications. We performed a sensitivity analysis restricted to only RCTs with low risk of selection bias, excluding one trial (Rahman 2010). The results of the sensitivity analysis were consistent with the main analysis (OR 1.57, 95% CI 0.78 to 3.14; I^2 = 41%; studies = 2, participants = 308; Analysis 2.1).

Figure 4. Forest plot of comparison: 1 Single intrauterine insemination (IUI) versus double IUI in controlled ovarian hyperstimulation cycles, outcome: 1.1 Live birth per woman randomised.



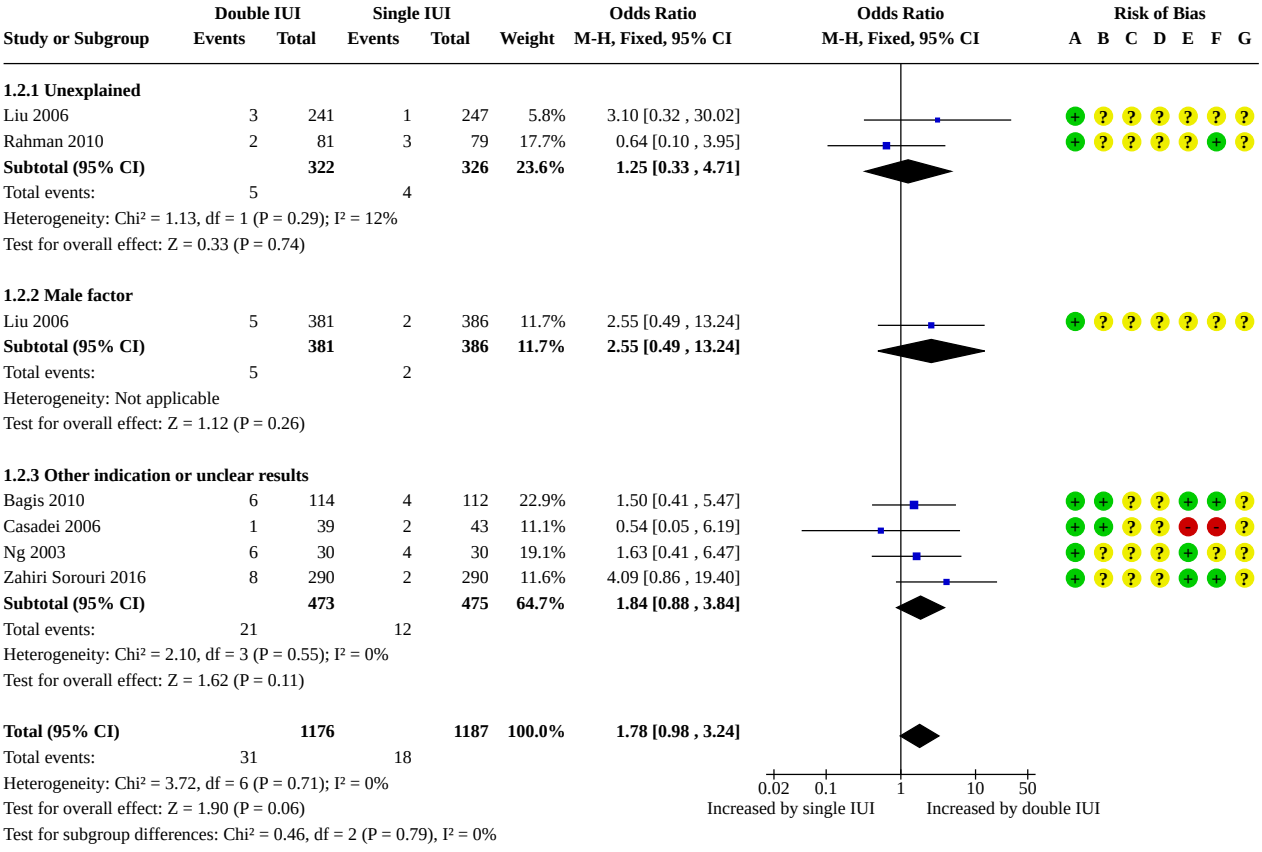
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

1.2 Miscarriage rate per woman

Six studies including 2365 participants reported miscarriage rate per treatment group (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003; Rahman 2010; Zahiri Sorouri 2016). We are uncertain whether double IUI has an effect on miscarriage rate compared to single IUI (OR 1.78, 95% CI 0.98 to 3.24; I^2 = 0%; studies = 6, participants = 2363; low quality evidence; Analysis 1.2; Figure 5). Subgroup analysis for miscarriage based on indications (male factor, unexplained and other indications) did not suggest differences based on indications. The evidence suggests that chance of miscarriage following single IUI is 1.5% and the chance following double IUI would be between 1.5% and 4.8%. This result could have been affected because of more pregnancies in the double IUI group. Therefore, we analysed miscarriage rate per pregnancy. The results were consistent with the miscarriage rate per woman (OR 1.49, 95% CI 0.78 to 2.87; I^2 = 0%; studies = 6, participants = 389; Analysis 2.2). We performed a sensitivity analysis restricted to only RCTs with low risk of selection bias including two trials (Bagis 2010; Casadei 2006). The results were consistent with the main analysis (OR 1.19, 95% CI 0.39 to 3.62; I^2 = 0%; studies = 2, participants = 308; Analysis 2.3). Ragni

1999a and Ragni 1999b reported miscarriages, but for the total trial group instead of per treatment group (rate 2%).

Figure 5. Forest plot of comparison: 1 Single intrauterine insemination (IUI) versus double IUI in controlled ovarian hyperstimulation cycles, outcome: 1.2 Miscarriage rate per woman randomised.



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

1.3 Clinical pregnancy rate per woman randomised

All but one study (Silverberg 1992) reported clinical pregnancy rate per woman, including 2716 participants in the meta-analysis. Pregnancy rate may be increased overall in the double IUI group (OR 1.51, 95% CI 1.23 to 1.86; I^2 = 34%; studies = 9, participants = 2716; low quality evidence; Analysis 1.3). The evidence suggests that if chance of pregnancy following single IUI is 14%, the chance following double IUI would be between 16% and 23%. When performing subgroup analysis based on indications, there was significant difference between subgroups, suggesting a larger effect in the male factor subgroup. Caution is warranted because the pregnancy rate in one study was remarkably high (Liu 2006), and stark subgroup differences between unexplained and mild male factor were difficult to explain. When performing sensitivity analysis restricted to studies with low risk of bias the effect was no longer apparent (OR 1.49, 95% CI 0.81 to 2.75; I^2 = 0%; studies = 2, participants = 308; Analysis 2.4).

1.4 Multiple pregnancy rate per woman randomised

Five studies including 2203 participants reported multiple pregnancy rate per woman in each treatment group (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003; Zahiri Sorouri 2016). We are uncertain whether double IUI has an effect on the rate for multiple pregnancy compared to single IUI (OR 2.04, 95% CI 0.91 to 4.56; I^2 = 8%; studies = 5, participants = 2203; low quality evidence; Analysis 1.4). The evidence suggests that chance of multiple pregnancy following single IUI is 0.7% and the chance following double IUI would be between 0.85% and 3.7%.

Subgroup analysis for multiple pregnancy based on indications (male factor, unexplained and other indications) showed

comparable results. The sensitivity analysis was consistent with the main analysis. The Ragni trial also reported multiple pregnancies, but a rate for the total trial group was given as 4.8%, instead of per treatment group, which makes it impossible to include this study in the meta-analysis (Ragni 1999a; Ragni 1999b).

1.5 Ectopic pregnancy per woman randomised

Four studies including 1048 participants reported ectopic pregnancy rate per woman in each treatment group (Bagis 2010; Casadei 2006; Liu 2006; Ng 2003). We are uncertain whether double IUI has an effect on ectopic pregnancy rate compared to single IUI (OR 1.22, 95% CI 0.35 to 4.28; I^2 = 0%; studies = 4, participants = 1048; low quality evidence; Analysis 1.5). The evidence suggests that chance of ectopic pregnancy following single IUI is 0.8% and the chance following double IUI would be between 0.3% and 3.2%.

Subgroup analysis for ectopic pregnancy based on indications (male factor, unexplained and other indications) showed comparable results.

Sensitivity analysis

We performed sensitivity analyses on the primary outcomes, pregnancy rate per woman randomised and multiple pregnancy. Since there were more pregnancies in the double IUI group, the results could have been distorted when the meta-analysis was per woman randomised, so we performed a sensitivity analysis with miscarriage per pregnancy (OR 1.49, 95% CI 0.78 to 2.87; I^2 = 0%; studies = 6, participants = 389; Analysis 2.2) and multiple pregnancy per pregnancy (OR 1.82, 95% CI 0.77 to 4.26; I^2 = 32%; studies = 5, participants = 339; Analysis 2.5).

DISCUSSION

Summary of main results

In women with subfertility the main analysis shows that we are uncertain whether double IUI results in higher live birth rate and lower miscarriage rate compared to single IUI. Performing a sensitivity analysis restricted to only RCTs with low risk of selection bias showed similar results.

The reported pregnancy rate per woman randomised may improve in the double IUI group. These results should be interpreted with caution since the evidence of effect was determined by one study (Liu 2006). We are uncertain whether double IUI reduces multiple pregnancy rate compared to single IUI. The sensitivity analysis (multiple pregnancy rate per pregnancy) was consistent with this result. We are uncertain whether double IUI reduces ectopic pregnancy when compared to single IUI.

Overall completeness and applicability of evidence

The only outcome that showed a positive effect of double IUI was clinical pregnancy. This result should be interpreted with caution. This effect was seen only in couples with mild male subfertility. It was explained by the authors by the fact that they included only mild male factor subfertility with a total sperm count of 10×10^6 per mL to 20×10^6 per mL (Liu 2006). However, this does not explain the difference that exists between male subfertility and unexplained subfertility, since mild male factor and unexplained subfertility are almost the same entity.

It is remarkable that the pregnancy rates in the male subfertility group were as high as with in vitro fertilisation (De Geyter 2018) which could be difficult to reproduce in future research. Furthermore, the total number of spermatozoa inseminated differed significantly between the male subfertility group and the unexplained subfertility group, with significantly more motile spermatozoa inseminated in the idiopathic subfertility group. In cases of male subfertility, the spermatozoa probably survive for an even shorter time in the female genital tract compared with normal sperm (Cohlen 1998). Although with double insemination a greater total number of spermatozoa are inseminated, the pregnancy rates were not related to sperm concentration in the 2006 study of Liu and co-authors. Altogether, there is no good explanation of why there were more pregnancies in the male subfertility group in the Liu 2006 study.

Although the number of studies for comparison was limited, the evidence appears relevant and answers the review question. In current practice, there is no consensus about this matter. Considering the financial burden of double IUI and the uncertainty about the effect of this intervention, the findings of the review do not support the routine use of double IUI in clinical practice. The American Society for Reproductive Medicine (ASRM) guideline on treatments for unexplained infertility recommends that single IUI should be performed (ASRM 2020).

Quality of the evidence

The overall quality of evidence was low due to unclear risk of bias and imprecision. Multiple studies did not report methods for allocation concealment and most studies were marked as unclear in most risk of bias domains. The studies included different causes of infertility, the timing of insemination was different and they used different regimens for ovulation induction. Number of events was also low, which makes it imprecise. In addition, we downgraded clinical pregnancy for indirectness due to the positive effect seen in only one study. The strengths of this review include the adequate randomisation of the studies, the subgroup and sensitivity analysis. One limitation was that only three studies reported one of the main outcomes, live birth. A second limitation is that due to small sample sizes, the quality of evidence was low and we therefore could not justify drawing conclusions about the effects of intervention.

Potential biases in the review process

The authors of this systematic review conducted a rigorous search of the evidence. The evidence included published and unpublished data and there was no restriction by language.

Agreements and disagreements with other studies or reviews

Our meta-analysis showed that we are uncertain about the effect of double IUI on live birth and miscarriage rate. Pregnancy rate may be increased overall in the double IUI group, but when performing subgroup analysis this was due to male factor infertility as for the other subgroup the effect was not evident. These results should be interpreted with caution since the effect of the interventions determined by one study (Liu 2006). Zavos 2013, a systematic review that compared double and single IUI in couples with male factor infertility, also found significant benefit in pregnancy rate in the double IUI group, this was also due one study (Liu 2006).

Another review, with subgroups with normal semen and mild male infertility, the outcomes were comparable (Arab-Zozani 2017). For clinical pregnancy, Arab-Zozani 2017 found no statistical difference overall, where in subgroups, there was a difference for mild male infertility. One reason for this is that the reviews included different studies, Arab-Zozani 2017 included also cross-over design, quasi-randomised studies and studies with only unpublished data. For live birth, miscarriage and ectopic pregnancy, there were no differences between groups.

Another review that analysed couples with unexplained infertility found no difference between single and double IUI (Polyzos 2010).

Another review concluded that OH with CC resulted in significantly higher pregnancy rates in double compared with single insemination (Osuna 2004). This was not seen with gonadotropin-stimulated cycles in the same review. One reason for this difference could be a reduced number of available oocytes at the moment of insemination when using CC, in which case two inseminations would be beneficial. In our review, one study stimulating ovulation with CC alone found no significantly better effect for double insemination (Zeyneloglu 2002).

More aggressive ovarian stimulation leads to more dominant follicles, which influences treatment outcomes, with higher pregnancy rates, and more adverse effects such as multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Studies that demonstrated a significant effect of double insemination (Liu 2006; Ragni 1999a; Silverberg 1992) reported a mean of three dominant follicles larger than 15 mm compared with a mean of 1.7 dominant follicles in the studies that did not report a significant difference between single and double insemination (Casadei 2006; Ng 2003; Ragni 1999b; Zeyneloglu 2002). Only Silverberg and co-authors reported a significantly higher mean number of follicles (larger than 16 mm) in the group receiving double insemination.

It may be concluded that double insemination may be effective only when more dominant follicles are available and which rupture at different intervals after administering hCG.

The timing of single and double inseminations was slightly different in each included study. The optimal timing of IUI has been discussed extensively, and one review found no difference in method used (Cantineau 2014). Regarding actual timing of insemination after hCG administration, randomised trials found no significant differences between various time frames that range from 24 hours to 48 hours (Cohlen 2018).

Finally, there were different techniques for semen preparation, swim-up or gradient techniques, which have similar pregnancy rate results (Boomsma 2019). One study by Hornstein 1992 reported significant decreases in semen volume, sperm concentration and sperm motility in semen samples obtained on the second day of consecutive-day inseminations. Sperm-washing procedures cannot overcome this natural reduction in semen quality produced by frequent ejaculation. Conclusively, a second insemination in the same cycle may not be as effective as the first. Apart from this, fertilisation with sperm of compromised quality, used in cases of male subfertility, can result in clinical pregnancy but could possibly result in a higher rate of miscarriage and eventually a lower rate of live birth than expected on the grounds of clinical pregnancy rates. Unfortunately, there are no current data in the literature to confirm this hypothesis.

AUTHORS' CONCLUSIONS

Implications for practice

Our main analysis with low quality of evidence shows that we are uncertain if double intrauterine insemination (IUI) increases live birth and reduces miscarriage compared to single IUI. Our sensitivity analysis restricted to studies with low risk of bias for both outcomes is consistent with the main analysis. Clinical pregnancy rate may increase in the double IUI group but this should be interpreted with caution due to the low quality evidence. We are uncertain if double IUI has an effect on multiple pregnancy rate and ectopic pregnancy rate compared to single IUI.

Implications for research

There are several good quality fertility trials that have been published since the late 2000s. Some older trials lack good methodology, partially as a result of small treatment groups, difficulties with blinding because insemination is an invasive procedure, different clinical protocols, and failure to express pregnancy outcomes or live births per couple. Adherence to the CONSORT guidelines results in massive improvement (Schulz 2010).

Research in the fertility field is also difficult because of the many possible confounding factors that introduce differences between studies and treatment groups. Important factors such as inclusion criteria, exclusion criteria, type of subfertility, duration of subfertility and previous fertility treatment, which influence the chance of becoming pregnant, are often not mentioned in trial reports.

Appropriate outcome measures also need to be used in trials. Live birth should be the most important outcome because this represents the final goal of treatment. Apart from this, miscarriage rate and ectopic pregnancy rate should be reported to detect the effect caused by sperm of compromised quality. The cost-effectiveness of double IUI and psychological burden remains a matter for debate, which should be an important element in future randomised trials.

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CHARACTERISTICS OF STUDIES

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

Bagis 2010

Study characteristics	
Methods	Single centre
	Trial design: parallel
	Allocation: random numbers table
	Concealment: consecutively numbered opaque, sealed envelopes
	Blinding: not stated
	Follow-up: 1 cycle

Bagis 2010 *(Continued)*

	Power calculation: yes Intention to treat analysis: no Country: Turkey
Participants	228 women Single IUI: 112 participants; 36 hours after hCG administration; double IUI: 114 participants; 18 and 40 hours after hCG Women's age: single IUI: mean 29.57 (SD 4.27) years; double IUI: mean 29.03 (SD 4.55) years Inclusion criteria: couple had not conceived after ≥ 1 year of unprotected intercourse; women aged < 37 years, with basal FSH levels 12 mIU/L and total antral follicle count on day 3 of the menstrual cycle > 6; and a diagnosis of unexplained (normal sperm parameters, normal tubal patency and confirmed ovulation) or mild male factor infertility (presence of oligospermia or asthenospermia or both but with total progressive motile sperm count ≥ 10 million was regarded as mild male factor infertility) Exclusion criteria: OH cycles with > 5 dominant follicles (15 mm in diameter) Type of subfertility: unexplained and mild male factor infertility Previous fertility treatment: not stated Primary or secondary infertility: not stated
Interventions	Method of COH: CC or rFSH preparations – follitropin alpha or follitropin beta or both (CC and rFSH) were used for OH. CC started on days 3–5 of cycle at 100 mg/day for 5 days. In some participants, rFSH 75 IU was added to the CC on the fourth day of the regimen. In women in the rFSH group, the starting dose, administered subcutaneously, was 50–150 IU/day according to bodyweight and antral follicle count, and was begun on CD3 of menstruation and continued until follicle maturation. The serial E2, LH and progesterone measurements were performed in all cycles to rule out premature luteinisation. Only the cycles with multifollicular development without premature luteinisation were included in the study Sperm preparation: sperm washing carried out using the gradient method Insemination procedure: with a 1- or 2-mL sterile syringe. Volumes were 0.6 mL in all cycles. The women remained supine for 10–15 minutes after IUI Number of cycles: 1 Method of pregnancy detection: not stated
Outcomes	Primary outcome: LBR compared in single and double IUI groups Secondary outcomes: LBR in subgroups (unexplained infertility, mild male factor, follicle number and duration of infertility) Pregnancy defined as vital pregnancy or a visible pregnancy Miscarriage defined as non-vital pregnancy or loss of a previously visible pregnancy Multiple pregnancy Ectopic pregnancy
Notes	Multifollicular development without premature luteinisation (progesterone levels 0.1 ng/mL on the day of hCG) were included in the study. Trial registration number: ClinicalTrials.gov: NCT00993902.
Risk of bias	

Bagis 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	Consecutively numbered opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants in the single IUI group were excluded from the analysis due to dropout. This small number was not expected to have an impact on the overall outcome.
Selective reporting (reporting bias)	Low risk	Non-statistically significant results were reported, which suggests that no selective reporting occurred.
Other bias	Unclear risk	Insufficient information to assess whether an important bias exists.

Casadei 2006

Study characteristics	
Methods	Single centre Trial design: parallel Allocation: computer-generated random numbers Concealment: sealed masked envelopes Blinding: none Follow-up: until 7 weeks of gestation Power calculation: yes Intention to treat analysis: no, but possible to perform when dropouts per group were known Country: Italy
Participants	94 women; 138 cycles Single IUI: 43 couples, 48 cycles; double IUI: 39 couples, 43 cycles; single IUI + timed intercourse: 38 couples, 47 cycles Women's age: single IUI: mean 34.9 (SD 4.2) years; double IUI: mean 34.7 (SD 4.0) years; single IUI + timed intercourse: mean 35.5 (SD 4.3) years Inclusion criteria: ≥ 1 year of subfertility; male factor, ≥2 criteria of the following: sperm analysis with 10–20 × 10^6 sperm/mL, 15–25% progressive motility or < 20 million progressively motile spermatozoa

Casadei 2006 *(Continued)*

	in the ejaculate (or both), 30–50% normal morphology; unilateral tubal factor: evidence of ≥ 1 patent fallopian tube; PCOS: oligomenorrhoea-amenorrhoea combined with 3 criteria (polycystic appearance of ovaries; obesity; hirsutism; elevated LH, fasting insulin, fasting glucose levels); endometriosis: minimal or mild endometriosis diagnosed visually Unexplained infertility: no evidence of fertility disorder found by standard fertility evaluation Previous fertility treatment: not stated Primary or secondary infertility: not stated
Interventions	rFSH 75 IU for 6 days from CD2 For tubal factor: initial dose of 150 IU used for 5 days; dose reduced to 75 IU when a dominant follicle of 14 mm seen For PCOS: initial dose 37.5–75 IU/day; hCG 5000 IU; 36 hours after hCG, single IUI and timed intercourse on day of hCG; 36 hours after hCG; single IUI 12 and 36 hours after hCG Sperm preparation: husband's semen with swim-up technique Insemination procedure: 0.3–0.5 mL suspension slowly injected using a Frydman catheter Number of cycles: maximum of 3 Third group with single IUI + timed intercourse
Outcomes	Pregnancy rates per cycle and per couple Live birth (calculated by subtracting miscarriage from pregnancy) Miscarriage Multiple pregnancy Clinical pregnancy (diagnosed 5 weeks after IUI by the presence of a gestational sac and by evidence of fetal heart activity
Notes	Total number of participants in table 2 was not comparable with the rest of the data. 3 treatment modalities. From 94 included participants, 64 withdrew at some point. It is not stated in which group the participants were randomised, and not all the reasons for withdrawal were known. Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Numbers masked in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.

Casadei 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	From 94 included participants, 44 withdrew after the first cycle and 20 withdrew after the second cycle. It is not stated in which group the participants were randomised, and not all the reasons for withdrawal were known.
Selective reporting (reporting bias)	High risk	There were no specific prespecified outcomes mentioned. There was a high dropout rate, this is not calculated into the outcomes.
Other bias	Unclear risk	Included different types of infertility.

Liu 2006

Study characteristics	
Methods	Single centre Trial design: parallel Allocation: random number table Concealment: not stated Blinding: none Follow-up: 1 cycle Power calculation: no Intention to treat analysis: no Country: China
Participants	1270 women recruited; 1257 cycles completed Single IUI: 633 couples; double IUI: 624 couples; same number of cycles Women's age: mean 32.1 (SD 3.3) years for male factor; mean 34.9 (SD 3.5) years for unexplained subfertility; not reported per treatment group Inclusion criteria: ≥ 24 months of infertility; male factor diagnosed when ≥ 2 semen analyses were subnormal according to WHO guidelines; idiopathic infertility defined as couples with normal results and complete fertility workup Exclusion criteria: women with anovulation, oligo-ovulation, tubal disease, endometriosis, cervical factor, PCOS Duration of subfertility: mean 3.4 (SD 2.7) years for male factor; mean 4.9 (SD 5.2) years for idiopathic subfertility Previous fertility treatment: none Primary subfertility: not stated
Interventions	Starting with or without 50 mg CC/day from CD3 for 5 days hMG 75–150 IU given on days 5, 7 and 9 hCG 10,000 IU

Liu 2006 *(Continued)*

	Single IUI: 34 hours after hCG; double IUI: 18–24 hours and 36–48 hours after hCG Sperm preparation: husband's semen by Percoll density gradient Insemination procedure: slow injection of 0.5 mL prepared semen Number of cycles: unclear
Outcomes	Pregnancy rates per couple and per cycle (confirmed by the detection of fetal heart beats by transvaginal ultrasonography examination at 6 weeks of gestation age) Miscarriage rate Multiple pregnancy rate Number of OHSS
Notes	Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were separately randomised into single or double IUI group using a random number table.
Allocation concealment (selection bias)	Unclear risk	Not clearly stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Stated there were 13 dropouts because of "various" reasons (considered vague). Furthermore, the percentage of dropouts was quite low for this type of study (< 1%). Insufficient information from the study to mark this as low risk of bias.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Insufficient information to assess whether an important bias exists.

Ng 2003

Study characteristics

Methods	Single centre Trial design: parallel Allocation: computer-generated randomisation list Concealment: not stated

Ng 2003 *(Continued)*

	Blinding: none Follow-up: 3 cycles Power calculation: yes Intention to treat analysis: no Country: Hong Kong
Participants	90 women, 204 cycles Single IUI: 30 women, 68 cycles; double IUI: 30 women, 76 cycles; fallopian tube sperm perfusion: 30 women, 59 cycles Women's age: single IUI: mean 32.7 (SD 2.4) years; double IUI: mean 32.9 (SD 2.7) years Inclusion criteria: women's age < 40 years, duration of subfertility > 2 years; regular ovulatory cycles with MLP > 30 mmol/L; bilateral tubal patency and absence of peritubal adhesions; total number of motile spermatozoa during work-up > 10 million Exclusion criteria: previous artificial insemination cycles, total number of motile spermatozoa < 10 million Duration of subfertility: single IUI: mean 4.4 (SD 1.7) years; 2 IUI: mean 4.2 (SD 2.1) years Previous fertility treatment: none Primary or secondary infertility: not stated
Interventions	Starting with or without CC 50 mg/day from CD3 for 5 days hMG 75–150 IU given on days 5, 7 and 9 hCG 10,000 IU Single IUI: 34 hours after hCG; double IUI: 18–24 hours and 36–48 hours after hCG Sperm preparation: husband's semen with percoll density gradient Insemination procedure: slow injection of 0.5 mL prepared semen Number of cycles: unclear hMG 150 IU from CD3; dosage titrated later according to ovarian response hCG 10,000 IU Single IUI: 38 hours after hCG; double IUI: 18 and 38 hours after hCG Sperm preparation: husband's semen by density gradient centrifugation IUI procedure: 0.3–0.5 mL with Tomcat catheter Number of cycles: maximum 3
Outcomes	Clinical pregnancy rates per couple, per cycle Number of miscarriages (abortions) Number of multiple pregnancies Pregnancy defined as presence of intrauterine gestational sac
Notes	Trial registration number: not available.

Ng 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Not clearly stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not suspected. All randomised participants analysed/no missing data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important bias exists.

Ragni 1999a

Study characteristics	
Methods	Single centre Trial design: parallel Allocation: computerised randomisation Concealment: unclear Blinding: not stated Follow-up: not stated Power calculation: yes Intention to treat analysis: no Country: Italy
Participants	Overall: 273 women, 449 cycles Single IUI: 90 participants, 156 cycles; double IUI: 92 participants, 144 cycles Women's age: single IUI: mean 32.0 (SD 3.4) years; double IUI: mean 32.5 (SD 3.0) years Inclusion criteria: male infertility with ≥ 2 abnormal semen analyses; unexplained infertility with normal semen analysis, normal PRL level, progesterone level > 10 ng/mL, PCT not performed; normal HSG, hysteroscopy and laparoscopy; at least 3 years of infertility

Ragni 1999a *(Continued)*

	Exclusion criteria: women aged > 38 years, ovarian cysts, PCO, BMI > 25, > 6 follicles > 18 mm on day of ovulation trigger Type of subfertility: male factor, unexplained Duration of subfertility: ≥ 3 years Previous fertility treatment: not stated Primary or secondary infertility: not stated
Interventions	hMG 150 IU from CD3; dosage titrated later according to ovarian response hCG 10,000 IU Single IUI: 38 hours after hCG; double IUI: 18 and 38 hours after hCG Sperm preparation: husband's semen by density gradient centrifugation IUI procedure: 0.3–0.5 mL with Tomcat catheter Number of cycles: maximum 3 CC for 5 days, FSH, hCG 5000 IU Single IUI: 12 hours after hCG; double IUI: 12 and 34 hours after hCG Sperm preparation: husband's semen used; medium gradient techniques Insemination procedure: slow injection 0.5 mL prepared semen into uterine cavity with Kremer De La Fontaine catheter 1 or 2 inseminations Number of cycles: maximum 2
Outcomes	LBR per couple: not stated Clinical pregnancy rate per couple: single IUI: 14.4%; double IUI: 30.4% Pregnancy rate per cycle: single IUI: 8.3%; double IUI: 19.3% Multiple pregnancies: total 13 OHSS per woman: 0% Miscarriage: total 9 (17.9%) Ectopic pregnancies: total 3 (5.9%) Costs: not stated Clinical pregnancy: confirmed by evidence of fetal heart activity on ultrasound examination
Notes	3 treatment modalities: Ragni 1999a performed double IUI after 12 and 34 hours and Ragni 1999b performed double IUI after 34 and 60 hours. To each treatment group, half of the control single IUI group (34 hours after HCG) was assigned in order to allow both treatment arms of the study to be included in the meta-analysis. This made it possible to detect the results of each treatment group separately, as well as the overall result by pooling them. Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement

Ragni 1999a *(Continued)*

Random sequence generation (selection bias)	Low risk	Computerised randomisation.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; the number of participants used for the outcomes were the same as the included participants.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important bias existed.

Ragni 1999b

Study characteristics	
Methods	Single centre Trial design: parallel Allocation: computerised randomisation Concealment: unclear Blinding not stated Follow-up: not stated Power calculation: yes Intention to treat analysis: no Country: Italy
Participants	Overall: 273 women, 449 cycles Single IUI: 45 participants, 34 hours after hCG; double IUI: 91 participants 34 and 60 hours after hCG Women's age: single IUI: mean 32.0 (SD 3.4) years; double IUI: mean 32.5 (SD 3.0) years Inclusion criteria: male infertility with ≥ 2 abnormal semen analyses; unexplained infertility with normal semen analysis, normal PRL level, progesterone level > 10 ng/mL, PCT not performed; normal HSG, hysteroscopy and laparoscopy; at least 3 years of infertility Exclusion criteria: women aged > 38 years, ovarian cysts, PCO, BMI > 25, > 6 follicles > 18 mm on day of ovulation trigger

Ragni 1999b *(Continued)*

	Type of subfertility: male factor, unexplained
	Duration of subfertility: ≥ 3 years
	Previous fertility treatment: not stated
	Primary or secondary infertility: not stated
Interventions	hMG 150 IU from CD3; dosage titrated later according to ovarian response
	hCG 10,000 IU
	Single IUI: 45 participants, 34 hours after HCG; double IUI: 91 participants 34 and 60 hours after hCG
	Sperm preparation: husband's semen by density gradient centrifugation
	IUI procedure: 0.3–0.5 mL with Tomcat catheter
	Number of cycles: maximum 3
	CC for 5 days, FSH, hCG 5000 IU
	Single IUI: 12 hours after hCG; double IUI: 12 and 34 hours after hCG
	Sperm preparation: husband's semen used; medium gradient techniques
	Insemination procedure: slow injection 0.5 mL prepared semen into uterine cavity with Kremer De La Fontaine catheter
	One or two inseminations
	Number of cycles: maximum 2
Outcomes	LBR per couple: not stated
	Clinical pregnancy rate per couple: single IUI: 14.4%; double IUI: 30.4%
	Pregnancy rate per cycle: single IUI: 8.3%; double IUI: 19.3%
	Multiple pregnancies: total 13
	OHSS per woman: 0%
	Miscarriage: total 9 (17.9%)
	Ectopic pregnancies: total 3 (5.9%)
	Costs: not stated
	Clinical pregnancy: confirmed by evidence of fetal heart activity on ultrasound examination
Notes	3 treatment modalities: Ragni 1999a performed double IUI after 12 and 34 hours and Ragni 1999b performed double IUI after 34 and 60 hours. To each treatment group, half of the control single IUI group (34 hours after HCG) was assigned in order to allow both treatment arms of the study to be included in the meta-analysis. This made it possible to detect the results of each treatment group separately, as well as the overall result by pooling them.
	Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement

Ragni 1999b *(Continued)*

Random sequence generation (selection bias)	Low risk	Computerised randomisation.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; all randomised women were analysed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important bias exists.

Rahman 2010

Study characteristics	
Methods	Multicentre Trial design: parallel Allocation: computer-generated randomisation list Concealment: not stated Blinding: none Follow-up: maximum 4 cycles Power calculation: yes Intention to treat analysis: no Country: India
Participants	160 women Single IUI: 79 women, 195 cycles; double IUI: 81 women, 204 cycles Women's age: single IUI: mean 28.3 (SD 3.3) years; double IUI: mean 27.2 (SD 3.5) years Inclusion criteria: unexplained infertility (means: husband semen analysis according to WHO criteria, early follicular phase hormonal assay (FSH, LH, TSH, PRL), HSG, and diagnostic laparoscopy and hysteroscopy were normal) Exclusion criteria: women with PCOS, anovulatory infertility, tubal factor infertility, or mild/minimal endometriosis and men with sperm count < 20 million/mL

Rahman 2010 *(Continued)*

	Type of subfertility: unexplained Previous fertility treatment: not stated Primary or secondary infertility: not stated
Interventions	Method of COH: CC 50 mg; when no response, maximum 150 mg/day Follicle growth monitored by serial transvaginal sonography beginning day 10, until a dominant follicle of R18 mm was attained, when injection of hCG 5000 U given intramuscularly Number of inseminations: single IUI: 34 hours after hCG injection; double IUI: 12 and 34 hours after hCG injection Semen preparation: density centrifugation method Insemination procedure: with flexible intrauterine catheter introduced to the cervix after using all the aseptic precautions. Rest 20 minutes Number of cycles: maximum 4 Method of pregnancy detection: β-hCG was measured if a participant missed menstruation 16–18 days after IUI Clinical pregnancy through fetal heart activity at 6-week ultrasound
Outcomes	Live birth (delivery rate) Pregnancy rates between single IUI and double IUI group; pregnancy confirmed at 6-week ultrasound, clinical pregnancy defined as the presence of fetal heart activity Miscarriage Ectopic pregnancy
Notes	There was a significant fall (P < 0.005) in sperm count between the 12th hour (from 43.8 million/mL to 24.8 million/mL) and 34th hour (from 33.1 million/mL to 23.1 million/mL) in the double-IUI group; however, there was no significant difference (P = 0.16) regarding sperm motility between the 12-hour (from 55% to 12%) and 34-hour (from 53% to 12%) samples. Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.

Rahman 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts described. Exclusion group not mentioned or described. No power calculation made.
Selective reporting (reporting bias)	Low risk	Reported non-statistically significant results in addition to statistically significant results, which suggests there was no selective reporting. No protocol available.
Other bias	Unclear risk	There was a significant fall (P<.005) in sperm count between the 12th hour and 34th hour in the double-IUI group; however, there was no significant difference regarding sperm motility between the 12-hour and 34-hour samples.

Silverberg 1992

Study characteristics	
Methods	Single centre Trial design: parallel Allocation: computer-generated random numbers Concealment: not stated Blinding: none Follow-up: stated Power calculation: no Intention to treat analysis: no Country: USA
Participants	31 women, 49 cycles 23 cycles in each treatment group Women's age: single IUI: mean 33.7 (SD 0.5) years; double IUI: mean 32.7 (SD 0.8) years Inclusion criteria: not stated Exclusion criteria: not stated Type of subfertility: ovulatory dysfunction, unexplained subfertility, male factor infertility, treated endometriosis, cervical factor, ≥ 2 infertility factors Duration of subfertility: not stated Previous fertility treatment: not stated Primary or secondary infertility: not stated
Interventions	Method of COH: hMG and hCG 10,000 IU Single IUI: 34 hours after hCG; double IUI: 18 and 42 hours after hCG Sperm preparation: husband's semen used: washed with human tubal fluid; cryopreserved donor semen used: swim-up technique Insemination procedure: Tomcat catheter 500 µL aliquot

Silverberg 1992 *(Continued)*

	Number of inseminations: 1 or 2
	Number of cycles per participant: unclear
Outcomes	LBR per couple: not stated
	Pregnancy rate per couple: not stated
	Pregnancy rate per cycle: single IUI: 8.7%; double IUI: 52%
	Multiple pregnancy rate per woman: not stated
	OHSS per woman: not stated
	Miscarriage rate per woman: not stated
	Ectopic pregnancy rate per woman: not stated
	Costs: not stated
	Pregnancy diagnosed with transvaginal sonography; chorionic villi
Notes	Small groups, data per cycle not per woman.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Not clearly stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts were described. However, there was no power calculation or description of how many patients were eligible for inclusion. Therefore, bias could not be ruled out.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Different types of infertility and donor semen were merged. This may have influenced outcome.

Zahiri Sorouri 2016

Study characteristics

Methods	Single centre

Zahiri Sorouri 2016 *(Continued)*

	Trial design: parallel Allocation: block randomisation method Concealment: not stated Blinding: not stated Follow-up: 1 cycle Power calculation: yes Intention to treat analysis: yes Country: Iran
Participants	580 woman Single IUI: 290 women; IUI performed 36 hours after hCG administration; double IUI: 290 women; IUIs performed 18 and 40 hours after hCG Women's age: single IUI: mean 30.57 (SD 5.46) years; double IUI: mean 29.77 (SD 5.31) years Inclusion criteria: IUI candidate women with mild male factor infertility (oligospermia or asthenospermia (or both) with 10 million progressive sperm, unexplained infertility (couples with normal sperm parameters, unblocked fallopian tubes and ovulation), and PCOS (ruling out pregnancy, hypothalamic-hypopituitarism disorders and other causes of hyperandrogenism). Also, 2/3 criteria including oligo-ovulation or anovulation, hyperandrogenism, PCO that were defined by ultrasound indicated PCOS), who could not become pregnant even after being induced 6 times and producing dominant follicle. Women with 2–5 dominant follicles ≥ 18 mm in size and basal FSH levels 12 mIU/L were included. Exclusion criteria: blocked fallopian tubes and endometriosis Type of subfertility: mild male factor, unexplained, PCOS Previous fertility treatment: induced 6 times and producing dominant follicle Primary or secondary infertility: not stated
Interventions	Method of COH: CC or letrozole with or without hMG. Type and dose of administrated medications were used based on the response of participants that was chosen by the physician. Follicle monitoring was performed by serial transvaginal ultrasonography and when there were 2–5 dominant follicles ≥ 18 mm in size, hCG 5000 IU was administered. Semen preparation: standard swim-up technique Method of insemination: injection catheter with 0.5 mL sample was entered for 10–30 seconds in the cervical orifice and driven directly into the uterine cavity. Participants remained supine for 15 minutes after IUI Number of cycles: 1 Method of pregnancy detection: β-hCG assessed 15 days after IUI for women who experience a missed menstrual period. Clinical pregnancy defined as detection of fetal cardiac activity
Outcomes	Primary outcome Clinical pregnancy defined as detection of fetal cardiac activity Secondary outcomes Miscarriage Multiple pregnancy

Zahiri Sorouri 2016 *(Continued)*

	Ectopic pregnancy
Notes	Women with 2–5 dominant follicles of 18 mm in size were included. Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation method.
Allocation concealment (selection bias)	Unclear risk	Not clearly stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were described. Power calculation was performed. It was described how many participants were eligible for inclusion; intention to treat analysis.
Selective reporting (reporting bias)	Low risk	Reported non-statistically significant results in addition to statistically significant results, which suggests there was no selective reporting. No protocol available.
Other bias	Unclear risk	Different types of infertility and donor semen were merged. Woman with multiple dominant follicles were included. This may have influence outcome.

Zeyneloglu 2002

Study characteristics

Methods	Single centre (?) Trial design: parallel Allocation: computer-generated random number table Concealment: not stated Blinding: not stated Follow-up: not stated Power calculation: yes; would need 35 participants in each group to double PR over control group Intention to treat analysis: no Country: Turkey
Participants	82 women, 82 cycles

Zeyneloglu 2002 *(Continued)*

	Single IUI: 42 participants, 42 cycles; double IUI: 40 participants, 40 cycles
	Women's age: not stated
	Inclusion criteria: not stated
	Exclusion criteria: not stated
	Duration of infertility: not stated
	Type of subfertility: unexplained infertility or mild male factor
	Previous treatment: not stated
	Primary or secondary infertility: not stated
Interventions	CC 100 mg for 5 days, hCG
	Single IUI: 36 hours after hCG; double IUI: 18 and 42 hours after hCG
	Semen preparation: husband's semen used; 2 gradient particle separation method. Subsequent sperm swim-up for 45 minutes
	Insemination procedure: not stated
	1 or 2 inseminations
	1 cycle
Outcomes	LBR per couple: not stated
	Pregnancy rate per couple: single IUI: 9.5%, double IUI: 10%
	Pregnancy rate per cycle: single IUI: 9.5%, double IUI: 10%
	Multiple pregnancy rate per woman: not stated
	Miscarriage rate per woman: not stated
	OHSS rate per woman: not stated
	Ectopic pregnancy rate per woman: not stated
	Costs: not stated
	Pregnancy diagnosed: fetal heart activity on ultrasound
Notes	Third group not included in analysis: single IUI 36 hours after hCG with misoprostol; 20 women (1 pregnancy).
	Third group terminated prematurely: 55% experienced uterine cramps and vaginal bleeding.
	Trial registration number: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Zeyneloglu 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information in this abstract to permit judgment of low risk or high risk.
Selective reporting (reporting bias)	Unclear risk	Insufficient information in this abstract to permit judgment of low risk or high risk.
Other bias	Unclear risk	Insufficient information in this abstract to permit judgment of low risk or high risk.

β-hCG: β-human chorionic gonadotrophin; BMI: body mass index; CC: clomiphene citrate; CD: cycle day; COH: controlled ovarian hyperstimulation; E2: oestradiol; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotrophin; hMG: human menopausal gonadotropin; HSG: hysterosalpingography; IU: international units; IUI: intrauterine insemination; LBR: live birth rate; LH: luteinising hormone; MLP: mid-luteal phase; OHSS: ovarian hyperstimulation syndrome; PCO: polycystic ovaries; PCOS: polycystic ovary syndrome; PCT: procalcitonin; PRL: prolactin; rFSH: recombinant follicle-stimulating hormone; SD: standard deviation; TSH: thyroid-stimulating hormone; WHO: World Health Organization.

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

Study	Reason for exclusion
Alborzi 2003	Cross-over design.
Calderon 2000	Pseudo-randomisation by day of the week. Stated to be a retrospective design.
Centola 1990	Not a randomised controlled trial; parallel design. Intracervical insemination.
Deary 1997	Not a randomised controlled trial; design unclear. Type of intervention: single vs double intracervical inseminations.
Gezginç 2008	Quasi-randomised.
Ghanem 2011	Quasi-randomised.
Karlström 2000	Type of intervention: 118/161 participants got inseminated by direct intraperitoneal insemination instead of IUI. Data of the small IUI group were not available.
Kemmann 1985	Randomisation not clearly stated; design unclear. Type of intervention: single vs double and triple artificial insemination with donor sperm intracervical application.
Khalifa 1995	Not a randomised controlled trial. Parallel design.
Kovacs 1988	Not a randomised controlled trial; design unclear. Compared pericervical insemination.
Liu 2005	Abstract of Liu 2006, containing the same data.

Study	Reason for exclusion
Malhotra 2007	Limited information from abstract available, the same authors as Rahman 2010. Seems to be the same research.
Matilsky 1998	Not truly randomised; day of the week that the participant was due to receive hCG was used.
Peddie 1997	There were only unpublished data available through the authors. The information in the unpublished data was too brief for inclusion. It was unclear if the study was a randomised controlled trial and parallel design. No additional data available.
Ransom 1994	Cross-over study. 120 women entered the study, with 78 in the single IUI group and 64 in the double IUI group. According to the author, some women were participants in both treatment arms.
Rawal 2003	Was in the previous version characterised as ongoing. We were unable to find the study. We contacted the authors but received no response.
Ruiz Anguas 2005	Quasi-randomised.
Tonguc 2010	Quasi-randomised.
Yang 1998	Type of intervention: to study the combined effects of factors (e.g. number of treatment cycles) influencing pregnancy rates after controlled ovarian hyperstimulation and IUI. No comparison of single with double IUI.

hCG: human chorionic gonadotrophin; IUI: intrauterine insemination.

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

Jindal 2018

Methods	Single centre No blinding stated
Participants	Infertile couples 426 women included from 2015 to 2017 Age: < 40 years
Interventions	Women were randomly assigned to single (213 women) or double (213 women) IUI groups. Single IUI: 36–38 hours after hCG administration; double IUI: 2 IUIs performed 18–20 and 40–42 hours after hCG administration.
Outcomes	Main outcome: clinical pregnancy
Notes	This was published in ESHRE 2018, the only results available in this article were: pregnancy rate was 10.2% in the single IUI group and 11.4% in the double IUI group. We attempted to contact the authors for further information and data to determine its eligibility, but received no reply.

hCG: human chorionic gonadotrophin; IUI: intrauterine insemination.

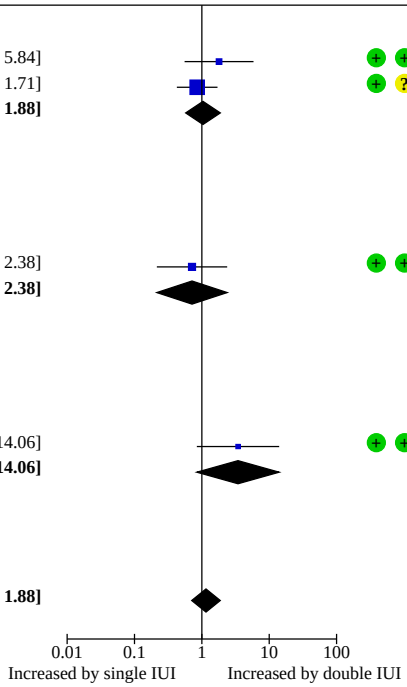
DATA AND ANALYSES

Comparison 1. Double intrauterine insemination (IUI) versus single IUI in controlled ovarian hyperstimulation cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth rate per woman randomised	3	468	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.71, 1.88]
1.1.1 Unexplained	2	254	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.58, 1.88]
1.1.2 Male factor	1	132	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.21, 2.38]
1.1.3 Other indication or unclear results	1	82	Odds Ratio (M-H, Fixed, 95% CI)	3.44 [0.84, 14.06]
1.2 Miscarriage rate per woman randomised	6	2363	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.98, 3.24]
1.2.1 Unexplained	2	648	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.33, 4.71]
1.2.2 Male factor	1	767	Odds Ratio (M-H, Fixed, 95% CI)	2.55 [0.49, 13.24]
1.2.3 Other indication or unclear results	4	948	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [0.88, 3.84]
1.3 Clinical pregnancy rate per woman randomised	9	2716	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [1.23, 1.86]
1.3.1 Unexplained	4	860	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.73, 1.57]
1.3.2 Male factor	3	874	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [1.74, 3.67]
1.3.3 Other indication or unclear results	7	982	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.90, 1.78]
1.4 Multiple pregnancy rate per woman randomised	5	2203	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.91, 4.56]
1.4.1 Unexplained	1	488	Odds Ratio (M-H, Fixed, 95% CI)	5.17 [0.25, 108.19]
1.4.2 Male factor	1	767	Odds Ratio (M-H, Fixed, 95% CI)	4.08 [0.45, 36.72]
1.4.3 Other indication or unclear result	4	948	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.61, 3.93]
1.5 Ectopic pregnancy per woman randomised	4	1048	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.35, 4.28]
1.5.1 Unexplained	1	160	Odds Ratio (M-H, Fixed, 95% CI)	2.96 [0.12, 73.82]
1.5.2 Other indication or unclear result	3	888	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.25, 4.04]

Analysis 1.1. Comparison 1: Double intrauterine insemination (IUI) versus single IUI in controlled ovarian hyperstimulation cycles, Outcome 1: Live birth rate per woman randomised

Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Unexplained						
Bagis 2010	9	49	5	45	14.1%	1.80 [0.55 , 5.84]
Rahman 2010	21	81	23	79	57.2%	0.85 [0.43 , 1.71]
Subtotal (95% CI)		**130**		**124**	**71.4%**	**1.04 [0.58 , 1.88]**
Total events:	30		28			
Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.1.2 Male factor						
Bagis 2010	5	65	7	67	21.1%	0.71 [0.21 , 2.38]
Subtotal (95% CI)		**65**		**67**	**21.1%**	**0.71 [0.21 , 2.38]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.1.3 Other indication or unclear results						
Casadei 2006	8	39	3	43	7.5%	3.44 [0.84 , 14.06]
Subtotal (95% CI)		**39**		**43**	**7.5%**	**3.44 [0.84 , 14.06]**
Total events:	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**234**		**234**	**100.0%**	**1.15 [0.71 , 1.88]**
Total events:	43		38			
Heterogeneity: Chi² = 4.20, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Chi² = 3.04, df = 2 (P = 0.22), I² = 34.2%						

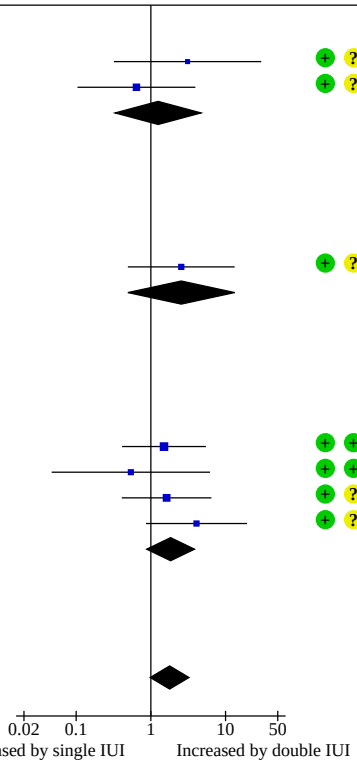


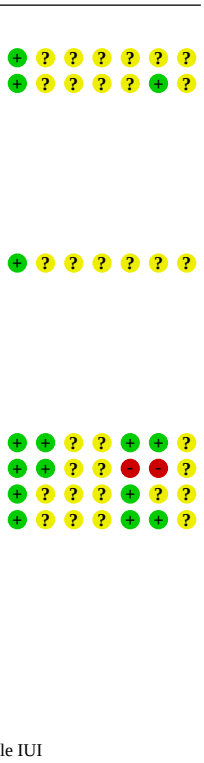
Risk of bias legend

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

Analysis 1.2. Comparison 1: Double intrauterine insemination (IUI) versus single IUI in controlled ovarian hyperstimulation cycles, Outcome 2: Miscarriage rate per woman randomised

Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Unexplained						
Liu 2006	3	241	1	247	5.8%	3.10 [0.32 , 30.02]
Rahman 2010	2	81	3	79	17.7%	0.64 [0.10 , 3.95]
Subtotal (95% CI)		**322**		**326**	**23.6%**	**1.25 [0.33 , 4.71]**
Total events:	5		4			
Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² = 12%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.2.2 Male factor						
Liu 2006	5	381	2	386	11.7%	2.55 [0.49 , 13.24]
Subtotal (95% CI)		**381**		**386**	**11.7%**	**2.55 [0.49 , 13.24]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
1.2.3 Other indication or unclear results						
Bagis 2010	6	114	4	112	22.9%	1.50 [0.41 , 5.47]
Casadei 2006	1	39	2	43	11.1%	0.54 [0.05 , 6.19]
Ng 2003	6	30	4	30	19.1%	1.63 [0.41 , 6.47]
Zahiri Sorouri 2016	8	290	2	290	11.6%	4.09 [0.86 , 19.40]
Subtotal (95% CI)		**473**		**475**	**64.7%**	**1.84 [0.88 , 3.84]**
Total events:	21		12			
Heterogeneity: Chi² = 2.10, df = 3 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.11)						
Total (95% CI)		**1176**		**1187**	**100.0%**	**1.78 [0.98 , 3.24]**
Total events:	31		18			
Heterogeneity: Chi² = 3.72, df = 6 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Test for subgroup differences: Chi² = 0.46, df = 2 (P = 0.79), I² = 0%						



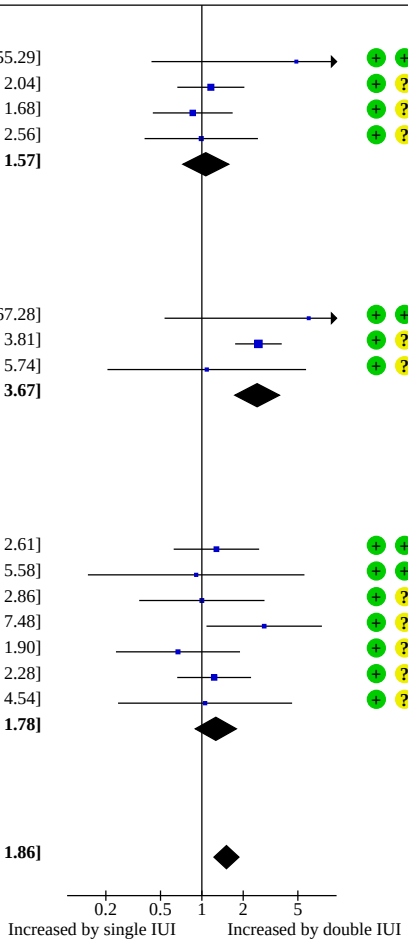


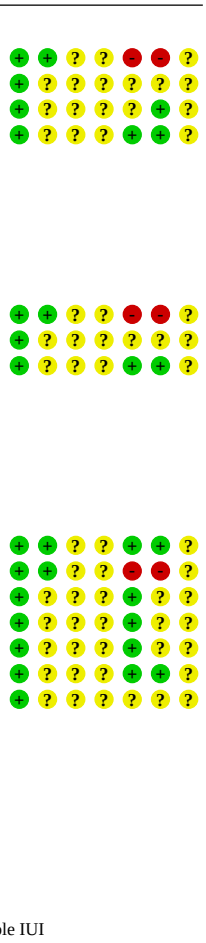
Risk of bias legend

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

Analysis 1.3. Comparison 1: Double intrauterine insemination (IUI) versus single IUI in controlled ovarian hyperstimulation cycles, Outcome 3: Clinical pregnancy rate per woman randomised

Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Unexplained						
Casadei 2006	3	11	1	14	0.4%	4.88 [0.43 , 55.29]
Liu 2006	29	241	26	247	15.6%	1.16 [0.66 , 2.04]
Rahman 2010	24	81	26	79	12.8%	0.86 [0.44 , 1.68]
Zahiri Sorouri 2016	9	89	10	98	5.9%	0.99 [0.38 , 2.56]
Subtotal (95% CI)		**422**		**438**	**34.8%**	**1.07 [0.73 , 1.57]**
Total events:	65		63			
Heterogeneity: Chi² = 2.02, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.74)						
1.3.2 Male factor						
Casadei 2006	3	11	1	17	0.4%	6.00 [0.54 , 67.28]
Liu 2006	95	381	44	386	22.7%	2.58 [1.75 , 3.81]
Zahiri Sorouri 2016	3	38	3	41	1.8%	1.09 [0.21 , 5.74]
Subtotal (95% CI)		**430**		**444**	**24.9%**	**2.53 [1.74 , 3.67]**
Total events:	101		48			
Heterogeneity: Chi² = 1.49, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 4.86 (P < 0.00001)						
1.3.3 Other indication or unclear results						
Bagis 2010	20	114	16	112	9.2%	1.28 [0.62 , 2.61]
Casadei 2006	3	14	3	13	1.7%	0.91 [0.15 , 5.58]
Ng 2003	11	30	11	30	4.8%	1.00 [0.35 , 2.86]
Ragni 1999a	28	92	6	45	3.9%	2.84 [1.08 , 7.48]
Ragni 1999b	10	91	7	45	5.8%	0.67 [0.24 , 1.90]
Zahiri Sorouri 2016	27	163	21	151	12.6%	1.23 [0.66 , 2.28]
Zeyneloglu 2002	4	40	4	42	2.4%	1.06 [0.25 , 4.54]
Subtotal (95% CI)		**544**		**438**	**40.3%**	**1.26 [0.90 , 1.78]**
Total events:	103		68			
Heterogeneity: Chi² = 4.51, df = 6 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
Total (95% CI)		**1396**		**1320**	**100.0%**	**1.51 [1.23 , 1.86]**
Total events:	269		179			
Heterogeneity: Chi² = 19.63, df = 13 (P = 0.10); I² = 34%						
Test for overall effect: Z = 3.86 (P = 0.0001)						
Test for subgroup differences: Chi² = 11.41, df = 2 (P = 0.003), I² = 82.5%						

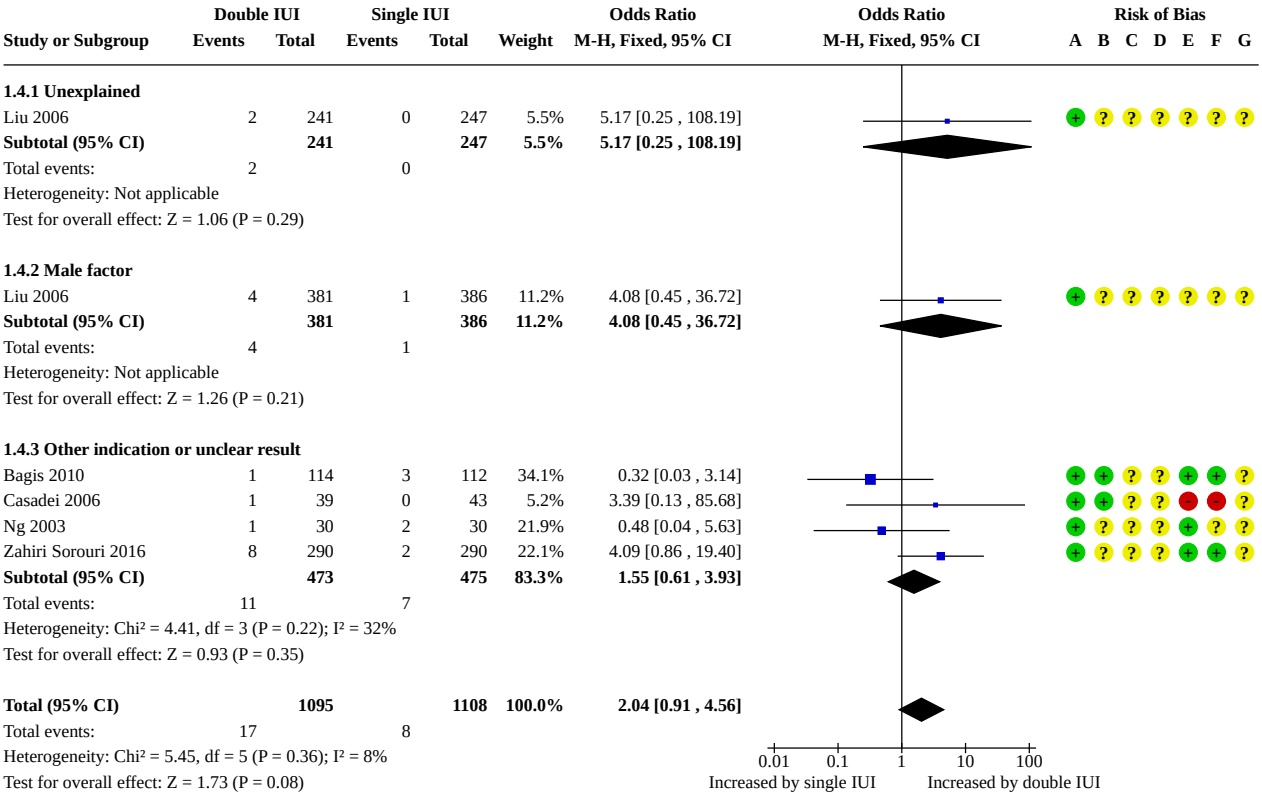




Risk of bias legend

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

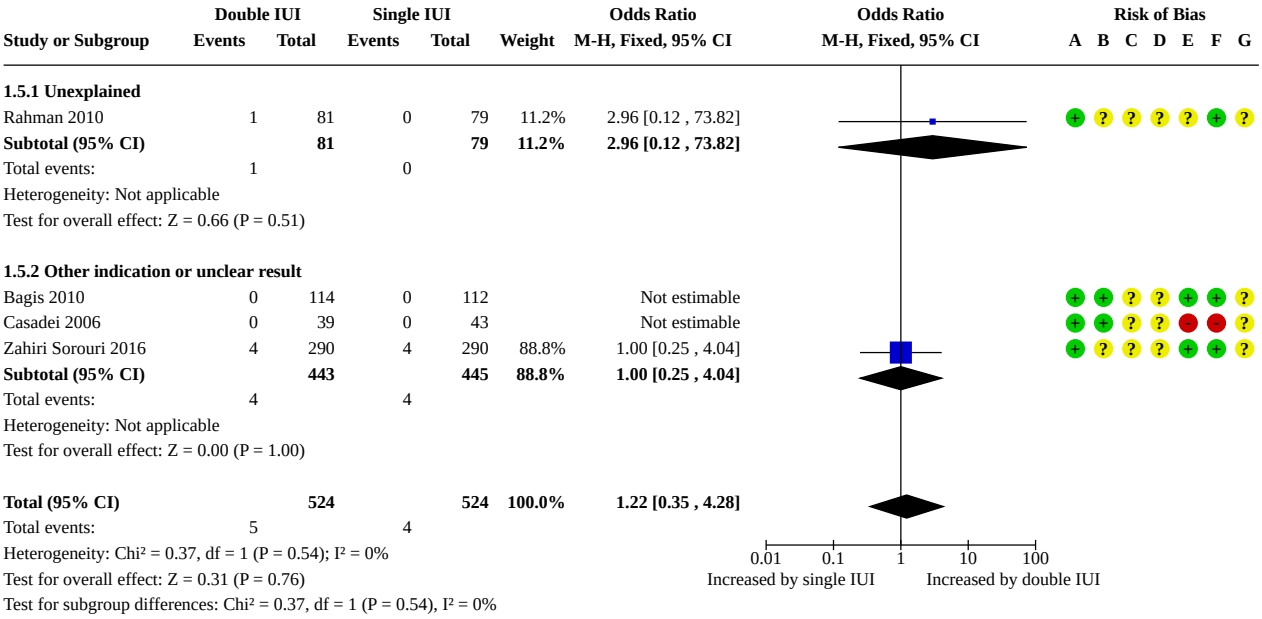
Analysis 1.4. Comparison 1: Double intrauterine insemination (IUI) versus single IUI in controlled ovarian hyperstimulation cycles, Outcome 4: Multiple pregnancy rate per woman randomised



Risk of bias legend

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

Analysis 1.5. Comparison 1: Double intrauterine insemination (IUI) versus single IUI in controlled ovarian hyperstimulation cycles, Outcome 5: Ectopic pregnancy per woman randomised



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

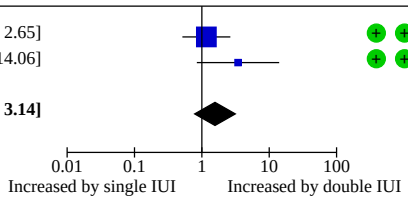
Comparison 2. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth rate per woman randomised	2	308	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [0.78, 3.14]
2.2 Miscarriage rate per pregnancy	6	389	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.78, 2.87]
2.3 Miscarriage rate per woman randomised	2	308	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.39, 3.62]
2.4 Clinical pregnancy rate per woman	2	308	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.81, 2.75]
2.5 Multiple pregnancy rate per pregnancy	5	339	Odds Ratio (M-H, Fixed, 95% CI)	1.82 [0.77, 4.26]

Analysis 2.1. Comparison 2: Sensitivity analysis, Outcome 1: Live birth rate per woman randomised

Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Bagis 2010	14	114	12	112	82.4%	1.17 [0.51 , 2.65]	+ + ? ? + + ?
Casadei 2006	8	39	3	43	17.6%	3.44 [0.84 , 14.06]	+ + ? ? - - ?
Total (95% CI)		**153**		**155**	**100.0%**	**1.57 [0.78 , 3.14]**	
Total events:	22		15				

Heterogeneity: Chi² = 1.70, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.27 (P = 0.21)
Test for subgroup differences: Not applicable

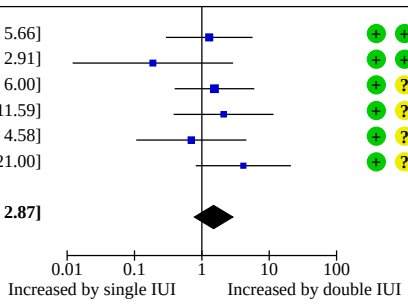


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.2. Comparison 2: Sensitivity analysis, Outcome 2: Miscarriage rate per pregnancy

Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Bagis 2010	6	20	4	16	20.5%	1.29 [0.29 , 5.66]	+ + ? ? + + ?
Casadei 2006	1	9	2	5	15.1%	0.19 [0.01 , 2.91]	+ + ? ? - - ?
Liu 2006	8	124	3	70	23.7%	1.54 [0.40 , 6.00]	+ ? ? ? ? ? ?
Ng 2003	6	11	4	11	12.0%	2.10 [0.38 , 11.59]	+ ? ? ? + ? ?
Rahman 2010	2	24	3	26	17.4%	0.70 [0.11 , 4.58]	+ ? ? ? ? + ?
Zahiri Sorouri 2016	8	39	2	34	11.2%	4.13 [0.81 , 21.00]	+ ? ? ? + + ?
Total (95% CI)		**227**		**162**	**100.0%**	**1.49 [0.78 , 2.87]**	
Total events:	31		18				

Heterogeneity: Chi² = 4.52, df = 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable

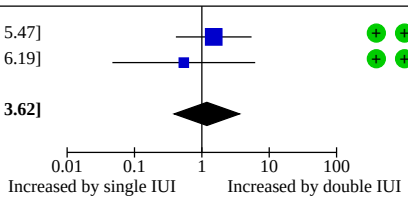


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.3. Comparison 2: Sensitivity analysis, Outcome 3: Miscarriage rate per woman randomised

Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Bagis 2010	6	114	4	112	67.3%	1.50 [0.41 , 5.47]	+ + ? ? + + ?
Casadei 2006	1	39	2	43	32.7%	0.54 [0.05 , 6.19]	+ + ? ? - - ?
Total (95% CI)		**153**		**155**	**100.0%**	**1.19 [0.39 , 3.62]**	
Total events:	7		6				

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable

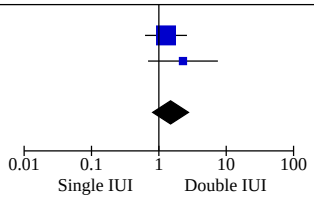


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.4. Comparison 2: Sensitivity analysis, Outcome 4: Clinical pregnancy rate per woman

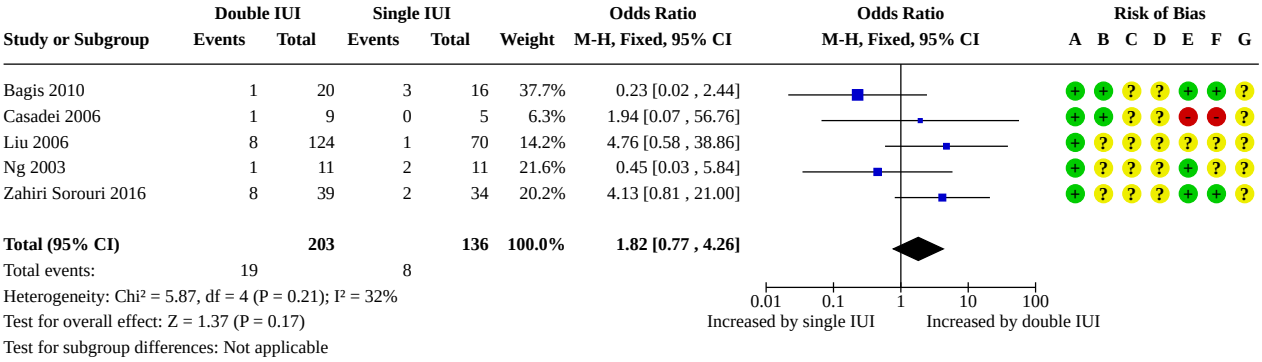
Study or Subgroup	Double IUI Events	Double IUI Total	Single IUI Events	Single IUI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Bagis 2010	20	114	16	112	78.4%	1.28 [0.62 , 2.61]	+ + ? ? + + ?
Casadei 2006	9	39	5	43	21.6%	2.28 [0.69 , 7.52]	+ + ? ? - - ?
Total (95% CI)		**153**		**155**	**100.0%**	**1.49 [0.81 , 2.75]**	
Total events:	29		21				

Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



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

Analysis 2.5. Comparison 2: Sensitivity analysis, Outcome 5: Multiple pregnancy rate per pregnancy



Risk of bias legend

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

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility (CGF) specialised register search strategy

ProCite platform

Searched 15 July 2020

Keywords CONTAINS "insemination" or "insemination-artificial by donor" or "artificial insemination by donor" or "artificial insemination by partner" or "artificial insemination" or "donor insemination" or "donor semen" or "donors" or "insemination-donor" or "IUI" or "Intrauterine Insemination" or "intrautero tuboperitoneal insemination" or Title CONTAINS "insemination" or "insemination-artificial by donor" or "artificial insemination by donor" or "artificial insemination by partner" or "artificial insemination" or "donor insemination" or "donor semen" or "donors" or "insemination-donor" or "IUI" or "Intrauterine Insemination" or "intrautero tuboperitoneal insemination"

AND

Keywords CONTAINS "single" or "single insemination" or "single intrauterine insemination" or "single vs multiple" or "Singular" or "double" or "double insemination" or "double intrauterine insemination" or "multiple insemination" or Title CONTAINS "single" or "single insemination" or "single intrauterine insemination" or "single vs multiple" or "Singular" or "double" or "double insemination" or "double intrauterine insemination" or "multiple insemination"

(169 records)

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

Web platform

Searched 15 July 2020

#1 MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES 361

#2 (inseminat* adj5 (single or double or one or two or regimen or multiple)):TI,AB,KY 139

#3 (single or double or one or two or regimen or multiple):TI,AB,KY 893948

#4 #1 AND #3 259

#5 #2 OR #4 352

Appendix 3. MEDLINE search strategy

Ovid platform

Searched from 1946 to 15 July 2020

1 exp Insemination, Artificial/ (11700)
2 (artificial adj3 insemination*).tw. (6848)
3 (intrauterine adj3 insemination*).tw. (2590)
4 (intra-uterine adj3 insemination*).tw. (235)
5 IUI.tw. (1776)
6 AIH.tw. (2456)
7 (eutelegeneses or eutelegenesis).tw. (6)
8 (inseminat* adj3 donor*).tw. (1286)
9 (heterologous adj3 inseminat*).tw. (111)
10 (homologous adj3 inseminat*).tw. (168)
11 (inseminat* adj3 (husband* or partner*)).tw. (254)
12 or/1-11 (18384)
13 (single or double).tw. (2021183)
14 (one or two).tw. (7070200)
15 regimen*.tw. (249891)
16 multiple*.tw. (1306270)
17 or/13-16 (9088169)
18 12 and 17 (7204)
19 randomized controlled trial.pt. (509414)
20 controlled clinical trial.pt. (93751)
21 randomized.ab. (485734)
22 randomised.ab. (96979)
23 placebo.tw. (215031)
24 clinical trials as topic.sh. (192041)
25 randomly.ab. (336864)
26 trial.ti. (221522)
27 (crossover or cross-over or cross over).tw. (85331)
28 or/19-27 (1366696)
29 exp animals/ not humans.sh. (4716887)
30 28 not 29 (1258368)
31 18 and 30 (606)

Appendix 4. Embase search strategy

Ovid platform

Searched from 1980 to 15 July 2020

1 exp artificial insemination/ (17206)
2 (artificial adj3 insemination*).tw. (6323)
3 (intrauterine adj3 insemination*).tw. (3837)
4 (intra-uterine adj3 insemination*).tw. (429)
5 IUI.tw. (3249)
6 AIH.tw. (4943)
7 (eutelegeneses or eutelegenesis).tw. (3)
8 (inseminat* adj3 donor*).tw. (1480)
9 (heterologous adj3 inseminat*).tw. (59)
10 (homologous adj3 inseminat*).tw. (154)
11 (inseminat* adj3 (husband* or partner*)).tw. (323)
12 or/1-11 (25071)
13 (single or double).tw. (2461545)
14 (one or two).tw. (8688977)
15 regimen*.tw. (380074)
16 multiple*.tw. (1740958)
17 or/13-16 (11180529)
18 12 and 17 (11635)
19 Clinical Trial/ (966569)

20 Randomized Controlled Trial/ (605488)
21 exp randomization/ (87261)
22 Single Blind Procedure/ (39339)
23 Double Blind Procedure/ (170682)
24 Crossover Procedure/ (63463)
25 Placebo/ (337966)
26 Randomi?ed controlled trial$.tw. (231169)
27 Rct.tw. (37551)
28 random allocation.tw. (2020)
29 randomly.tw. (441649)
30 randomly allocated.tw. (35317)
31 allocated randomly.tw. (2548)
32 (allocated adj2 random).tw. (817)
33 Single blind$.tw. (24781)
34 Double blind$.tw. (203046)
35 ((treble or triple) adj blind$).tw. (1156)
36 placebo$.tw. (303445)
37 prospective study/ (609409)
38 or/19-37 (2440151)
39 case study/ (70135)
40 case report.tw. (404300)
41 abstract report/ or letter/ (1102167)
42 or/39-41 (1565958)
43 38 not 42 (2385928)
44 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5988282)
45 43 not 44 (2220753)
46 18 and 45 (1450)

Appendix 5. CINAHL search strategy

Searched from 1961 to 4 March 2019, all later CINAHL output was captured in the CENTRAL search of 15 July 2020

Ebsco platform

#	Query	Results
S23	S10 AND S22	326
S22	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	1,305,802
S21	TX allocat* random*	9,892
S20	(MH "Quantitative Studies")	21,880
S19	(MH "Placebos")	11,146
S18	TX placebo*	55,496
S17	TX random* allocat*	9,892
S16	(MH "Random Assignment")	53,574
S15	TX randomi* control* trial*	164,034
S14	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	1,004,218

(Continued)

S13	TX clinic* n1 trial*	239,080
S12	PT Clinical trial	86,754
S11	(MH "Clinical Trials+")	254,529
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	1,387
S9	TX(inseminat* N3 (husband* or partner*))	21
S8	TX(homologous N3 inseminat*)	4
S7	TX(heterologous N3 inseminat*)	3
S6	TX(inseminat* N3 donor*)	132
S5	TX(IUI or AIH)	598
S4	TX(intra-uterine N3 insemination*)	27
S3	TX(intrauterine N3 insemination*)	440
S2	TX(artificial N3 insemination*)	742
S1	(MM "Insemination, Artificial")	411

Appendix 6. LILACS search strategy

Web platform

Searched on 28 February 2021

" single double IUI infertile patients"

(Six records, three were useful but already included).

Appendix 7. Google scholar search strategy

Web platform

Searched on 28 February 2021

" single double IUI infertile patients"

(17,200 records of which first ten were checked. The articles that seemed eligible were already included).

Appendix 8. Epistemonikos search strategy

Web platform

Searched on 28 February 2021

"single double IUI infertile patients"

(There were eight records, four eligible that were already included).

WHAT'S NEW

Date	Event	Description
15 July 2020	New search has been performed	We added 3 new studies (Bagis 2010; Rahman 2010; Zahiri Sorouri 2016).
15 July 2020	New citation required and conclusions have changed	The addition of 3 new studies has led to changes in the conclusions.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 1, 2003

Date	Event	Description
11 February 2009	New citation required but conclusions have not changed	Review updated June 2007
13 May 2008	Amended	Converted to new review format.
6 October 2007	New citation required and conclusions have changed	Substantive amendment
8 June 2007	New search has been performed	This review was updated June 2007

CONTRIBUTIONS OF AUTHORS

AEPC: took the lead in writing the protocol.

LR and EK conducted the literature search, selection of relevant trials for inclusion in the review, data extraction and statistical analyses, together with completion of the review.

BJC performed previous work that became the foundation of the current study and developed the title. This author contributed to the background section, selection criteria, search strategy and methods, and analysed important articles and proofread the update.

DECLARATIONS OF INTEREST

LR: none.

EK: none.

BJC: none.

AEPC: received an unrestricted research grant Ferring B.V.; support for attending ESHRE meeting – Ferring B.V., Theramex B.V.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title to "Double versus single intrauterine insemination (IUI) in stimulated cycles for subfertile couples."

We updated the methods according to current Cochrane guidelines and included a summary of findings table.

After a discussion with the editorial team, we did not include the outcomes incidence of ovarian hyperstimulation syndrome (OHSS) per woman and costs per cycle.

We performed a post-hoc subgroup analysis on indications (one study revealed a significant effect of double insemination with male factor and not with unexplained infertility).

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [epidemiology]; Bias; Confidence Intervals; Infertility, Female [*therapy]; Insemination, Artificial, Homologous [*methods] [statistics & numerical data]; Live Birth [epidemiology]; Odds Ratio; Ovulation Induction; Pregnancy Rate; Pregnancy, Ectopic [epidemiology]; Pregnancy, Multiple [statistics & numerical data]; Randomized Controlled Trials as Topic; Retreatment [methods]; Selection Bias

MeSH check words

Female; Humans; Male; Pregnancy