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Interventions for unexplained infertility: a systematic review and network meta-analysis (Review)

Wang R, Danhof NA, Tjon-Kon-Fat RI, Eijkemans MJC, Bossuyt PMM, Mochtar MH, van der Veen F, Bhattacharya S, Mol BWJ, van Wely M

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[Intervention Review]

Interventions for unexplained infertility: a systematic review and network meta-analysis

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ABSTRACT

Background

Clinical management for unexplained infertility includes expectant management as well as active treatments, including ovarian stimulation (OS), intrauterine insemination (IUI), OS-IUI, and in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI).

Existing systematic reviews have conducted head-to-head comparisons of these interventions using pairwise meta-analyses. As this approach allows only the comparison of two interventions at a time and is contingent on the availability of appropriate primary evaluative studies, it is difficult to identify the best intervention in terms of effectiveness and safety. Network meta-analysis compares multiple treatments simultaneously by using both direct and indirect evidence and provides a hierarchy of these treatments, which can potentially better inform clinical decision-making.

Objectives

To evaluate the effectiveness and safety of different approaches to clinical management (expectant management, OS, IUI, OS-IUI, and IVF/ICSI) in couples with unexplained infertility.

Search methods

We performed a systematic review and network meta-analysis of relevant randomised controlled trials (RCTs). We searched electronic databases including the Cochrane Gynaecology and Fertility Group Specialised Register of Controlled Trials, the Cochrane Central Register of Studies Online, MEDLINE, Embase, PsycINFO and CINAHL, up to 6 September 2018, as well as reference lists, to identify eligible studies. We also searched trial registers for ongoing trials.

Selection criteria

We included RCTs comparing at least two of the following clinical management options in couples with unexplained infertility: expectant management, OS, IUI, OS-IUI, and IVF (or combined with ICSI).

Data collection and analysis

Two review authors independently screened titles and abstracts identified by the search strategy. We obtained the full texts of potentially eligible studies to assess eligibility and extracted data using standardised forms. The primary effectiveness outcome was a composite of cumulative live birth or ongoing pregnancy, and the primary safety outcome was multiple pregnancy. We performed a network meta-analysis within a random-effects multi-variate meta-analysis model. We presented treatment effects by using odds ratios (ORs) and 95% confidence intervals (CIs). For the network meta-analysis, we used Confidence in Network Meta-analysis (CINeMA) to evaluate the overall certainty of evidence.

Main results

We included 27 RCTs (4349 couples) in this systematic review and 24 RCTs (3983 couples) in a subsequent network meta-analysis. Overall, the certainty of evidence was low to moderate: the main limitations were imprecision and/or heterogeneity.

Ten RCTs including 2725 couples reported on live birth. Evidence of differences between OS, IUI, OS-IUI, or IVF/ICSI versus expectant management was insufficient (OR 1.01, 95% CI 0.51 to 1.98; low-certainty evidence; OR 1.21, 95% CI 0.61 to 2.43; low-certainty evidence; OR 1.61, 95% CI 0.88 to 2.94; low-certainty evidence; OR 1.88, 95 CI 0.81 to 4.38; low-certainty evidence). This suggests that if the chance of live birth following expectant management is assumed to be 17%, the chance following OS, IUI, OS-IUI, and IVF would be 9% to 28%, 11% to 33%, 15% to 37%, and 14% to 47%, respectively. When only including couples with poor prognosis of natural conception (3 trials, 725 couples) we found OS-IUI and IVF/ICSI increased live birth rate compared to expectant management (OR 4.48, 95% CI 2.00 to 10.1; moderate-certainty evidence; OR 4.99, 95 CI 2.07 to 12.04; moderate-certainty evidence), while there was insufficient evidence of a difference between IVF/ICSI and OS-IUI (OR 1.11, 95% CI 0.78 to 1.60; low-certainty evidence).

Eleven RCTs including 2564 couples reported on multiple pregnancy. Compared to expectant management/IUI, OS (OR 3.07, 95% CI 1.00 to 9.41; low-certainty evidence) and OS-IUI (OR 3.34 95% CI 1.09 to 10.29; moderate-certainty evidence) increased the odds of multiple pregnancy, and there was insufficient evidence of a difference between IVF/ICSI and expectant management/IUI (OR 2.66, 95% CI 0.68 to 10.43; low-certainty evidence). These findings suggest that if the chance of multiple pregnancy following expectant management or IUI is assumed to be 0.6%, the chance following OS, OS-IUI, and IVF/ICSI would be 0.6% to 5.0%, 0.6% to 5.4%, and 0.4% to 5.5%, respectively.

Trial results show insufficient evidence of a difference between IVF/ICSI and OS-IUI for moderate/severe ovarian hyperstimulation syndrome (OHSS) (OR 2.50, 95% CI 0.92 to 6.76; 5 studies; 985 women; moderate-certainty evidence). This suggests that if the chance of moderate/severe OHSS following OS-IUI is assumed to be 1.1%, the chance following IVF/ICSI would be between 1.0% and 7.2%.

Authors' conclusions

There is insufficient evidence of differences in live birth between expectant management and the other four interventions (OS, IUI, OS-IUI, and IVF/ICSI). Compared to expectant management/IUI, OS may increase the odds of multiple pregnancy, and OS-IUI probably increases the odds of multiple pregnancy. Evidence on differences between IVF/ICSI and expectant management for multiple pregnancy is insufficient, as is evidence of a difference for moderate or severe OHSS between IVF/ICSI and OS-IUI.

PLAIN LANGUAGE SUMMARY

Interventions for unexplained infertility: a systematic review and meta-analysis

Review question
Researchers in Cochrane reviewed the evidence on the effectiveness and safety of ovarian stimulation (OS), intrauterine insemination (IUI), OS-IUI, and in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI) versus expectant management in couples with unexplained infertility.

Background
Treatment options for unexplained infertility include expectant management as well as active treatments such as ovarian stimulation (OS), intrauterine insemination (IUI), OS-IUI, and in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI). Network meta-analysis synthesises evidence of direct and indirect comparisons of interventions and enables researchers to simultaneously assess the effectiveness of more than two interventions for the same condition, so that clinicians can use the evidence to offer the best treatment. Therefore, we compared all these different treatment options by using network meta-analysis, to better inform clinical decision-making.

Study characteristics
We found 27 randomised controlled trials comparing these treatments with each other in a total of 4349 couples with unexplained infertility. The evidence is current to September 2018.

Key results

Evidence of differences in live birth between expectant management and the other four treatments (OS, IUI, OS-IUI, and IVF/ICSI) was insufficient. If the chance of live birth following expectant management is assumed to be 17%, the chance following OS, IUI, OS-IUI, and IVF would be 9% to 28%, 11% to 33%, 15% to 37%, and 14% to 47%, respectively. Compared to expectant management/IUI, OS may increase the chances of multiple pregnancy, and OS-IUI probably increases the chances of multiple pregnancy. Evidence showing differences between IVF/ICSI and expectant management for multiple pregnancy was insufficient. If the chance of multiple pregnancy following expectant management/IUI is assumed to be 1%, the chance following OS, OS-IUI, and IVF/ICSI would be 1% to 5%, 1% to 5%, and 0% to 6%, respectively.

Certainty of the evidence

The certainty of evidence overall was low to moderate. The main limitations were imprecision (not enough couples have been studied) and heterogeneity (couples in existing studies had different clinical characteristics).

Summary of findings for the main comparison. Summary of findings - live birth or ongoing pregnancy

Estimates of effects, confidence intervals, and certainty of the evidence for live birth in couples with unexplained infertility

Patient or population: couples with unexplained infertility

Intervention: OS, IUI, OS-IUI, or IVF/ICSI

Comparator: expectant management, OS, IUI, or OS-IUI

Outcome: live birth

Setting: outpatient

All comparisons (10 RCTs, 2725 couples)		**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)****	**Quality of the evidence (GRADE)**
Comparator	**Intervention (number of RCTs and number of couples in direct comparison)**	**Assumed risk with comparator**	**Corresponding risk with intervention**		
Expectant management	OS (2 RCTs, 527 couples)	166 per 1000	**167 per 1000** (92 to 282)	**OR 1.01** (0.51 to 1.98)	⊕⊕⊖⊖ LOW[a]
	IUI (1 RCT, 386 couples)	166 per 1000	**194 per 1000** (108 to 325)	**OR 1.45** (0.61 to 2.43)	⊕⊕⊖⊖ LOW[a]
	OS-IUI (2 RCTs, 454 couples)	166 per 1000	**242 per 1000** (149 to 369)	**OR 1.61** (0.88 to 2.94)	⊕⊕⊖⊖ LOW[b]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	166 per 1000	**272 per 1000** (139 to 465)	**OR 1.88** (0.81 to 4.38)	⊕⊕⊖⊖ LOW[a]
OS	IUI (1 RCT, 387 couples)	174 per 1000	**201 per 1000** (107 to 346)	**OR 1.20** (0.57 to 2.52)	⊕⊕⊖⊖ LOW[a]

	OS-IUI (1 RCT, 184 couples)	174 per 1000	**252 per 1000** (145 to 399)	**OR 1.60** (0.81 to 3.16)	⊕⊕⊖⊖ LOW[a]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	174 per 1000	**281 per 1000** (136 to 492)	**OR 2.63** (0.75 to 4.61)	⊕⊕⊖⊖ LOW[a]
IUI	OS-IUI (2 RCTs, 636 couples)	166 per 1000	**209 per 1000** (128 to 323)	**OR 1.33** (0.67 to 3.58)	⊕⊕⊖⊖ LOW[a]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	166 per 1000	**235 per 1000** (117 to 416)	**OR 1.55** (0.67 to 3.58)	⊕⊕⊖⊖ LOW[a]
OS-IUI	IVF/ICSI (3 RCTs, 731 couples)	319 per 1000	**354 per 1000** (230 to 498)	**OR 1.17** (0.64 to 2.12)	⊕⊕⊖⊖ LOW[a]

CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

***The corresponding risk in the intervention group** (and its 95% CI) is based on the mean risk in the comparator group and the relative effect of the intervention (and its 95% CI).

**All ORs and 95% CIs are based on network estimates.

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]Downgraded by two levels for very serious imprecision.
[b]Downgraded by two levels for serious imprecision and serious heterogeneity.

Summary of findings 2. Summary of findings - multiple pregnancy

Estimates of effects, confidence intervals, and certainty of the evidence for multiple pregnancy in couples with unexplained infertility

Patient or population: couples with unexplained infertility

Intervention: OS, OS-IUI, or IVF/ICSI

Comparator: expectant management/IUI, OS, or OS-IUI

Outcome: multiple pregnancy

Setting: outpatient

All comparisons (11 RCTs, 2564 couples)		**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)****	**Quality of the evidence (GRADE)**
Comparator	**Intervention (number of RCTs and number of couples in direct comparison)**	**Assumed risk with comparator**	**Corresponding risk with intervention**		
Expectant management/IUI	OS (3 RCTs, 934 couples)	6 per 1000	**17 per 1000** (6 to 50)	**OR 3.07** (1.00 to 9.41)	⊕⊕⊖⊖ LOW[a]
	OS-IUI (3 RCTs, 625 couples)	6 per 1000	**18 per 1000** (6 to 54)	**OR 3.34** (1.09 to 10.29)	⊕⊕⊕⊖ MODERATE[b]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	6 per 1000	**15 per 1000** (4 to 55)	**OR 2.66** (0.68 to 10.43)	⊕⊕⊖⊖ LOW[c]
OS	OS-IUI (2 RCTs, 274 couples)	23 per 1000	**26 per 1000** (9 to 70)	**OR 1.09** (0.38 to 3.15)	⊕⊖⊖⊖ VERY LOW[d]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	23 per 1000	**20 per 1000** (6 to 72)	**OR 0.87** (0.23 to 3.24)	⊕⊕⊖⊖ LOW[c]
OS-IUI	IVF/ICSI (3 RCTs, 731 couples)	27 per 1000	**22 per 1000** (10 to 47)	**OR 0.80** (0.37 to 1.73)	⊕⊕⊖⊖ LOW[c]

CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

***The corresponding risk in the intervention group** (and its 95% CI) is based on the mean risk in the comparator group and the relative effect of the intervention (and its 95% CI).

**All ORs and 95% CIs are based on network estimates.

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]Downgraded by two levels for serious imprecision and serious heterogeneity.
[b]Downgraded by one level for serious imprecision.
[c]Downgraded by two levels for very serious imprecision.
[d]Downgraded by three levels for serious study limitations and very serious imprecision.

Summary of findings 3. Summary of findings - clinical pregnancy

Estimates of effects, confidence intervals, and certainty of the evidence for clinical pregnancy in couples with unexplained infertility

Patient or population: couples with unexplained infertility

Intervention: OS, IUI, OS-IUI, or IVF/ICSI

Comparator: expectant management, OS, IUI, or OS-IUI

Outcome: clinical pregnancy

Setting: outpatient

All comparisons (23 RCTs, 3792 couples)		**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)****	**Quality of the evidence (GRADE)**
Comparator	**Intervention (number of RCTs and number of couples in direct comparison)**	**Assumed risk with comparator**	**Corresponding risk with intervention**		
Expectant management	OS (6 RCTs, 939 couples)	157 per 1000	**234 per 1000** (155 to 337)	**OR 1.64** (0.99 to 2.73)	⊕⊖⊖⊖ VERY LOW[a]
	IUI (3 RCTs, 528 couples)	157 per 1000	**182 per 1000** (102 to 305)	**OR 1.20** (0.61 to 2.36)	⊕⊕⊖⊖ LOW[b]
	OS-IUI	157 per 1000	**301 per 1000**	**OR 2.32**	⊕⊕⊖⊖

	(4 RCTs, 525 couples)		(205 to 420)	(1.39 to 3.90)	LOW[c]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	157 per 1000	**360 per 1000** (197 to 563)	**OR 3.03** (1.32 to 6.94)	⊕⊕⊖⊖ LOW[c]
OS	IUI (2 RCTs, 407 couples)	213 per 1000	**165 per 1000** (93 to 277)	**OR 0.73** (0.38 to 1.42)	⊕⊖⊖⊖ VERY LOW[d]
	OS-IUI (8 RCTs, 763 couples)	213 per 1000	**276 per 1000** (199 to 371)	**OR 1.41** (0.92 to 2.18)	⊕⊖⊖⊖ VERY LOW[e]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	213 per 1000	**332 per 1000** (275 to 521)	**OR 1.84** (1.40 to 4.02)	⊕⊕⊖⊖ LOW[f]
IUI	OS-IUI (4 RCTs, 579 couples)	174 per 1000	**291 per 1000** (182 to 430)	**OR 1.94** (1.05 to 3.57)	⊕⊖⊖⊖ VERY LOW[a]
	IVF/ICSI (no direct evidence available; only indirect evidence used here)	174 per 1000	**347 per 1000** (180 to 566)	**OR 2.52** (1.04 to 6.16)	⊕⊕⊖⊖ LOW[f]
OS-IUI	IVF/ICSI (3 RCTs, 731 couples)	344 per 1000	**437 per 1000** (289 to 599)	**OR 1.30** (0.68 to 2.50)	⊕⊕⊖⊖ LOW[b]

CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

***The corresponding risk in the intervention group** (and its 95% CI) is based on the mean risk in the comparator group and the relative effect of the intervention (and its 95% CI).

**All ORs and 95% CIs are based on network estimates.

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]Downgraded by three levels for serious study limitations, imprecision, and heterogeneity.
[b]Downgraded by two levels for very serious imprecision.
[c]Downgraded by two levels for very serious heterogeneity.
[d]Downgraded by three levels for very serious imprecision and serious incoherence.
[e]Downgraded by three levels for very serious study limitations, serious imprecision, and serious heterogeneity.
[f]Downgraded by two levels for serious imprecision and serious heterogeneity.

Summary of findings 4. Summary of findings - moderate/severe OHSS

IVF/ICSI compared with OS-IUI for unexplained infertility

Patient or population: couples with unexplained infertility

Settings: outpatient

Intervention: IVF/ICSI

Comparison: OS-IUI

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk with OS-IUI	Corresponding risk with IVF/ICSI				
Moderate/severe OHSS	**11 per 1000**	**28 per 1000** (10 to 72)	**OR 2.50** (0.92 to 6.76)	958 (5 studies)	⊕⊕⊕⊖ MODERATE[a]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; 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]Downgraded by one level for serious imprecision.

BACKGROUND

Description of the condition

Up to one in eight couples who try to achieve pregnancy fail to do so after 12 months of unprotected intercourse (Boivin 2007; Datta 2016; Gnoth 2003). Routine fertility investigations comprising semen analysis, assessment of ovulation, and a tubal patency test fail to reveal any abnormality in 25% of couples who are said to have unexplained infertility (Brandes 2010; Hull 1985). In the absence of an obvious barrier to conception, many of these couples possess a good chance of achieving pregnancy without treatment (Brandes 2011).

Description of the intervention

Clinical guidelines for the management of unexplained infertility recommend starting with the least invasive intervention before moving on to those that are more invasive (ASRM 2006; NICE 2013; NVOG 2010). In clinical practice, this has led to a wide range of clinical management approaches, ranging from expectant management (i.e. sexual intercourse) to timed intercourse, ovarian stimulation (i.e. gonadotropins, aromatase inhibitors, or anti-oestrogens), intrauterine insemination (IUI) with or without ovarian stimulation, in vitro fertilisation (IVF), and intracytoplasmic sperm injection (ICSI).

Expectant management or timed intercourse

Couples have a good chance of achieving pregnancy without treatment. A cumulative ongoing pregnancy rate of 27% has been reported after 12 months of unprotected intercourse following completion of the fertility investigations (Hunault 2005; van Eekelen 2017).

Ovarian stimulation (OS)

Anti-oestrogens (e.g. clomiphene), gonadotropins (e.g. urinary or recombinant follicle-stimulating hormone), and aromatase inhibitors (e.g. letrozole) are the most commonly used medications for OS. OS is used to stimulate follicular growth to increase the number of mature oocytes available for fertilisation, assuming that this would increase the chance of a live birth.

IUI (with or without OS)

IUI is another treatment option for unexplained infertility. It involves placement of prepared sperm into the uterine cavity timed around ovulation (Kandavel 2018). IUI can be done in a natural cycle or in combination with OS. Live birth rates of approximately 6% to 10% per cycle have been reported for infertile couples with unexplained infertility undergoing IUI with or without ovarian stimulation (Huang 2018).

IVF and ICSI

Conventional IVF refers to the co-incubation of oocytes with sperm in vitro with the goal of achieving extracorporeal fertilisation (Zegers-Hochschild 2017); this was first used as a treatment option for tubal infertility (Steptoe 1978). ICSI is a procedure in which a single spermatozoon is injected into the oocyte cytoplasm (Zegers-Hochschild 2017); this was first used in couples with severe male factor infertility (Palermo 1992). In the last three decades, the indication for IVF and ICSI has expanded to embrace a wider range of couples with infertility, including those with unexplained infertility (Kamphuis 2014).

How the intervention might work

In couples with unexplained infertility, a biological cause for their involuntary childlessness has not been detected, and therefore the rationale for each possible treatment is based upon assumptions.

The concept behind timed intercourse is to aid couples in having intercourse at the best time for fertilisation through the use of cycle monitoring. Ovarian stimulation is used to stimulate follicular growth to increase the number of mature oocytes available for fertilisation. IUI brings the spermatozoa closer to the oocyte for fertilisation at the appropriate time. The combination of OS and IUI combines these effects. IVF bypasses the process of transport of spermatozoa. ICSI assists fertilisation in overcoming any subtle abnormalities of sperm-oocyte interaction.

Why it is important to do this review

Various reviews have examined interventions for couples with unexplained infertility (Athaullah 2002; Gunn 2016; Hughes 2010; Pandian 2015; Veltman-Verhulst 2016). These reviews have included head-to-head comparisons of two interventions. Given that no large randomised controlled trials (RCTs) have compared all these available treatments, it is still uncertain which one is the most effective and safe option. Network meta-analysis could synthesise and interpret the wider picture of existing evidence by incorporating both direct and indirect evidence of different interventions. This approach can also identify gaps in research that need to be addressed in the future.

OBJECTIVES

To evaluate the effectiveness and safety of different approaches of clinical management (expectant management, OS, IUI, OS-IUI, and IVF/ICSI) in couples with unexplained infertility.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) comparing the effectiveness and/or safety of one of the interventions versus the other intervention. We excluded quasi-randomised and non-randomised studies. Cross-over trials were included, but only data from the first phase were used.

Types of participants

Couples who had been trying to conceive for at least one year, women having at least one patent fallopian tube and an ovulatory cycle, and men having a pre-wash total motile sperm count > 3 * 10^6 were eligible. Among women with a diagnosis of endometriosis, only those with mild endometriosis (American Fertility Society (AFS) criteria I) were included.

Types of interventions

We considered all trials that compared at least two of the following clinical management options.

- Expectant management, including timed intercourse.

- OS using gonadotropins, aromatase inhibitors, anti-oestrogens, or their combination.
- IUI without ovarian stimulation.
- OS-IUI.
- IVF with a single embryo transfer, with a double embryo transfer, or combined with ICSI.

Expectant management and timed intercourse were combined in the same group if no invasive techniques were used. Studies comparing different OS protocols were excluded and those comparing OS with different protocols were pooled as one OS group. The five proposed interventions were jointly randomisable (i.e. a couple with unexplained infertility is theoretically able to be randomised to any of the five interventions). ICSI was not considered as a separate intervention, as it is indicated for couples with severe male factor infertility or with fertilisation failure in previous IVF cycles. Therefore, ICSI was not jointly randomisable with the other interventions and including ICSI will violate the transitivity assumption in this network meta-analysis. Moreover, trials including IVF as an intervention often also applied ICSI for couples with unexpected low sperm count on the day of oocyte retrieval, or with previous IVF failure in a multi-cycle intervention; therefore IVF with and without ICSI was considered as the same intervention. Studies with an embryo transfer policy allowing transfer of more than two embryos in an unselected population were included in the systematic review but were excluded from the network meta-analysis to make the transitivity assumption valid. Natural cycle IVF and modified natural cycle IVF were not included, as they are not comparable to other IVF protocols.

Types of outcome measures

Primary outcomes

- The primary effectiveness outcome was a composite of cumulative live birth or ongoing pregnancy per woman randomised. Live birth was defined as the birth of a living child after 24 weeks of gestation. Ongoing pregnancy was defined as at least one registered embryonic heartbeat on ultrasound at 12 weeks' gestation and was used in the analysis only when live birth was not reported. Cumulative refers to multiple attempts to achieve a live birth (i.e. multiple cycles of treatments). In IVF, cumulative refers to fresh embryo transfer followed by frozen embryo transfer cycles when applicable
- The primary safety outcome was multiple pregnancy per woman randomised (defined as at least two registered embryonic heartbeats on ultrasound)

Secondary outcomes

- Clinical pregnancy per woman randomised (defined as at least one registered embryonic heartbeat on ultrasound)
- Moderate/severe ovarian hyperstimulation syndrome (OHSS) per woman randomised (defined as moderate abdominal pain, nausea ± vomiting, the presence of ascites on ultrasound or clinical ascites, and ovarian size of at least 8 cm) (Mathur 2005)

Search methods for identification of studies

We searched for all published and unpublished RCTs, without language or date restrictions, in consultation with the Cochrane Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We searched the following electronic databases for relevant trials.

- The Cochrane Gynaecology and Fertility Group (CGF) Specialised Register of Controlled Trials, searched 6 September 2018 (Procite platform) (Appendix 1).
- The Cochrane Central Register of Studies Online, searched 6 Sptember 2018 (CRSO Web platform) (Appendix 2).
- MEDLINE, searched from 1946 to 6 September 2018 (Ovid platform) (Appendix 3).
- Embase, searched from 1980 to 6 September 2018 (Ovid platform) (Appendix 4).
- PsycINFO, searched from 1806 to 6 September 2018 (Ovid platform) (Appendix 5).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL), searched from 1961 to 6 September 2018 (Ebsco platform) (Appendix 6).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appeared in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0, Chapter 6, 6.4.11). Embase, PsycINFO, and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials will include the following.

- Trial registers for ongoing and registered trials.
  - www.clinicaltrials.gov (a service of the US National Institutes of Health).
  - www.who.int/trialsearch/Default.aspx (the World Health Organization International Trials Registry Platform search portal).
- Virtual Health Library Regional Portal (VHL) (bvsalud.org/portal/?lang=en), which includes Latin American Caribbean Health Sciences Literature (LILACS).
- PubMed and Google Scholar (for recent trials not yet indexed in the major databases).

Searching other resources

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

Data collection and analysis

Selection of studies

At least two review authors (from RW, RIT, NAD) independently assessed trial eligibility, according to the Criteria for considering studies for this review. We resolved disagreements through discussion with another review author (MvW). We drew a PRISMA flow diagram to show the results of the search and the numbers of included and excluded trials. Reasons for excluding from the (network) meta-analysis any potentially eligible studies identified by the search were documented.

Data extraction and management

For all included trials, two review authors (RW, NAD) independently extracted data using a data abstraction form and summarised trial characteristics in tables. From each included study, two review authors (RW, NAD) extracted baseline characteristics of couples, study settings, methods, types of interventions (used dose, type of preparation, regimen, co-interventions), and outcomes. We intended to contact the study investigators for further data on methods and results, if required.

Assessment of risk of bias in included studies

Two review authors (RW, NAD) independently assessed risk of bias for each eligible study by using the Cochrane 'Risk of bias' assessment tool (Higgins 2011), which included six domains: 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. Disagreements were resolved by discussion with a third review author (MvW). We described all judgements fully and presented our conclusions in the 'Risk of bias' table, which we incorporated into the interpretations of review findings by performing sensitivity analyses.

Measures of treatment effect

As all outcomes involved dichotomous data, we used the numbers of events in control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). We presented 95% confidence intervals (CIs) for all outcomes. Furthermore, we calculated the probability that an intervention was ranked first, second, and so on. We displayed this ranking graphically in cumulative rankograms for the primary and secondary outcomes using the surface under the cumulative ranking (SUCRA), where SUCRA values can range from zero (i.e. the intervention is certain to be the worst) to one (i.e. the intervention is certain to be the best) (Salanti 2011).

Unit of analysis issues

The primary unit of analysis was cumulative rates for each outcome per woman randomised. Multiple births were counted as one live birth event. Only first-phase data from cross-over trials were included. Trials comparing the same number of cycles/months of expectant management, OS, IUI, and OS-IUI were included. As one cycle of IVF takes longer than the other treatments, studies comparing the same cycles of IVF and other treatments were not included in the network meta-analysis but were included in the systematic review. Trials comparing IVF and other treatments within the same period of time were included in the network meta-analysis.

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 existing Cochrane Reviews or from the original trialists. If data could not be obtained, we assumed the missing values as a non-event outcome and undertook imputation of individual values only for the primary outcome. For other outcomes, we analysed only available data. Any imputation undertaken was subjected to sensitivity analysis.

Assessment of heterogeneity

Clinical and methodological heterogeneity

To identify clinical and methodological heterogeneity, we compared descriptive statistics for trial and study population characteristics across all eligible trials comparing each pair of interventions. Additionally, we considered whether there was sufficient similarity in the studied interventions and the characteristics of couples across all included studies for inclusion in the network meta-analysis (i.e. the assumption of transitivity in network meta-analyses). We explored the distribution of potential effect modifiers across various interventions (i.e. female age, and duration of infertility). In this study, we expected the transitivity assumption to hold true assuming the following.

- The nature of the common intervention used for indirect comparisons was consistent (e.g. IUI in an RCT comparing IUI with expectant management was the same as IUI in an RCT comparing IUI with IVF/ICSI).
- All pairwise comparisons did not differ with respect to the distribution of effect modifiers (e.g. design and study characteristics of an RCT comparing IUI vs expectant management were similar to those of an RCT comparing IUI vs IVF/ICSI).

Statistical heterogeneity and inconsistency

Within each pairwise comparison, we assessed statistical heterogeneity by using the I^2 statistic. An I^2 value greater than 50% was taken as an indication of substantial heterogeneity (Higgins 2011).

In the network meta-analysis, we assessed inconsistency in the network through two approaches: the design-by-treatment method for global approach (Higgins 2012), and the side-splitting method for local approach (Dias 2010). The design-by-treatment interaction model allowed for global statistical testing for the presence of inconsistency in the whole network (Higgins 2012). The local approach identified disagreements between direct and indirect comparisons within each comparison within closed loops in the network (Dias 2010).

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. If we included ten or more studies in an analysis, we used a comparison-adjusted 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) (Chaimani 2013).

Data synthesis

We compared interventions using odds ratios (ORs) with their respective 95% confidence intervals (CIs). If more than two studies compared the same treatments, a random-effects summary OR was calculated in a pairwise meta-analysis.

We conducted a network meta-analysis based on all investigated comparisons between treatments, in which the indirect analysis was performed by utilising all pathways within the network. An indirect estimate of A versus B can be calculated by comparing

direct comparisons of A versus C with comparisons of B versus C. In this way, the OR for comparing A and B can be calculated using the following principle: ln(ORAvsB) = ln(ORAvsC) − ln(ORBvsC). We performed a frequentist network meta-analysis within a random-effects multi-variate meta-analysis model (White 2015). We assumed a common estimate for the heterogeneity variance across the different comparisons. We used Review Manager (version 5.3, The Cochrane Collaboration) for pairwise meta-analyses and Stata software (version 15.1, Statacorp) for network meta-analyses (Chaimani 2015; White 2015).

Subgroup analysis and investigation of heterogeneity

If data were available from at least two studies, we conducted subgroup analyses for the primary outcomes only to determine the separate evidence within the following subgroups.

- Women aged ≦ 38 years versus women aged > 38 years.
- Short duration of infertility （≦ 2 years) versus long duration of infertility (> 2 years).
- IVF/ICSI with single embryo transfer policy and IVF/ICSI with non-single embryo transfer policy.

Sensitivity analysis

We conducted sensitivity analyses for live birth/ongoing 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 with no domains at high risk of bias;
- alternative imputation strategies had been implemented;
- eligibility had varied by publication type (abstract vs full text); or
- only studies with the outcome live birth had been included.

Overall certainty of the body of evidence: 'Summary of findings' table

We presented overall certainty of the body of evidence for the main review outcomes for each comparison in 'Summary of findings' tables. We evaluated the overall certainty of the evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in line with a framework developed by Salanti and colleagues in an online tool - Confidence in Network Meta-analysis (CINeMA) (CINeMA 2017; Salanti 2014). Domains included study limitations (risk of bias), inconsistency, imprecision, indirectness, and publication bias. For study limitations, we incorporated the contribution of each direct estimate into the overall network estimate when making judgements of study limitations. As blinding was not possible due to the nature of the interventions, we did not downgrade overall certainty if performance bias was the only issue in study limitations. For inconsistency, we evaluated both between-study heterogeneity and disagreements between direct and indirect evidence (i.e. incoherence). We evaluated heterogeneity by considering the agreement of conclusions based on confidence and prediction intervals in relation to the clinically important effect size, in which the major consideration was whether heterogeneity impacts clinical decisions. If heterogeneity (presented in a prediction interval) impacted decision-making based on a confidence interval, we downgraded the certainty of evidence. We evaluated incoherence by assessing local and global inconsistency. For comparisons with local inconsistency, we downgraded the level of certainty in relevant comparisons. Judgements about evidence certainty (high, moderate, low, or very low) were justified, documented, and incorporated into the reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The initial electronic database search yielded 2095 articles, with nine additional articles identified through handsearches or searches of trial registers. After removing duplicates, we screened 1171 studies. Screening of titles and abstracts led to the exclusion of 1111 irrelevant studies; 60 full-text articles were further assessed for eligibility. Another 23 studies were further excluded, including five ongoing studies (NCT01992731; NCT02461173; NCT03455426; NTR5599; NCT02001870). Finally, 27 studies fulfilled the inclusion criteria as shown in Figure 1 (Agarwal 2004; Arcaini 1996; Arici 1994; Bensdorp 2015; Bhattacharya 2008; Crosignani 1991; Custers 2011; Deaton 1990; Elzeiny 2014; Farquhar 2017; Fisch 1989; George 2006; Glazener 1990; Goldman 2014; Goverde 2000; Guzick 1999; Harrison 1983; Ho 1998; Hughes 2004; Janko 1998; Karlstrom 1993; Kirby 1991; Leanza 2014; Martinez 1990; Melis 1995; Nandi 2017; Steures 2006). See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Figure 1. Study flow diagram.

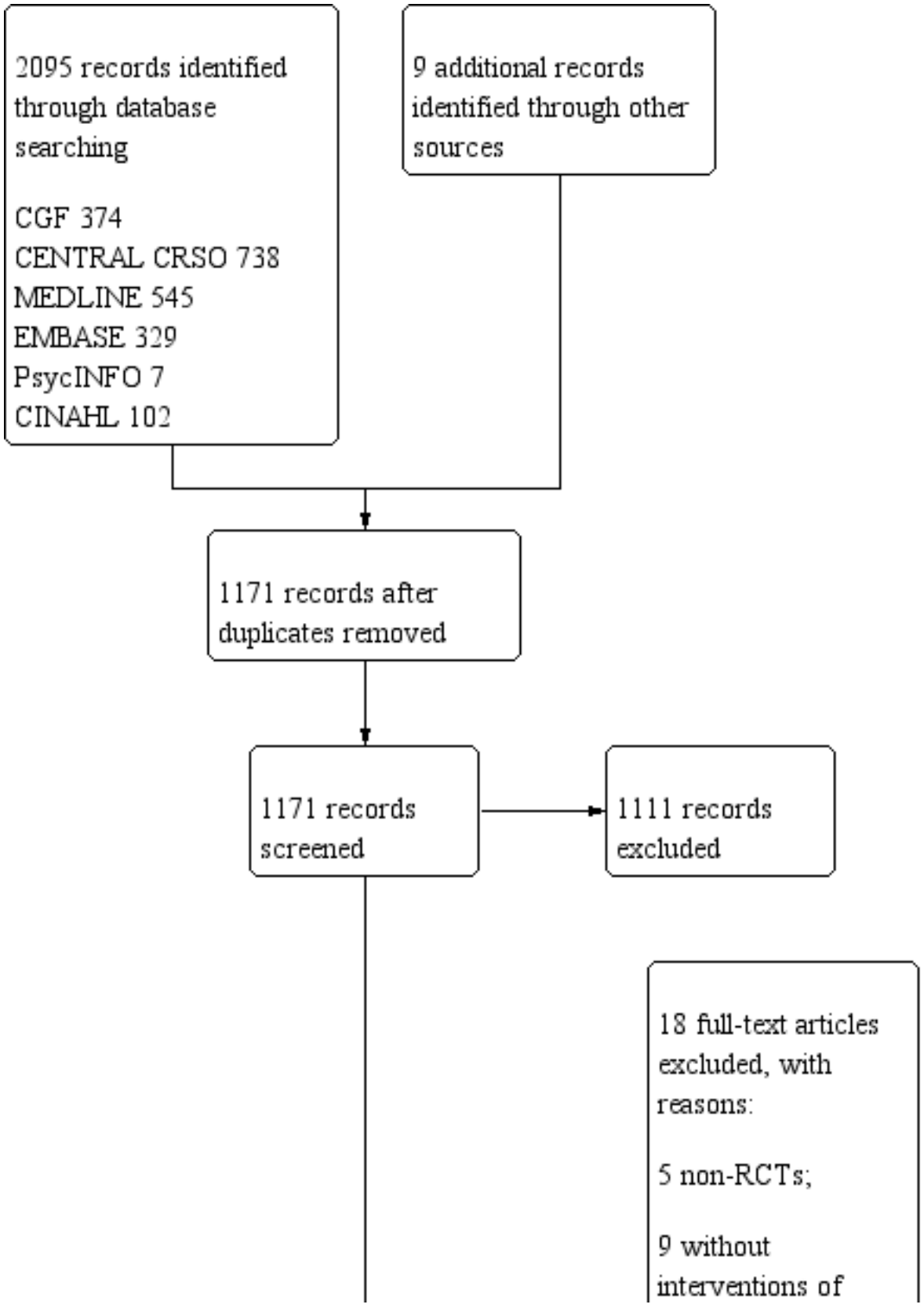
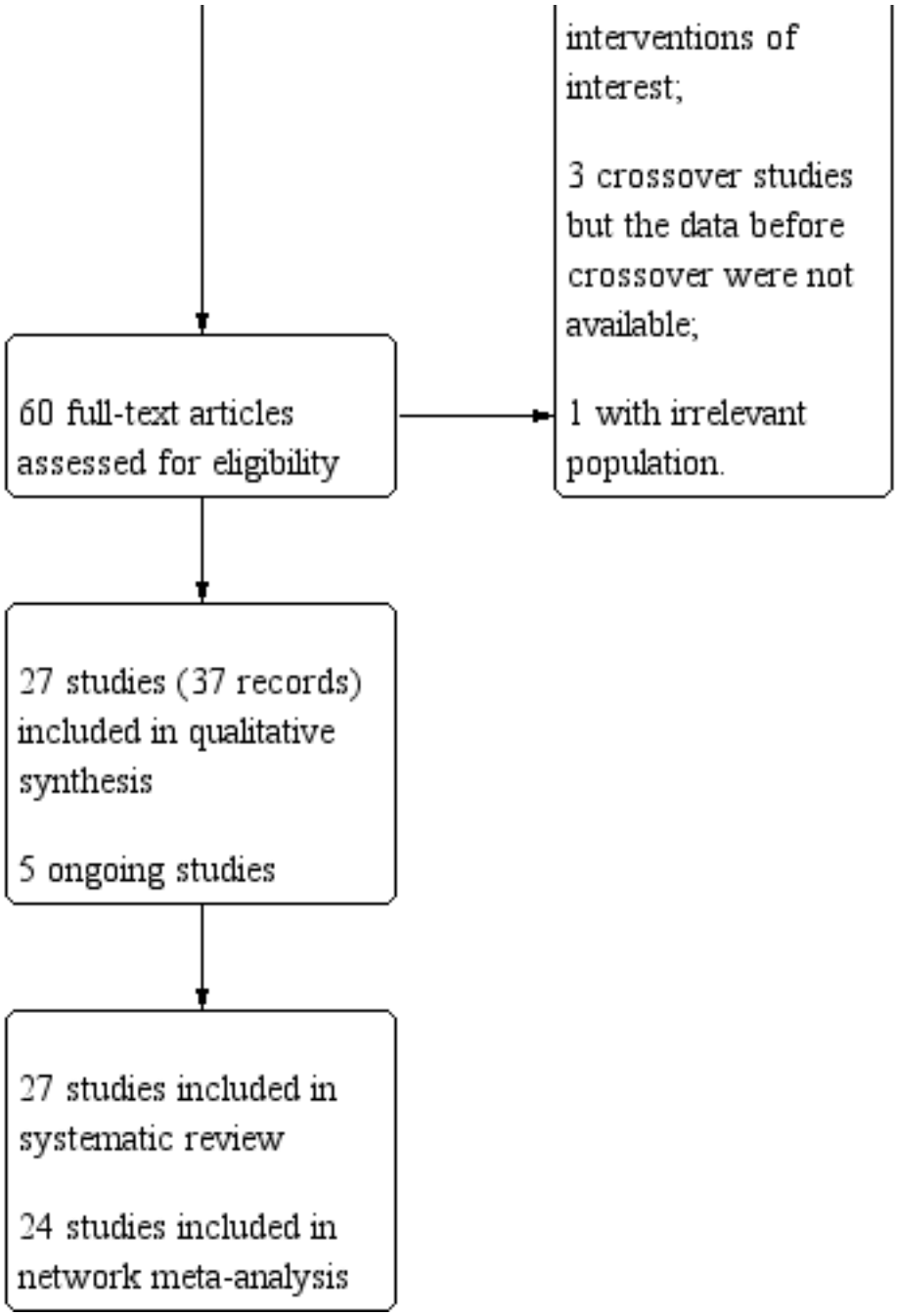


Figure 1. (Continued)



Included studies

Study design and setting

Of the 27 RCTs reporting on 4349 couples included in this systematic review, 21 had a parallel design (Agarwal 2004; Arcaini 1996; Bensdorp 2015; Bhattacharya 2008; Custers 2011; Elzeiny 2014; Farquhar 2017; Fisch 1989; George 2006; Goldman 2014; Goverde 2000; Guzick 1999; Ho 1998; Hughes 2004; Janko 1998; Karlstrom 1993; Kirby 1991; Leanza 2014; Melis 1995; Nandi 2017; Steures 2006), and the other six were cross-over studies (Arici 1994; Crosignani 1991; Deaton 1990; Glazener 1990; Harrison 1983; Martinez 1990). These studies were conducted in a variety of countries, including Netherlands (n = 5; Bensdorp 2015; Custers 2011; Goverde 2000; Martinez 1990; Steures 2006), USA (n = 4; Arici 1994; Deaton 1990; Goldman 2014; Guzick 1999), Italy (n = 3; Arici 1994; Leanza 2014; Melis 1995), UK (n = 3, Bhattacharya 2008; Glazener 1990; Nandi 2017), Australia (n = 2; Elzeiny 2014; Kirby 1991), Canada (n = 2; Fisch 1989; Hughes 2004), India (n = 2; Agarwal 2004; George 2006), China (n = 1; Ho 1998), New Zealand (n = 1; Farquhar 2017), Ireland (n = 1; Harrison 1983), Sweden (n = 1; Karlstrom 1993), and Slovakia (n = 1; Janko 1998). One study was conducted in a multi-country setting in Europe (Crosignani 1991).

Participants

These studies included 4349 couples with unexplained infertility. The mean female age across included studies ranged from 32 to 37 years, with most studies reporting a mean age younger than 35 years. The median or mean duration of infertility across included studies ranged from 23 to 78 months.

Interventions

One four-arm RCT compared expectant management, OS, IUI, and OS-IUI (Martinez 1990). We identified three three-arm RCTs: one compared expectant management, OS, and IUI (Bhattacharya 2008); another compared OS, OS-IUI, and IVF/ICSI (Crosignani 1991); and the third compared IUI, OS-IUI, and IVF/ICSI (Goverde 2000). The other 23 studies were two-arm studies. These studies compared OS versus expectant management (Fisch 1989; George 2006; Glazener 1990; Harrison 1983), IUI versus expectant management (Kirby 1991), OS-IUI versus expectant management (Deaton 1990; Farquhar 2017; Steures 2006), IVF/ICSI versus expectant management (Hughes 2004), OS-IUI versus OS (Agarwal 2004; Arcaini 1996; Ho 1998; Janko 1998; Karlstrom 1993; Melis 1995), OS-IUI versus IUI (Arici 1994; Leanza 2014; Guzick 1999), and IVF/ICSI versus OS-IUI (Bensdorp 2015; Custers 2011; Elzeiny 2014; Goldman 2014; Nandi 2017).

For RCTs comparing OS-IUI, IUI, and OS versus expectant management or each other, all compared the same number of cycles of different interventions - one cycle in five RCTs (Arici 1994; Crosignani 1991; Karlstrom 1993; Kirby 1991; Martinez 1990), three cycles in seven RCTs (Farquhar 2017; George 2006; Glazener 1990; Ho 1998; Janko 1998; Leanza 2014; Melis 1995), four cycles in three RCTs (Deaton 1990; Fisch 1989; Guzick 1999), five cycles in one RCT (Arcaini 1996), and six cycles in five RCTs (Agarwal 2004; Bhattacharya 2008; Goverde 2000; Harrison 1983; Steures 2006).

For RCTs comparing IVF/ICSI with other interventions, Hughes 2004 compared one cycle of IVF/ICSI versus three cycles of expectant management within 90 days; Bensdorp 2015 compared three cycles of IVF/ICSI versus six cycles of OS-IUI within 12 months; Custers 2011 compared one cycle of IVF/ICSI versus three cycles of OS-IUI within four months; and Nandi 2017 compared one cycle of IVF/ICSI versus three cycles of OS-IUI within six months. The other RCTs compared the same number of cycles of IVF versus other interventions without time limits: Crosignani 1991 compared one cycle of IVF/ICSI with one cycle of OS and OS-IUI; Elzeiny 2014 compared one cycle of IVF/ICSI versus one cycle of OS-IUI; Goldman 2014 compared two cycles of IVF/ICSI versus two cycles of OS-IUI; and Goverde 2000 compared six cycles of IVF/ICSI, six cycles of OS-IUI, and six cycles of IUI.

Elective or compulsive single embryo transfer policy was applied in three RCTs (Bensdorp 2015; Custers 2011; Nandi 2017). ICSI was used in three RCTs, only for couples with fertilisation failure in previous IVF or unexpected low sperm count on the day of oocyte retrieval (Bensdorp 2015; Goldman 2014; Nandi 2017).

Outcomes

Thirteen RCTs reported live birth (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Elzeiny 2014; Farquhar 2017; George 2006; Goldman 2014; Goverde 2000; Guzick 1999; Hughes 2004; Melis 1995; Nandi 2017; Steures 2006), and 14 RCTs reported multiple pregnancy (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Deaton 1990; Elzeiny 2014; Farquhar 2017; George 2006; Glazener 1990; Goldman 2014; Goverde 2000; Ho 1998; Melis 1995; Nandi 2017; Steures 2006). Twenty-six studies reported clinical pregnancy (Agarwal 2004; Arcaini 1996; Arici 1994; Bensdorp 2015; Bhattacharya 2008; Crosignani 1991; Custers 2011; Deaton 1990; Elzeiny 2014; Farquhar 2017; Fisch 1989; George 2006; Glazener 1990; Goldman 2014; Guzick 1999; Harrison 1983; Ho 1998; Hughes 2004; Janko 1998; Karlstrom 1993; Kirby 1991; Leanza 2014; Martinez 1990; Melis 1995; Nandi 2017; Steures 2006). Eight studies reported moderate/severe OHSS as an outcome (Bensdorp 2015; Deaton 1990; Elzeiny 2014; Goldman 2014; Goverde 2000; Ho 1998; Melis 1995; Nandi 2017).

Excluded studies

We excluded 18 studies from the review for the following reasons (Figure 1): five were non-RCTs (Fujii 1997; Nulsen 1993; Prentice 1995; Tjon Kon Fat 2014; Zayed 1997); nine did not include interventions of interest (Buvat 1993; Chung 1995; Goldman 2010; Leanza 2014a; Melis 1987; Murdoch 1991; Reindollar 2010; Shokeir 2006; Soliman 1993); three were cross-over studies but the data before cross-over were not available (Gregoriou 1995; Martinez 1991; Zikopoulos 1993); and one had an irrelevant population (i.e. included women with polycystic ovary syndrome) (Zolghadri 2012).

We identified five ongoing studies from Belgium (NCT01992731), China (NCT03455426), Egypt (NCT02461173), France (NCT02001870), and Netherlands (NTR5599), respectively.

Risk of bias in included studies

Allocation

Sequence generation

As shown in Figure 2 and Figure 3, 12 studies reported adequate methods for random sequence generation and therefore were rated as low risk of bias in sequence generation (Agarwal 2004; Arici 1994; Bensdorp 2015; Bhattacharya 2008; Custers 2011; Elzeiny 2014; Farquhar 2017; Fisch 1989; George 2006; Goverde 2000; Nandi 2017; Steures 2006). The other 16 studies did not describe the method used and were rated as unclear risk for this domain.

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

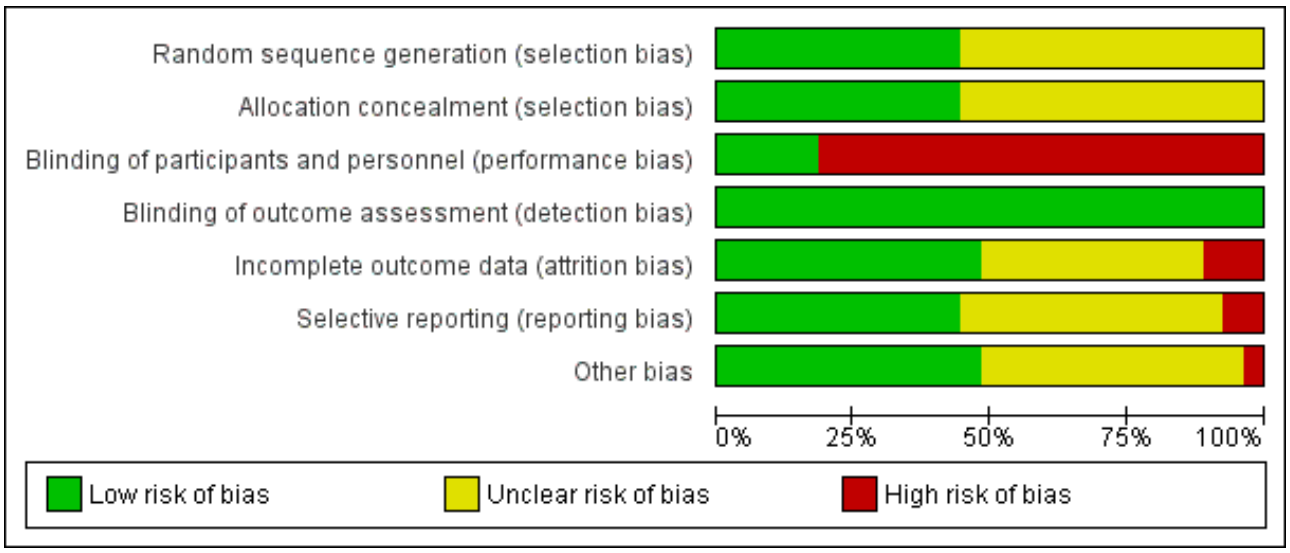
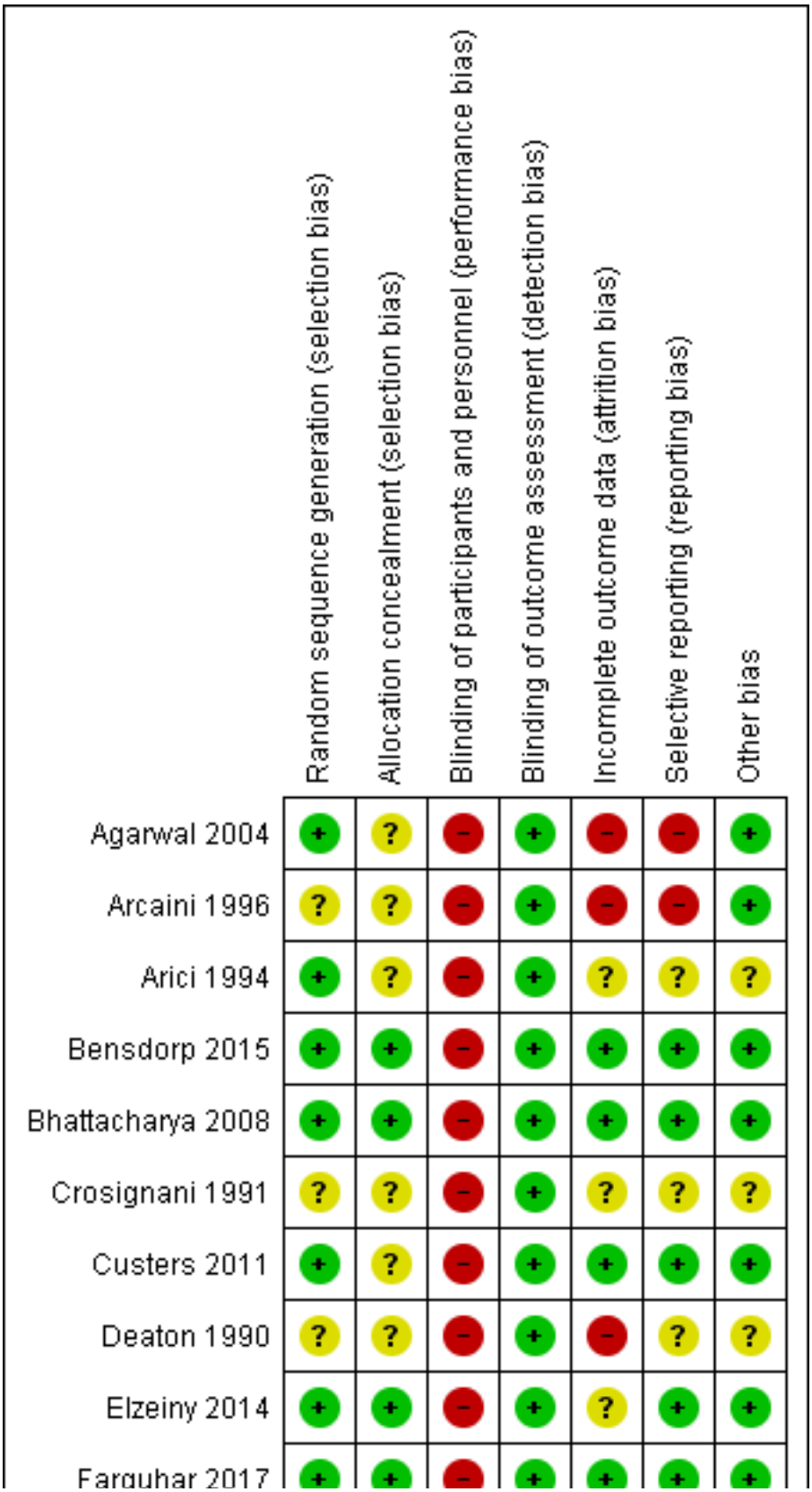


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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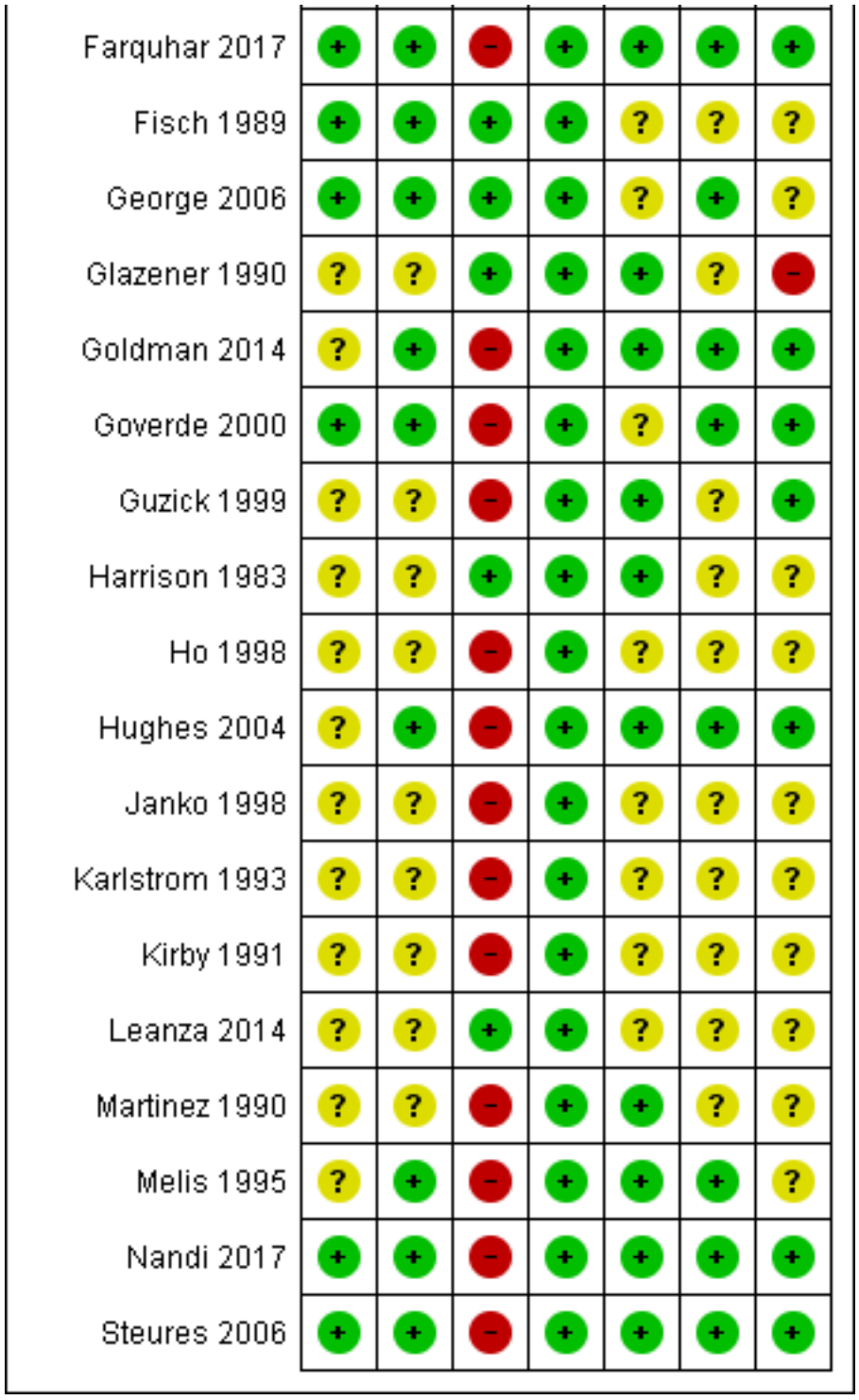


Allocation concealment

Twelve studies described adequate methods for allocation concealment (Bensdorp 2015; Bhattacharya 2008; Elzeiny 2014; Farquhar 2017; Fisch 1989; George 2006; Goldman 2014; Goverde 2000; Hughes 2004; Melis 1995; Nandi 2017; Steures 2006), and the other 16 studies did not describe methods of allocation concealment and were scored as unclear risk of bias for this domain.

Blinding

Blinding of participants and personnel (performance bias)

Five studies were rated as low risk of performance bias as placebos were used (Fisch 1989; George 2006; Glazener 1990; Harrison 1983;

Leanza 2014). The remaining studies were rated as high risk of performance bias as they were not blinded, although blinding was not possible due to the nature of the interventions.

Blinding of outcome assessors (detection bias)

Given that our outcomes of interest were objective outcomes, we considered that blinding was unlikely to impact these outcomes. Therefore, all studies were rated as low risk of detection bias.

Incomplete outcome data

Three studies had 19%, 20%, and 21% incomplete outcome data, respectively, and therefore were rated as high risk of attrition bias (Agarwal 2004; Arcaini 1996; Deaton 1990). Thirteen studies had low risk of attrition bias (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Farquhar 2017; Glazener 1990; Goldman 2014; Guzick 1999; Harrison 1983; Hughes 2004; Martinez 1990; Melis 1995; Nandi 2017; Steures 2006), and the other 11 studies were scored as unclear risk.

Selective reporting

Two studies did not report the outcome data for each group separately and were rated as high risk of reporting bias (Agarwal 2004; Arcaini 1996). Twelve studies reported both live birth and multiple pregnancy and were rated as low risk of reporting bias (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Elzeiny 2014; Farquhar 2017; George 2006; Goldman 2014; Goverde 2000; Hughes 2004; Melis 1995; Nandi 2017; Steures 2006). The other 14 studies were scored as unclear risk.

Other potential sources of bias

There was disagreement on the number of participants in the methods and results sections in one study and this was rated as high risk of bias (Glazener 1990). Thirteen studies were scored as low risk of other bias (Agarwal 2004; Arcaini 1996; Bensdorp 2015; Bhattacharya 2008; Custers 2011; Elzeiny 2014; Farquhar 2017; Goldman 2014; Goverde 2000; Guzick 1999; Hughes 2004; Nandi 2017; Steures 2006). The other 14 studies were scored as unclear risk.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings - live birth or ongoing pregnancy; **Summary of findings 2** Summary of findings - multiple pregnancy; **Summary of findings 3** Summary of findings - clinical pregnancy; **Summary of findings 4** Summary of findings - moderate/severe OHSS

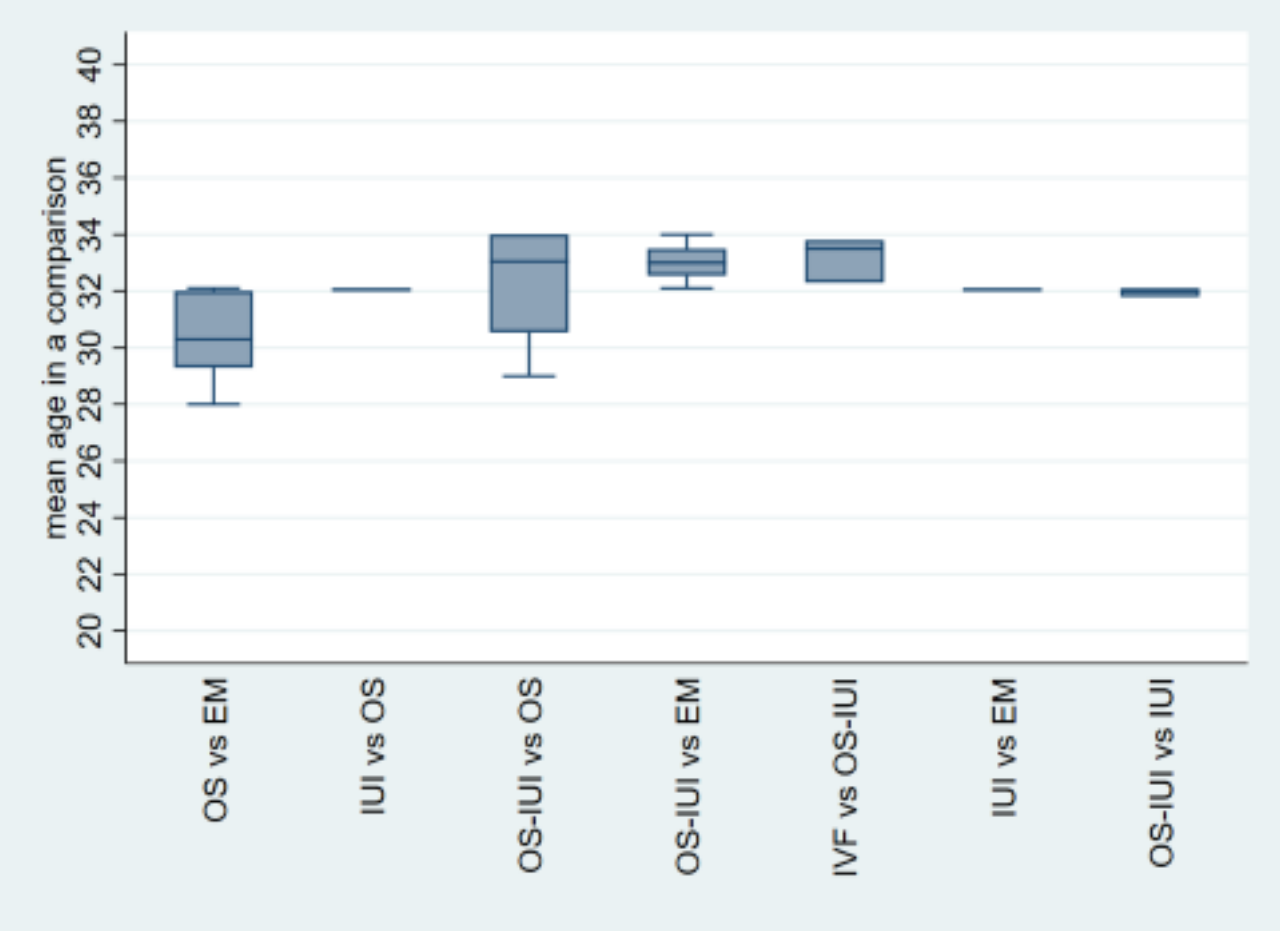
Network meta-analysis

Based on above-mentioned Unit of analysis issues, two RCTs - Elzeiny 2014; Goldman 2014 - and IVF/ICSI arms in two other RCTs - Crosignani 1991; Goverde 2000 - were excluded from this network meta-analysis, as these RCTs compared IVF/ICSI and other interventions in the same number of cycles. We further excluded Hughes 2004 from this network meta-analysis, as this RCT allowed transfer of up to four embryos. The remaining RCTs comparing IVF/ICSI all used single embryo transfer policy. Detailed data analyses for these five RCTs that were excluded from the network meta-analysis are presented in Analysis 3.1, Analysis 3.2, and Analysis 3.3. Finally, 24 RCTs reporting on 3983 couples with unexplained infertility were included in this network meta-analysis.

We observed high heterogeneity in the pairwise meta-analysis of OS-IUI and expectant management (EM) (I^2 = 91% for live birth). This is likely due to clinical heterogeneity among participants in the two included RCTs - Steures 2006 included couples with intermediate prognosis of natural conception, and Farquhar 2017 included couples with poor prognosis of natural conception. Both RCTs applied an existing prediction model to estimate the prognosis of natural conception (Hunault 2004). We included these RCTs in this network meta-analysis to estimate the average treatment effect in this comparison, and we downgraded the certainty of evidence due to heterogeneity based on criteria described in the methods. To further assess robustness of the evidence, we performed two additional post-hoc sensitivity analyses: excluding expectant management from the network; and limiting to RCTs including couples with poor prognosis of natural conception.

We assessed the transitivity assumption in this network meta-analysis by evaluating two potential effect modifiers: age and duration of infertility. The distribution of mean age in different studies across different comparisons is presented in Figure 4. The median value of mean age across different comparisons is around 32 years. Duration of infertility is very unlikely to be normally distributed; therefore reporting the mean seems inappropriate and can lead to overestimation of the median value. However, 10 RCTs reported mean duration of infertility (Agarwal 2004; Arcaini 1996; Arici 1994; Deaton 1990; Fisch 1989; Goverde 2000; Guzick 1999; Harrison 1983; Martinez 1990; Melis 1995), and seven other RCTs did not report median or mean duration of infertility (Crosignani 1991; George 2006; Ho 1998; Janko 1998; Karlstrom 1993; Kirby 1991; Leanza 2014). Therefore, it is impossible for us to assess the distribution of duration of infertility across different comparisons. However, as these five interventions are jointly randomisable for any participant with unexplained infertility, we considered the transitivity assumption valid.

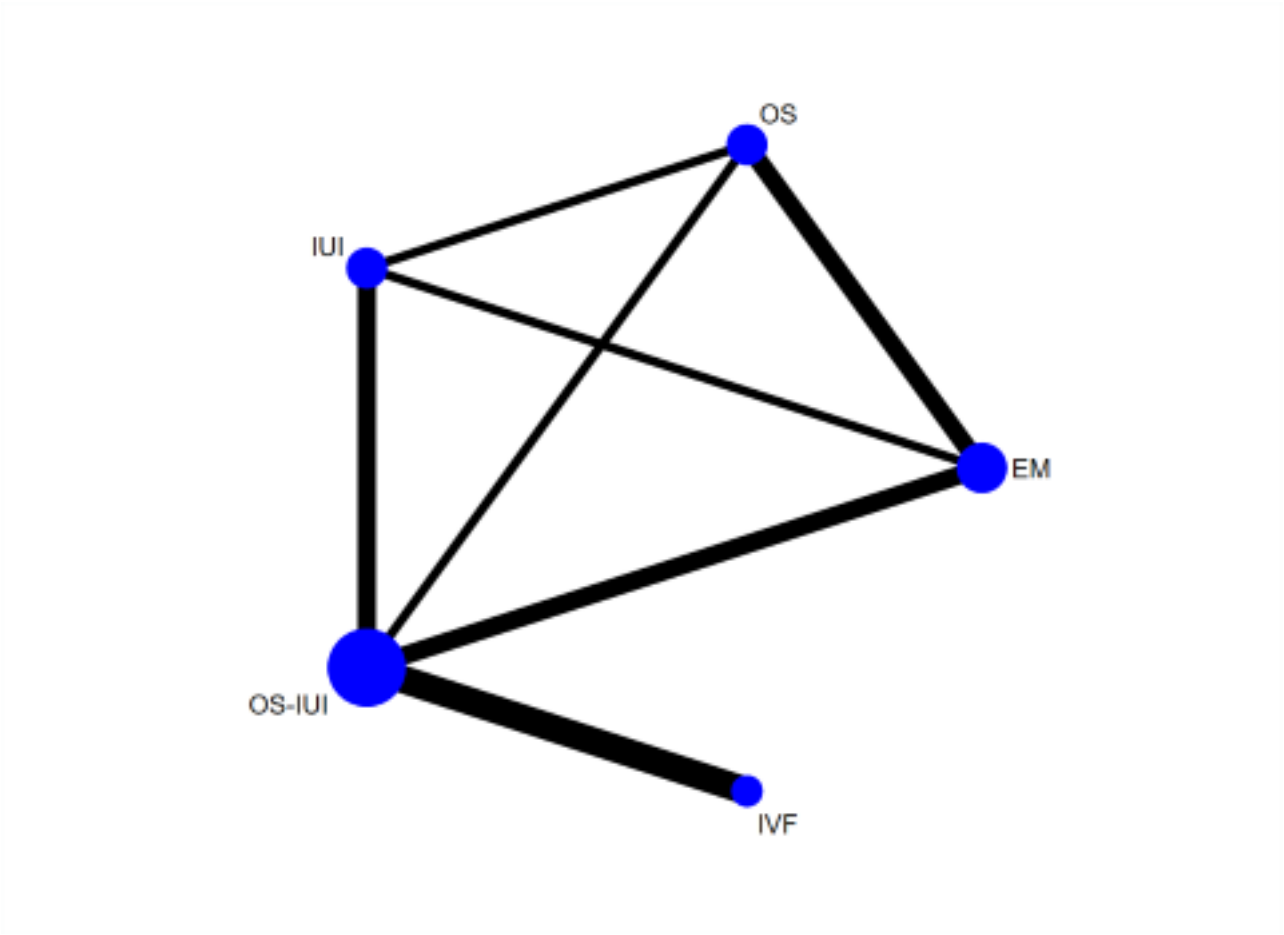
Figure 4. Box plot for the distribution of means of age in different studies across different comparisons.



Live birth

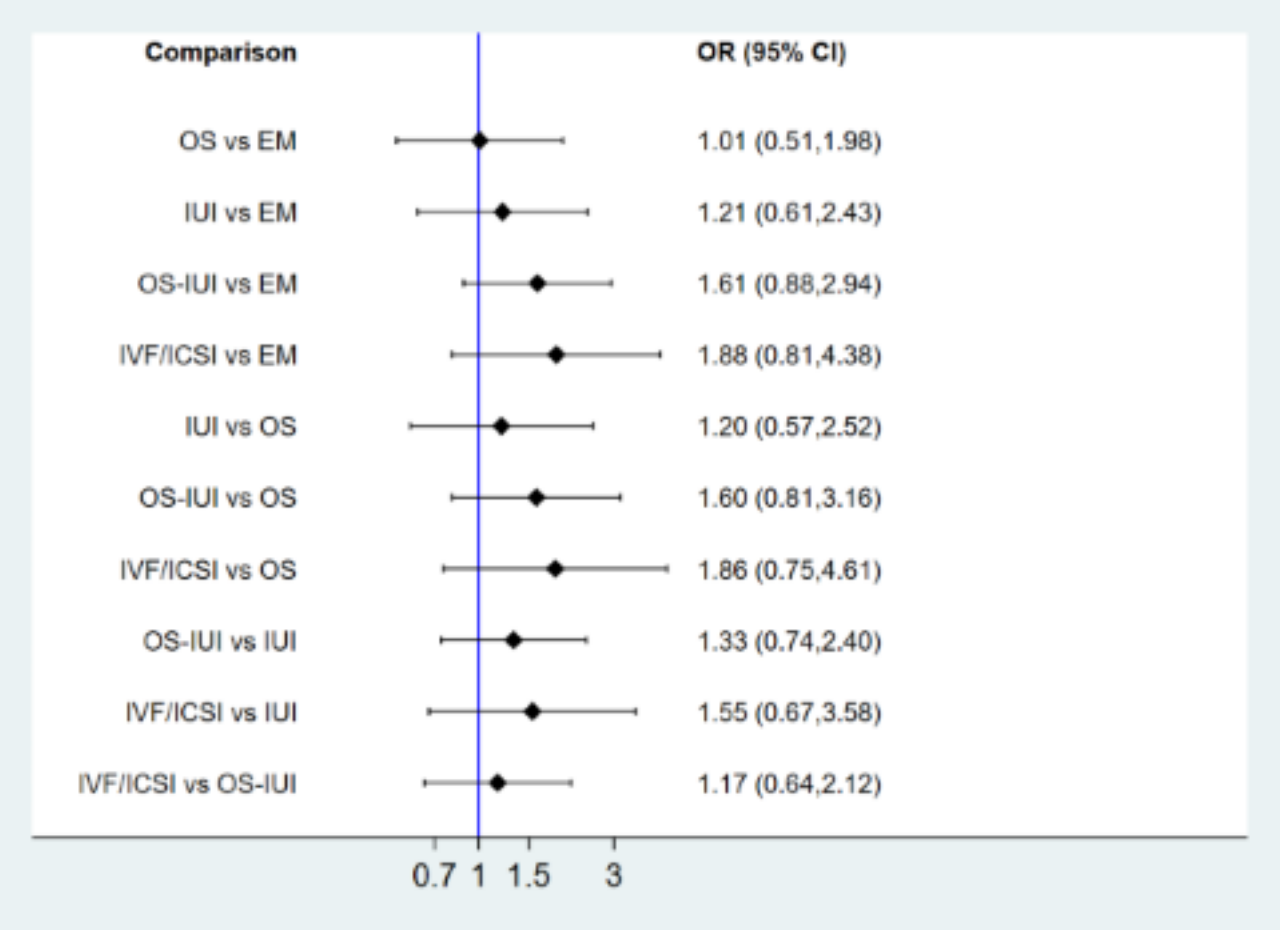
Ten studies reported live birth (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Farquhar 2017; George 2006; Goverde 2000; Guzick 1999; Melis 1995; Nandi 2017; Steures 2006). These RCTs included 2725 couples with unexplained infertility. A network plot for live birth is presented in Figure 5. Three RCTs compared IVF/ICSI versus OS-IUI (Bensdorp 2015; Custers 2011; Nandi 2017); two RCTs compared OS-IUI versus IUI (Goverde 2000; Guzick 1999); two RCTs compared OS versus expectant management (Bhattacharya 2008; George 2006); two RCTs compared OS-IUI versus expectant management (Farquhar 2017; Steures 2006); one RCT compared IUI versus expectant management (Bhattacharya 2008); and one RCT compared OS-IUI versus OS (Melis 1995).

Figure 5. Network plot for live birth. Each node represents an intervention, and the size of each node is proportional to the number of trials reporting such intervention. The widths of the lines are proportional to the numbers of trials comparing each pair of interventions.



The results of the network meta-analysis are shown in Figure 6. They showed insufficient evidence of a difference between OS, IUI, OS-IUI, or IVF/ICSI and expectant management (odds ratio (OR) 1.01, 95% confidence interval (CI) 0.51 to 1.98; low-certainty evidence; OR 1.21, 95% CI 0.61 to 2.43; low-certainty evidence; OR 1.61, 95% CI 0.88 to 2.94; low-certainty evidence; OR 1.88, 95% CI 0.81 to 4.38; low-certainty evidence). These data suggest that if the chance of live birth following expectant management is assumed to be 16.6%, the chance following OS, IUI, OS-IUI, and IVF would be 9.2% to 28.2%, 10.8% to 32.5%, 14.9% to 36.9%, and 13.9% to 46.5%, respectively.

Figure 6. Network meta-analysis for live birth. Each diamond represents the estimate summary odds ratio of each comparison; each horizontal line represents the confidence interval of each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the first intervention; odds ratio less than 1 favours the second intervention.



Evidence of a difference between IUI and OS (OR 1.20, 95% CI 0.57 to 2.52; low-certainty evidence), OS-IUI and OS (OR 1.60, 95% CI 0.81 to 3.16; low-certainty evidence), IVF/ICSI and OS (OR 1.86, 95% CI 0.75 to 4.61; low-certainty evidence), OS-IUI and IUI (OR 1.33, 95% CI 0.74 to 2.40; low-certainty evidence), IVF/ICSI and IUI (OR 1.55, 95% CI 0.67 to 3.58; low-certainty evidence), or IVF/ICSI and OS-IUI (OR 1.17, 95% CI 0.64 to 2.12; low-certainty evidence) was insufficient. Overall certainty of evidence in all comparisons was low due to concerns regarding imprecision and heterogeneity.

Results show no evidence of global inconsistency (P = 0.55) or local inconsistency in the network meta-analysis on live birth. The comparison-adjusted funnel plot seems symmetrical, implying the absence of small study effects in this network (Figure 7). Cumulative rankograms illustrate the probability per rank for each treatment in terms of live birth (Figure 8). The SUCRA values for expectant management, OS, IUI, OS-IUI, and IVF/ICSI were 23.1%, 24.1%, 43.7%, 74.2%, and 85.0%, respectively. This suggests that among all interventions, IVF/ICSI is more likely to result in more live births than the other interventions, followed by OS-IUI, IUI, OS, and expectant management.

Figure 7. Comparison-adjusted funnel plot for live birth. (A: expectant management; B: OS; C: IUI; D: OS-IUI; E: IVF/ICSI.)

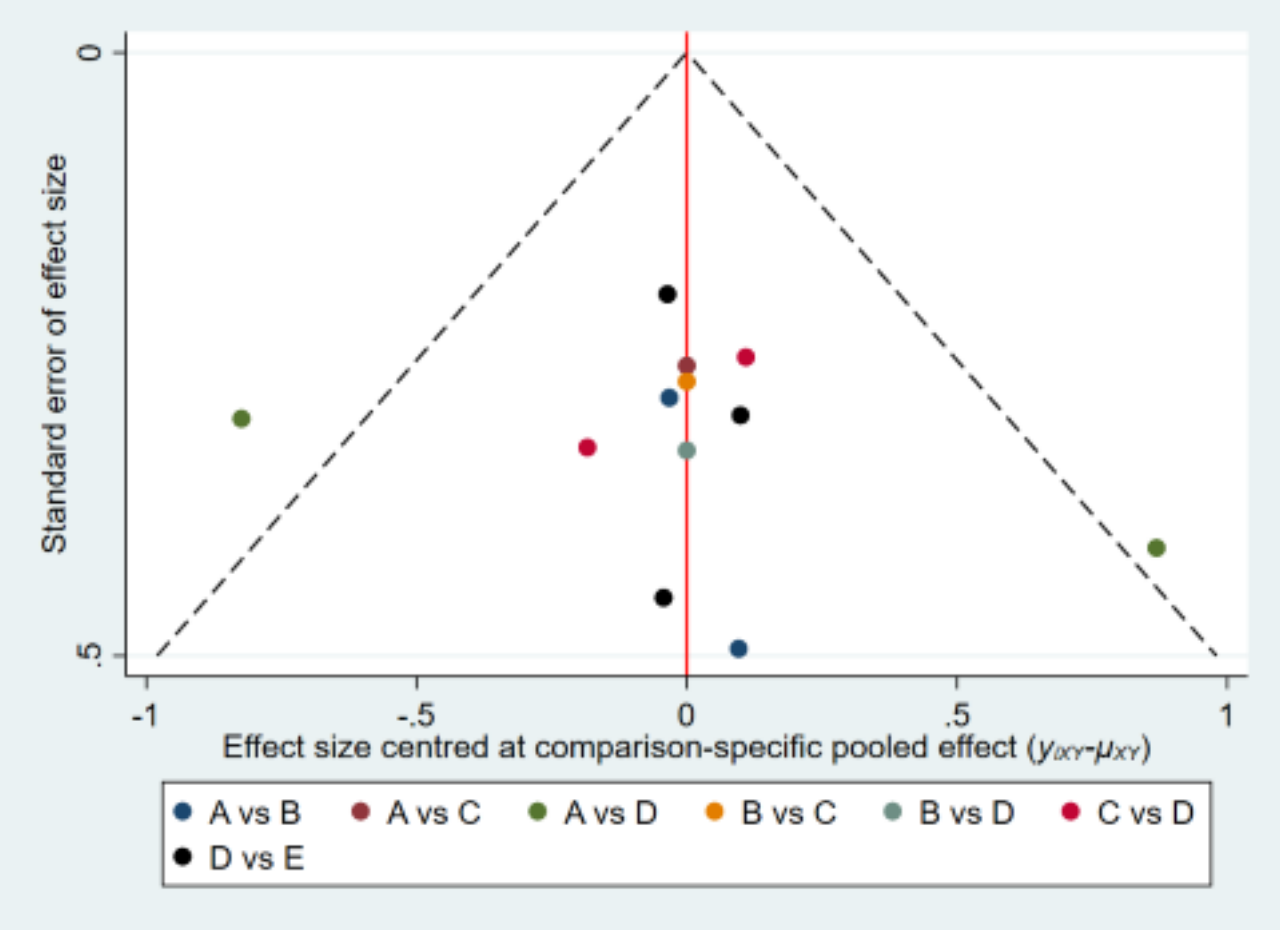
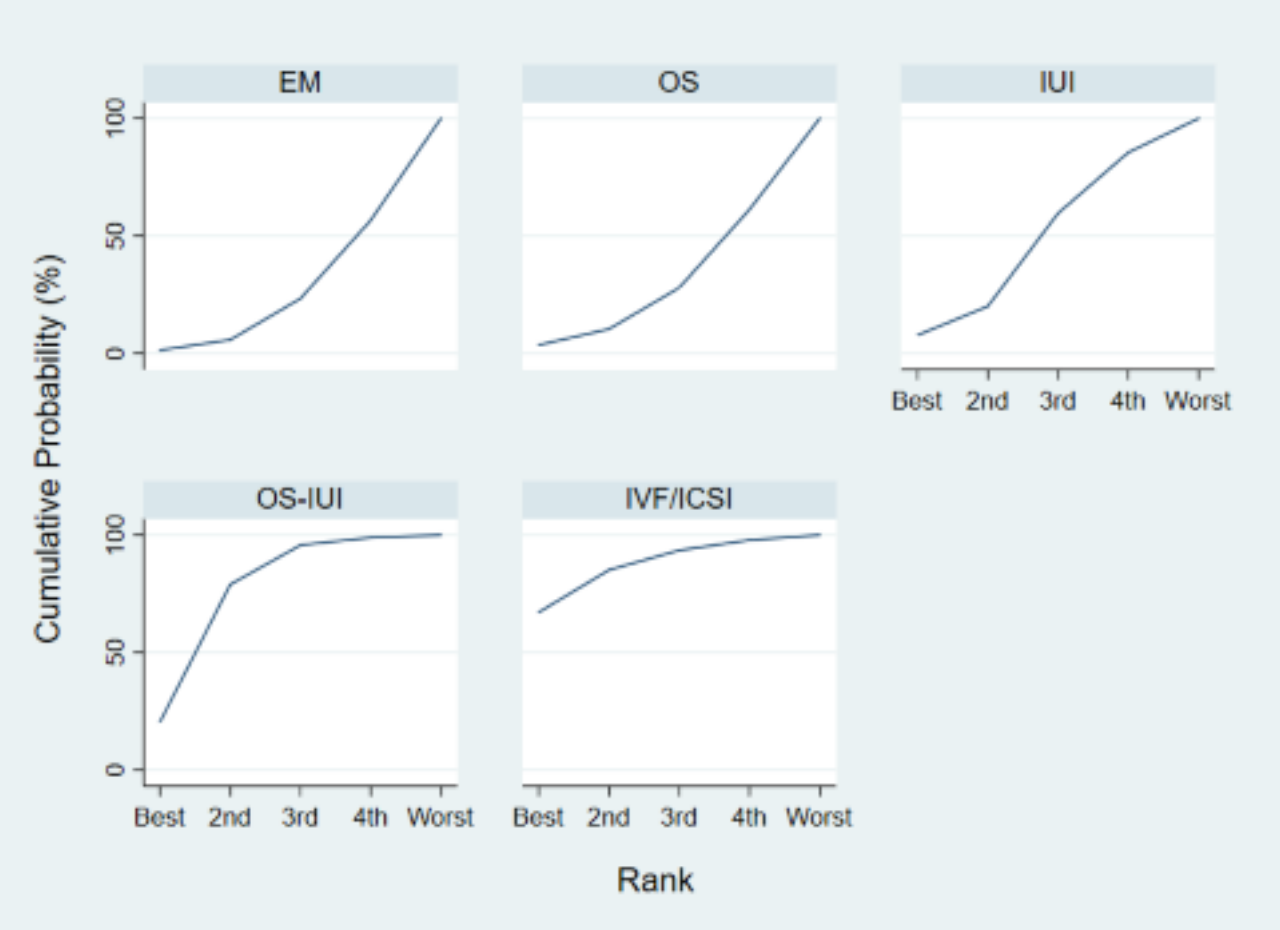


Figure 8. Cumulative rankograms of interventions for live birth. Each cumulative rankogram illustrates the cumulative probability of each ranking (from the best to the worst rank) for each intervention in terms of live birth.



Results of pairwise meta-analyses are presented in Analysis 1.1. Overall, results were consistent with those in network meta-analysis. As most comparisons included a very limited number of studies, wide confidence intervals were observed in all comparisons, implying imprecision of the evidence.

Subgroup analyses

Women ≤ 38 years versus women > 38 years

One RCT did not report details of age in the inclusion criteria or results (George 2006), and the other RCTs all reported a mean age < 35 years. As the breakdown data for women in different age groups were not available, this subgroup analysis was not performed.

Short duration of infertility (≤ 2 years) versus long duration of infertility (> 2 years)

As the breakdown data for women in different age groups were not available, we used median duration of infertility in different RCTs for this subgroup analysis. Therefore this subgroup analysis should be interpreted with caution, given that it was not based on the breakdown data for different groups.

One study did not report details of the duration of infertility in the inclusion criteria or the results (George 2006); therefore we excluded this study from the subgroup analysis. Two studies included couples with a median or mean duration of infertility ≤ 2 years (Nandi 2017; Steures 2006). One compared IVF/ICSI versus OS-IUI (Nandi 2017), and the other compared IVF/ICSI versus expectant management (Steures 2006). Network meta-analysis is presented in Figure 9. Evidence of a difference in live birth between OS-IUI or IVF/ICSI and expectant management was insufficient (OR 0.82, 95% CI 0.45 to 1.49; OR 1.05, 95% CI 0.46 to 2.43). Seven studies reported median duration of infertility > 2 years (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Farquhar 2017; Goverde 2000; Guzick 1999; Melis 1995). Network meta-analysis of these studies is presented in Figure 10. Effect sizes of IVF/ICSI and OS-IUI versus expectant management were larger than those in the main analysis.

Figure 9. Subgroup analysis for live birth - RCTs with a median duration of infertility ≤ 2 years.

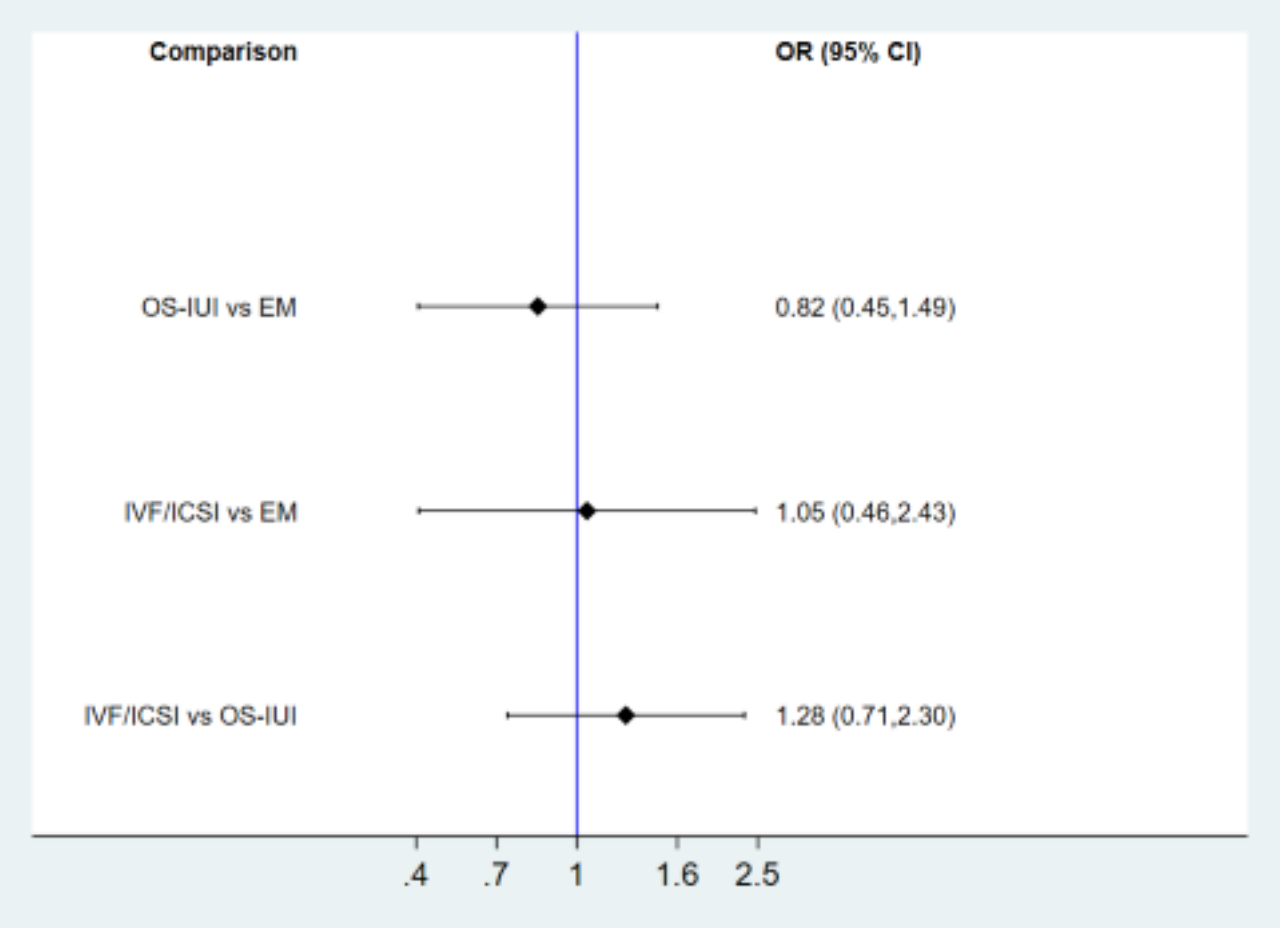
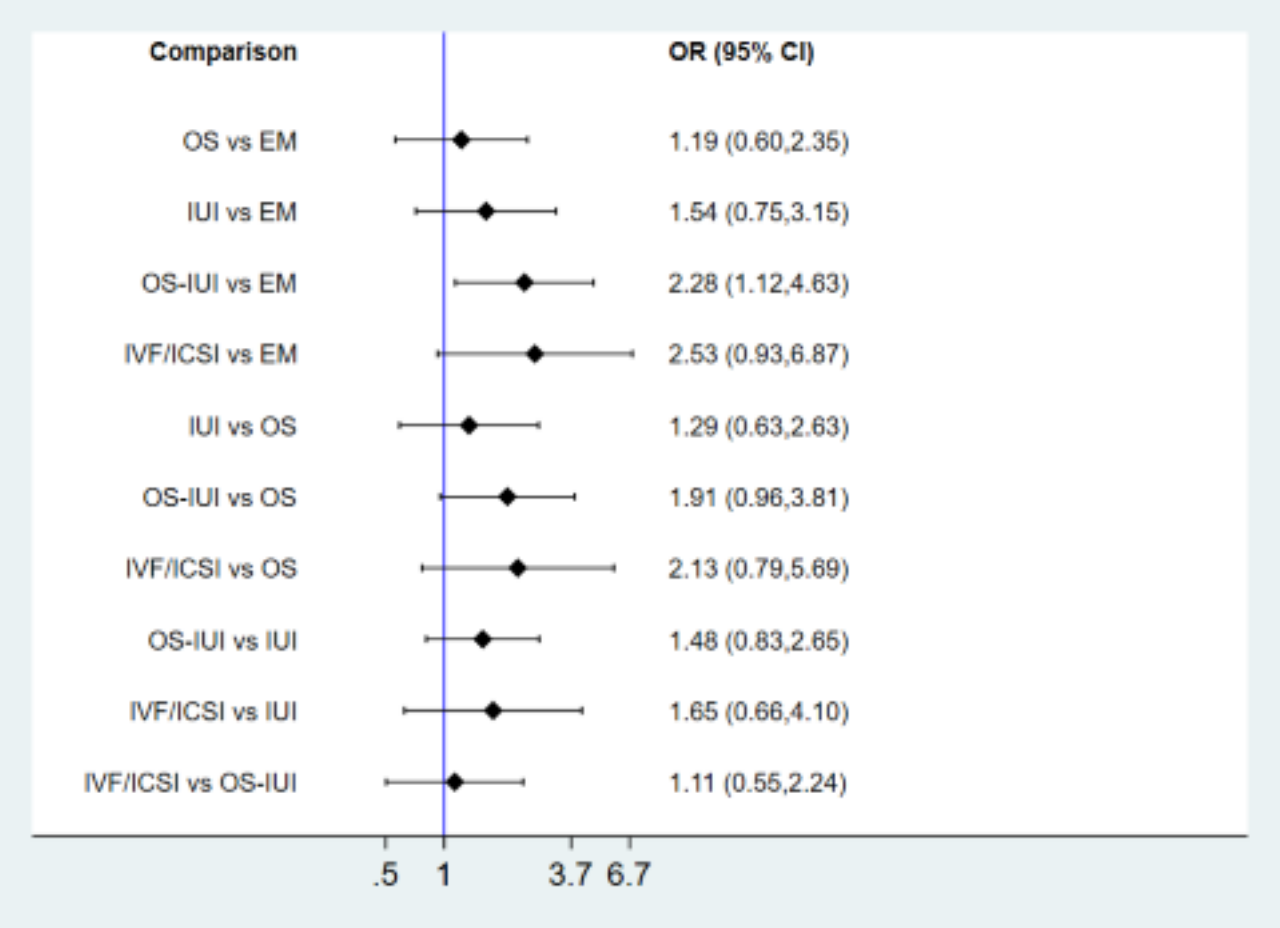


Figure 10. Subgroup analysis for live birth - RCTs with a median duration of infertility > 2 years.



IVF/ICSI with single embryo transfer policy and IVF/ICSI with non-single embryo transfer policy

As all RCTs including an IVF/ICSI arm applied single embryo transfer policy, this subgroup analysis was not performed.

Sensitivity analyses

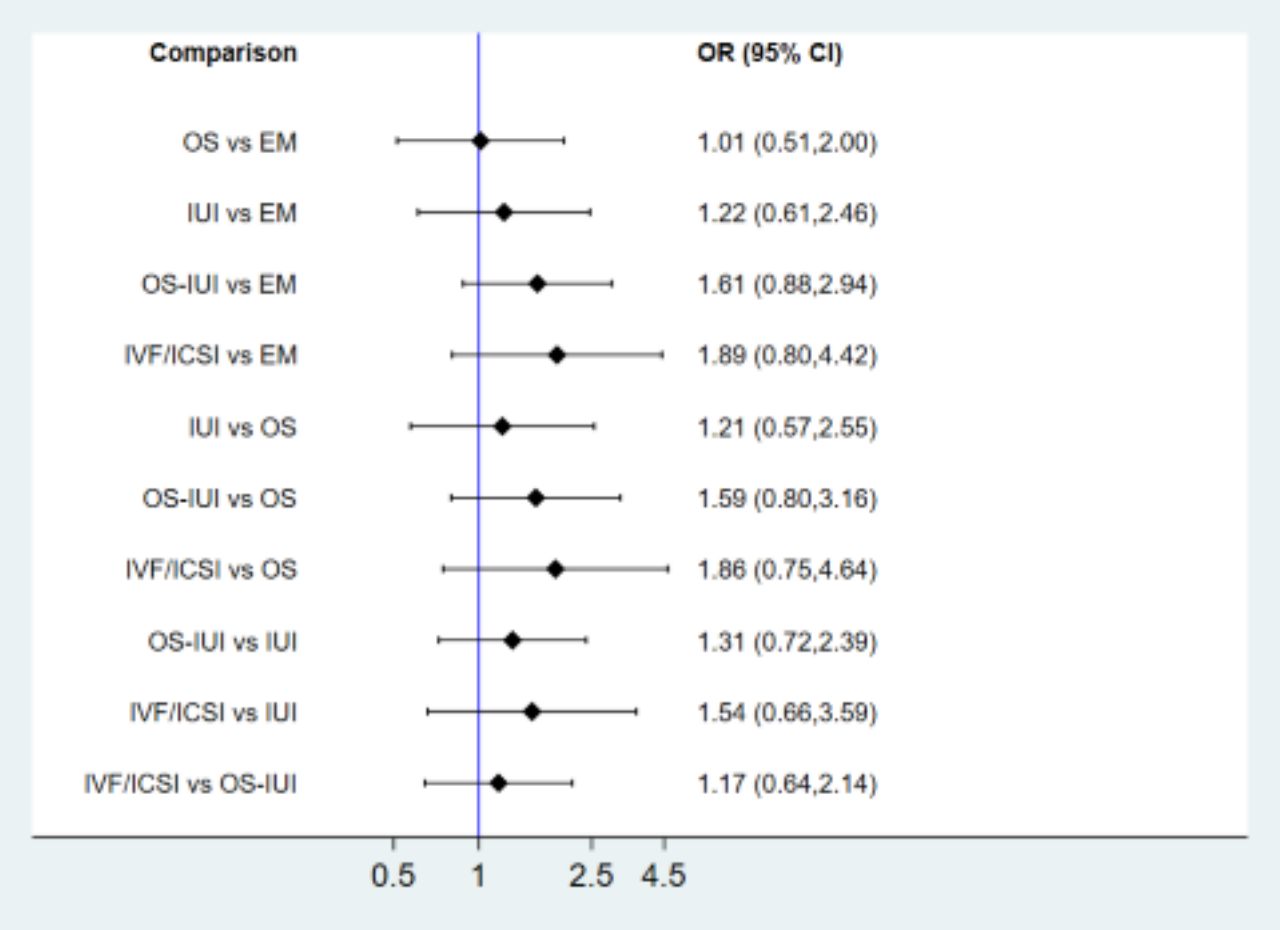
Restricting to RCTs with no domains at high risk of bias

Most RCTs were rated at high risk of performance bias; therefore this analysis was not possible.

Excluding participants with missing outcome data

After participants with missing outcome data were excluded, the results of network meta-analysis were consistent with the main analysis in all comparisons (Figure 11).

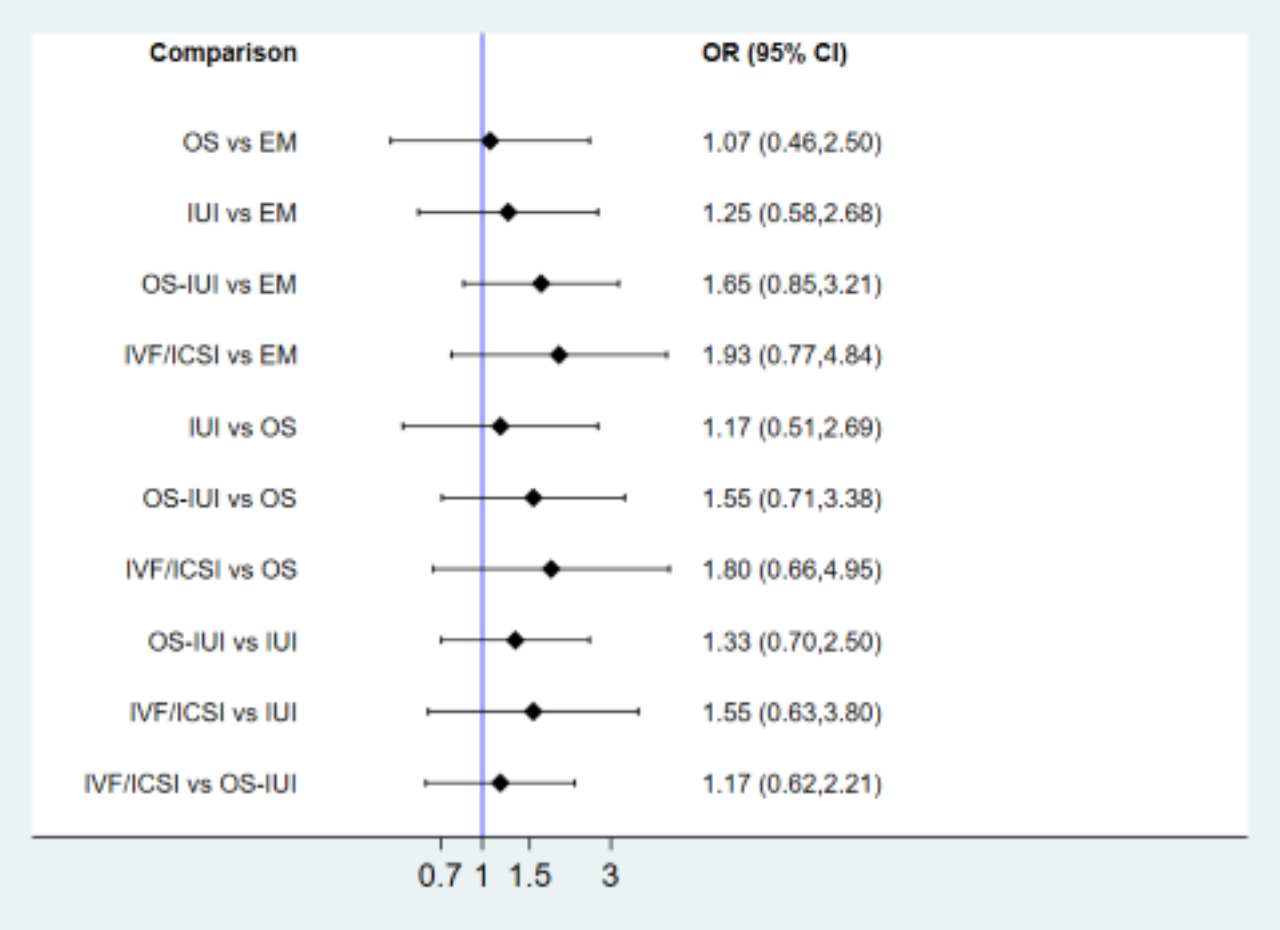
Figure 11. Sensitivity analysis for live birth by exclusion of participants with missing outcome data. Each diamond represents the estimate summary odds ratio for each comparison; each horizontal line represents the confidence interval for each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the first intervention; odds ratio less than 1 favours the second intervention.



Excluding abstract-only publications

One abstract was excluded from this sensitivity analysis (George 2006). Results of this sensitivity analysis were consistent with those of the main analysis for all comparisons (Figure 12).

Figure 12. Sensitivity analysis for live birth by exclusion of abstract-only publications. Each diamond represents the estimate summary odds ratio for each comparison; each horizontal lines represents the confidence interval for each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the first intervention; odds ratio less than 1 favours the second intervention.



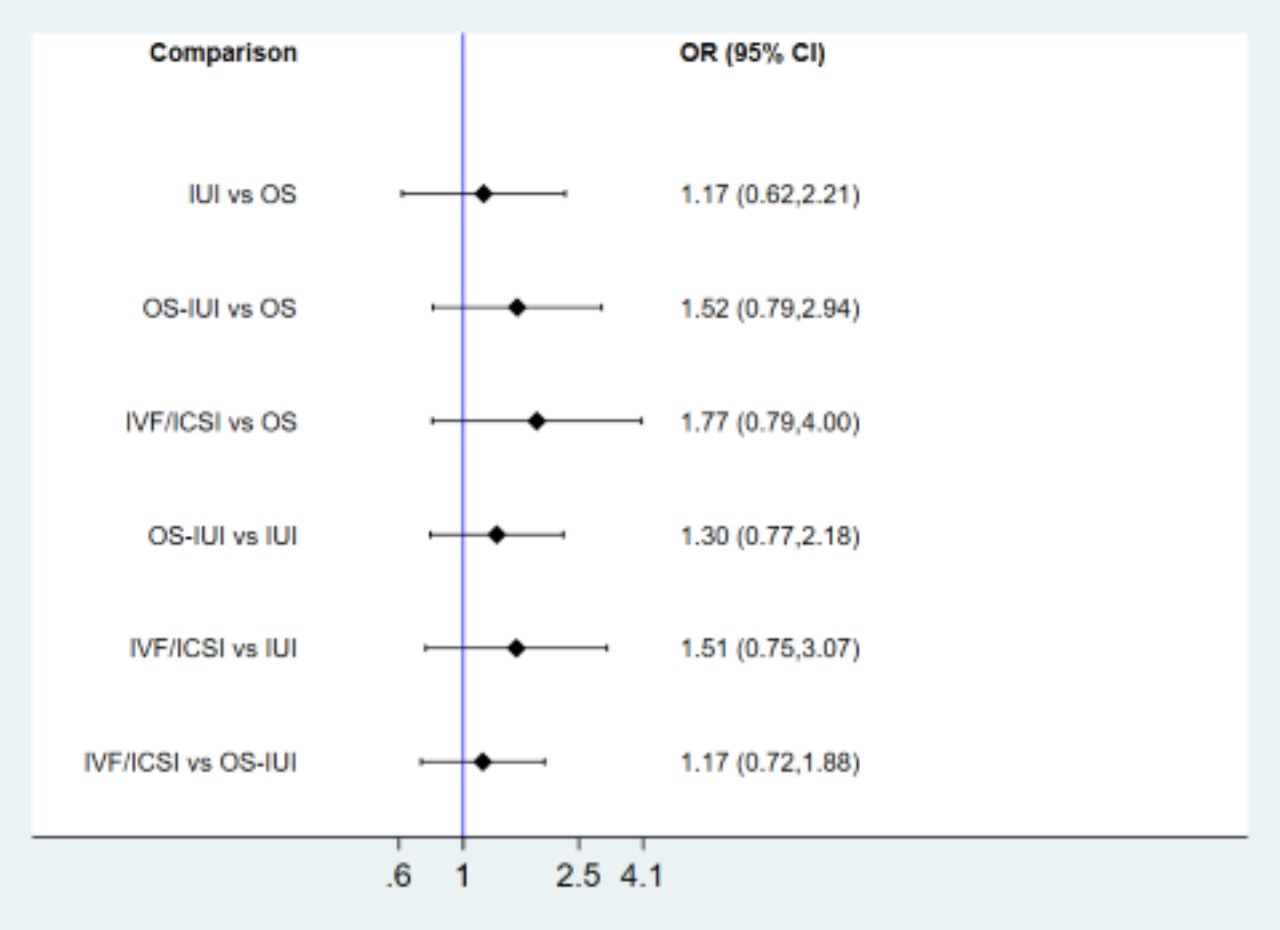
Including only RCTs with the outcome live birth

All 10 studies reported live birth; therefore this analysis was not performed.

Excluding expectant management from the network

Results of network meta-analysis of the remaining four interventions were consistent with results of the main analysis (Figure 13).

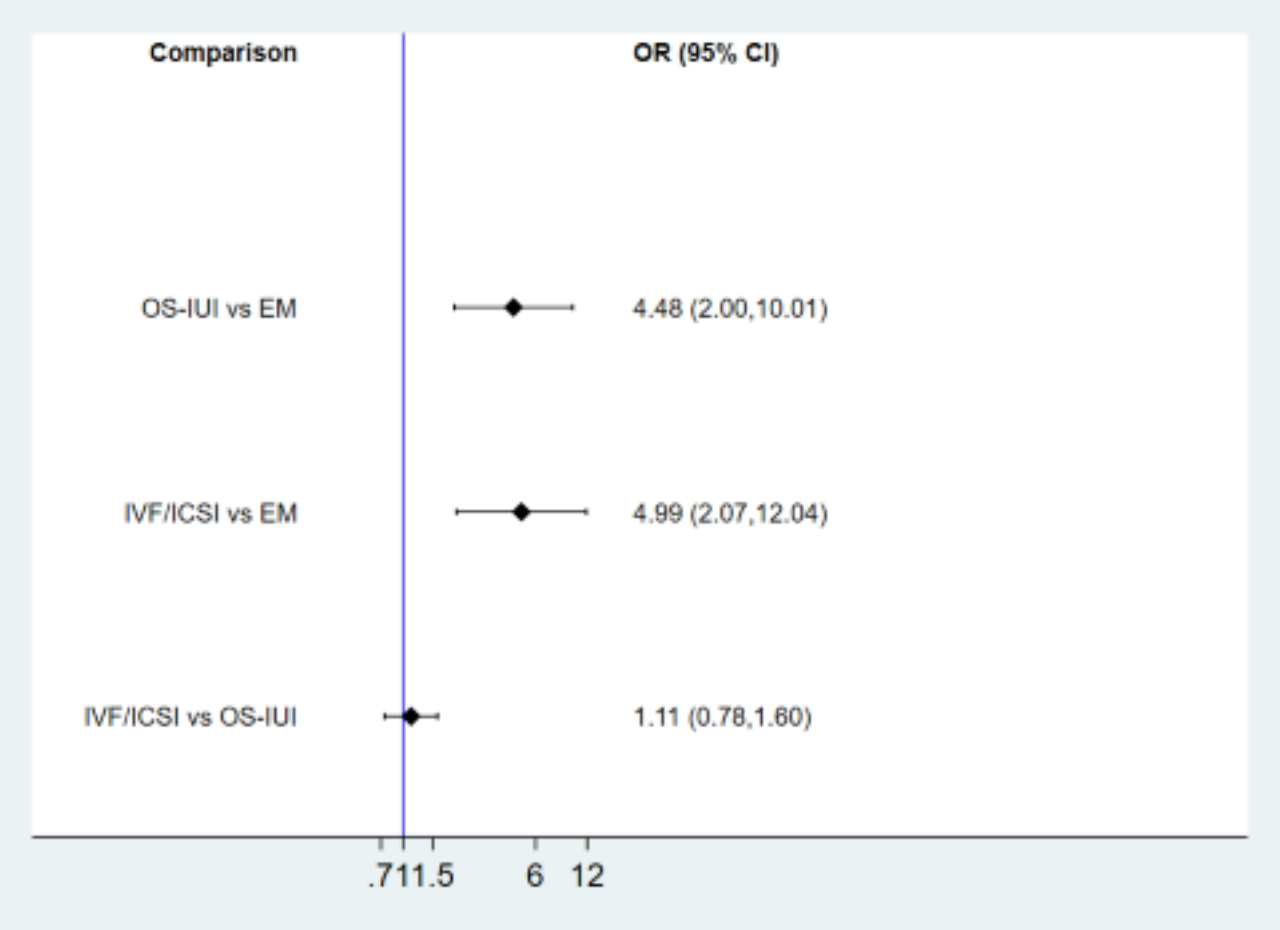
Figure 13. Sensitivity analysis for live birth excluding RCTs involving expectant management from the network. Each diamond represents the estimate summary odds ratio for each comparison; each horizontal lines represents the confidence interval for each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the first intervention; odds ratio less than 1 favours the second intervention.



Restricting to RCTs including couples with poor prognosis of natural conception

Three RCTs - Bensdorp 2015; Custers 2011; Farquhar 2017 - included couples with poor prognosis of natural conception based on an existing prediction model (Hunault 2004). Network meta-analysis (Figure 14) showed that compared to expectant management, OS-IUI (OR 4.48, 95% CI 2.00 to 10.1; moderate-certainty evidence) or IVF/ICSI (OR 4.99, 95 CI 2.07 to 12.04; moderate-certainty evidence) increased the odds of live birth, and there was insufficient evidence of a difference between IVF/ICSI and OS-IUI (OR 1.11, 95% CI 0.78 to 1.60; low-certainty evidence). This sensitivity analysis showed the clinically important differences of OS-IUI and IVF/ICSI versus expectant management.

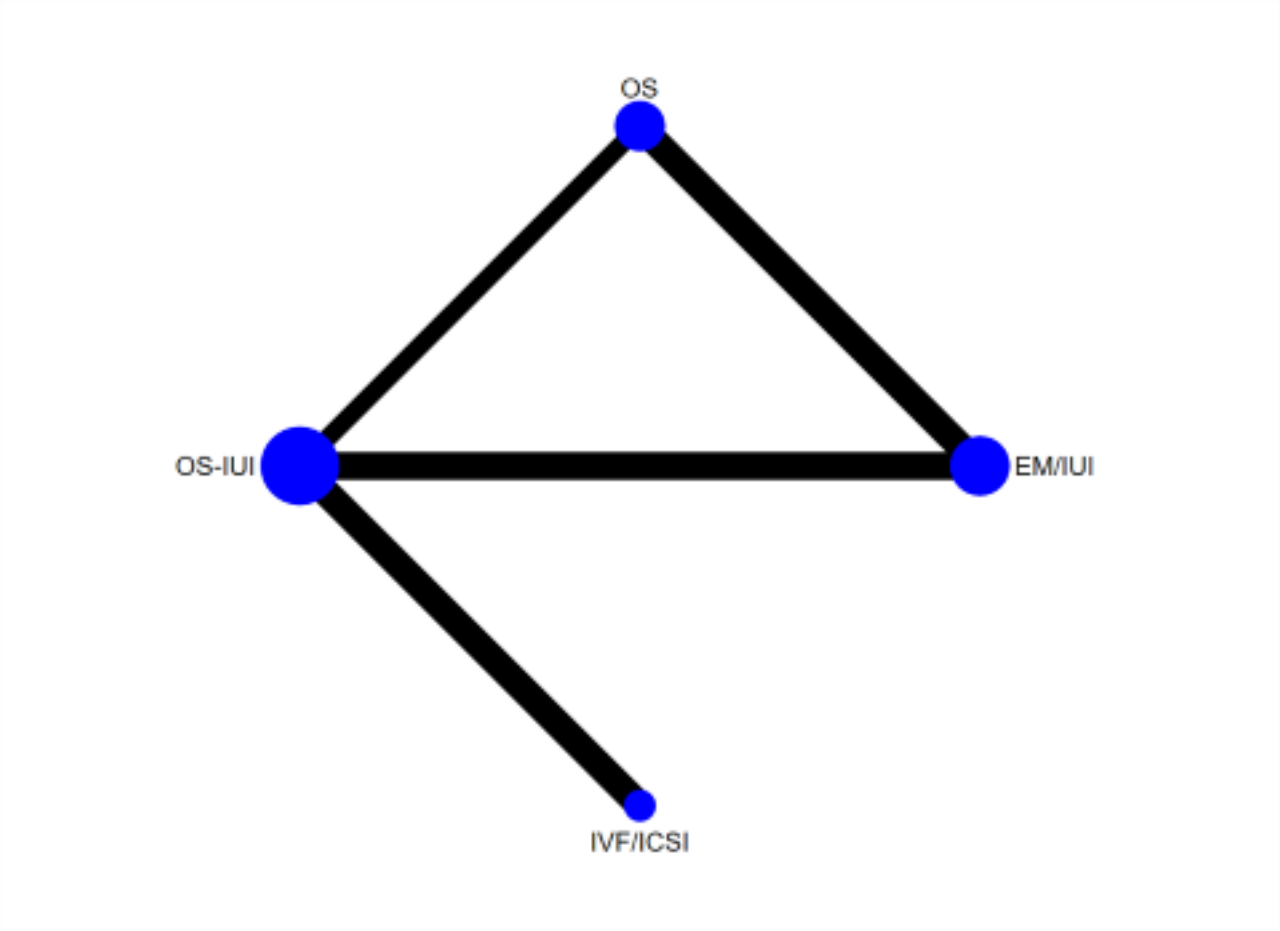
Figure 14. Sensitivity analysis for live birth by limiting to RCTs including couples with poor prognosis of natural conception. Each diamond represents the estimate summary odds ratio for each comparison; each horizontal lines represents the confidence interval for each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the first intervention; odds ratio less than 1 favours the second intervention.



Multiple pregnancy

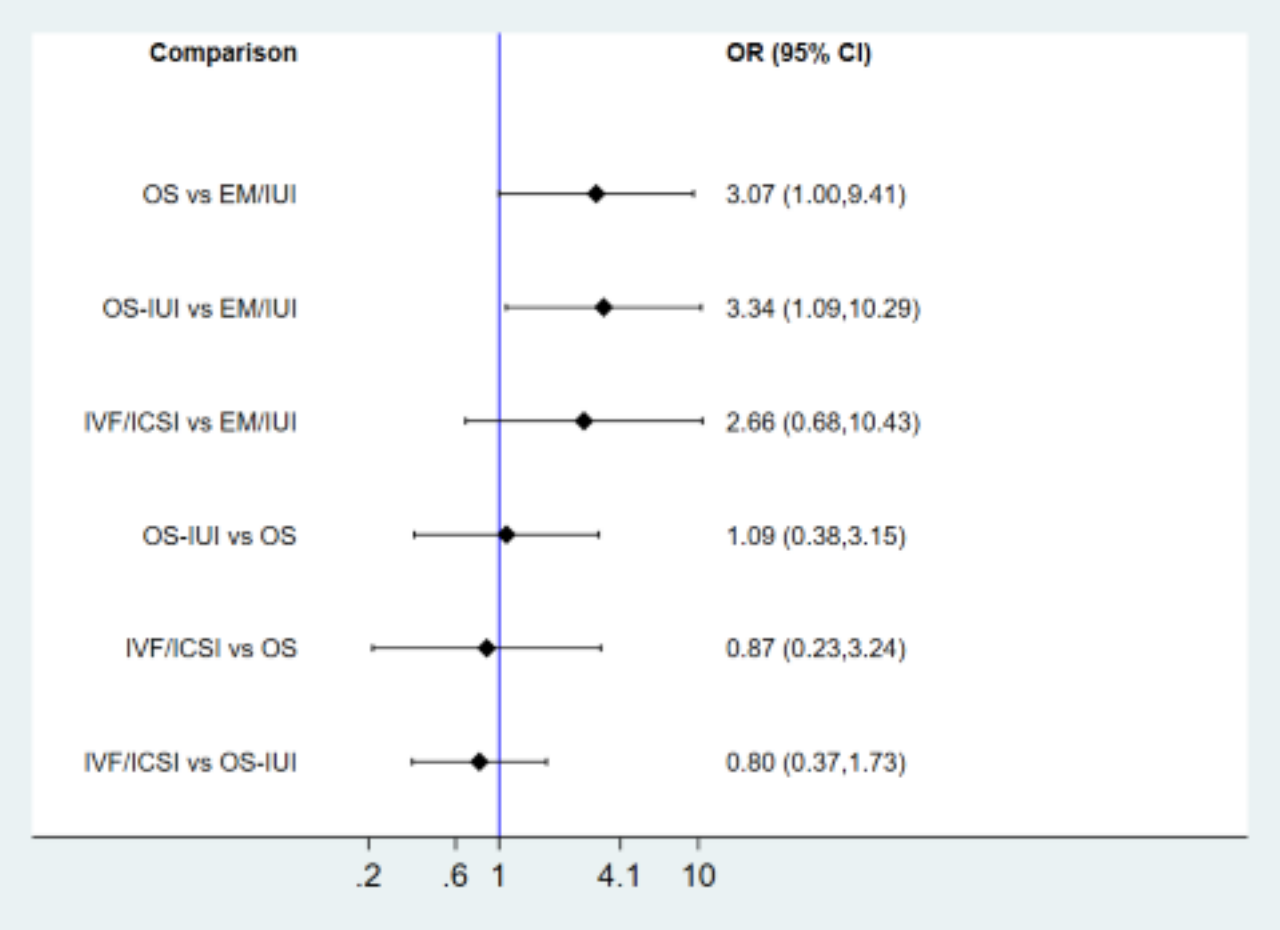
One study reported 0 events in both groups and was excluded from the analysis (Deaton 1990). Eleven RCTs reporting on 2564 couples were included in the network meta-analysis of multiple pregnancy (Bensdorp 2015; Bhattacharya 2008; Custers 2011; Farquhar 2017; George 2006; Glazener 1990; Goverde 2000; Ho 1998; Melis 1995; Nandi 2017; Steures 2006). The network plot for multiple pregnancy is presented in Figure 15.

Figure 15. Network plot for multiple pregnancy. Each node represents an intervention, and the size of each node is proportional to the number of trials reporting such interventions. The widths of lines are proportional to the numbers of trials comparing each pair of interventions.



Results of network meta-analysis are shown in Figure 16. Compared to expectant management/IUI, OS (OR 3.07, 95% CI 1.00 to 9.41; low-certainty evidence) or OS-IUI (OR 3.34, 95% CI 1.09 to 10.29; moderate-certainty evidence) increased the odds of multiple pregnancy, and there was insufficient evidence of a difference between IVF/ICSI and expectant management/IUI (OR 2.66, 95% CI 0.68 to 10.43; low-certainty evidence). These findings suggest that if the chance of multiple pregnancy following expectant management or IUI is assumed to be 0.6%, the chance following OS, OS-IUI, and IVF/ICSI would be 0.6% to 5.0%, 0.6% to 5.4%, and 0.4% to 5.5%, respectively.

Figure 16. Network meta-analysis for multiple pregnancy. Each diamond represents the estimate summary odds ratio for each comparison; each horizontal line represents the confidence interval for each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the second intervention; odds ratio less than 1 favours the first intervention.



These was insufficient evidence of a difference between OS-IUI and OS (OR 1.09, 95% CI 0.38 to 3.15; very-low-certainty evidence), IVF/ICSI and OS (OR 0.87, 95% CI 0.23 to 3.24; low-certainty evidence), or IVF/ICSI and OS-IUI (OR 0.80, 95% CI 0.37 to 1.73; low-certainty evidence).

There was no evidence of global inconsistency (P = 0.34) or local inconsistency in the network meta-analysis on multiple pregnancy. Cumulative rankograms illustrate the probability per rank for each treatment in terms of multiple pregnancy (Figure 17). The comparison-adjusted funnel plot seems symmetrical, implying the absence of small study effects in this network (Figure 18). The SUCRA values for expectant management/IUI, OS, OS-IUI, and IVF/ICSI were 95.3%, 33.8%, 24.5%, and 46.4%, respectively. This suggests that expectant management/IUI was more likely to result in fewer multiple pregnancies than other interventions, followed by IVF/ICSI, OS, and OS-IUI.

Figure 17. Cumulative rankograms of interventions for multiple pregnancy. Each cumulative rankogram illustrates the cumulative probability of each ranking (from the best to the worst rank) for each intervention in terms of multiple pregnancy .

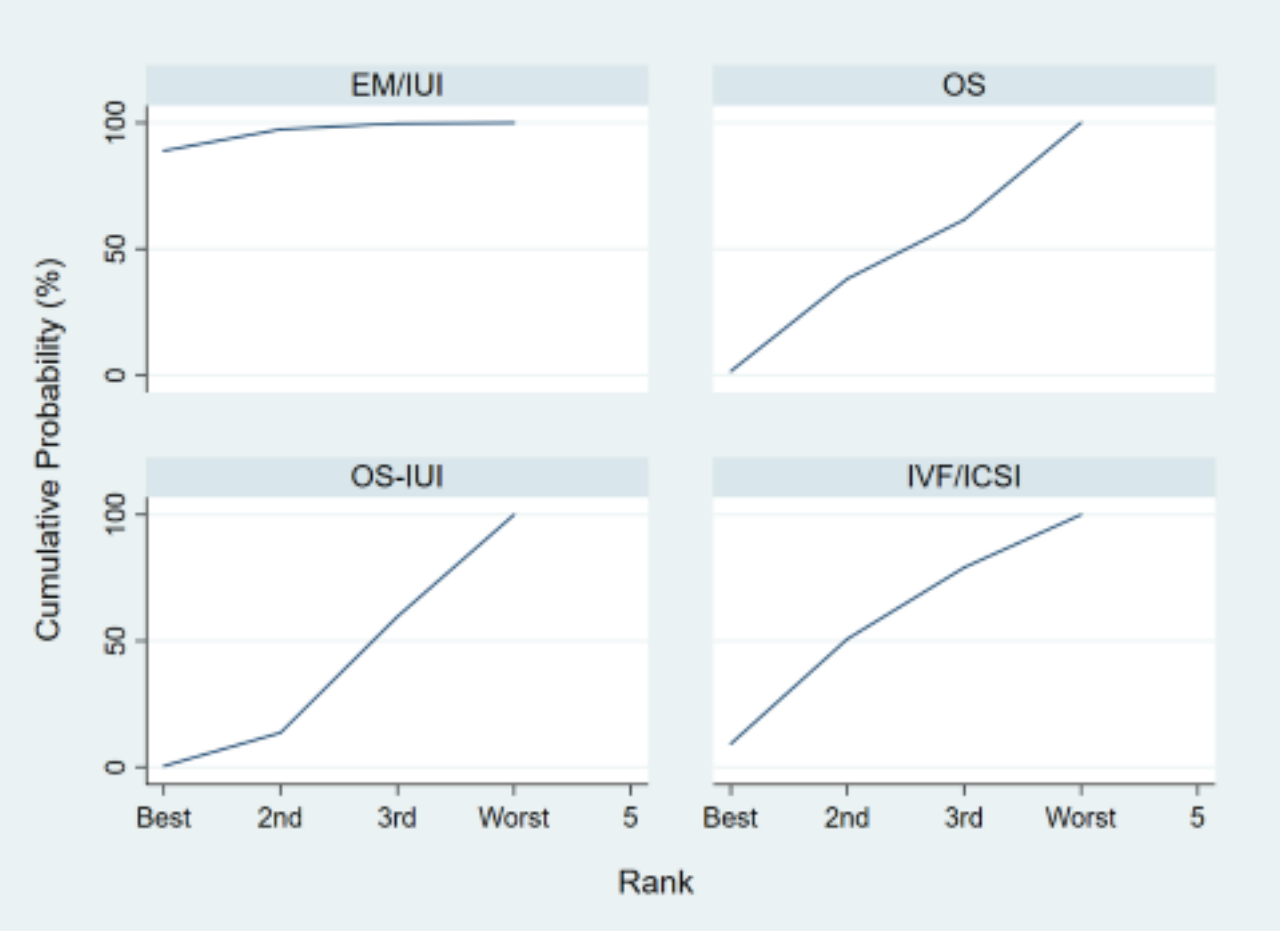
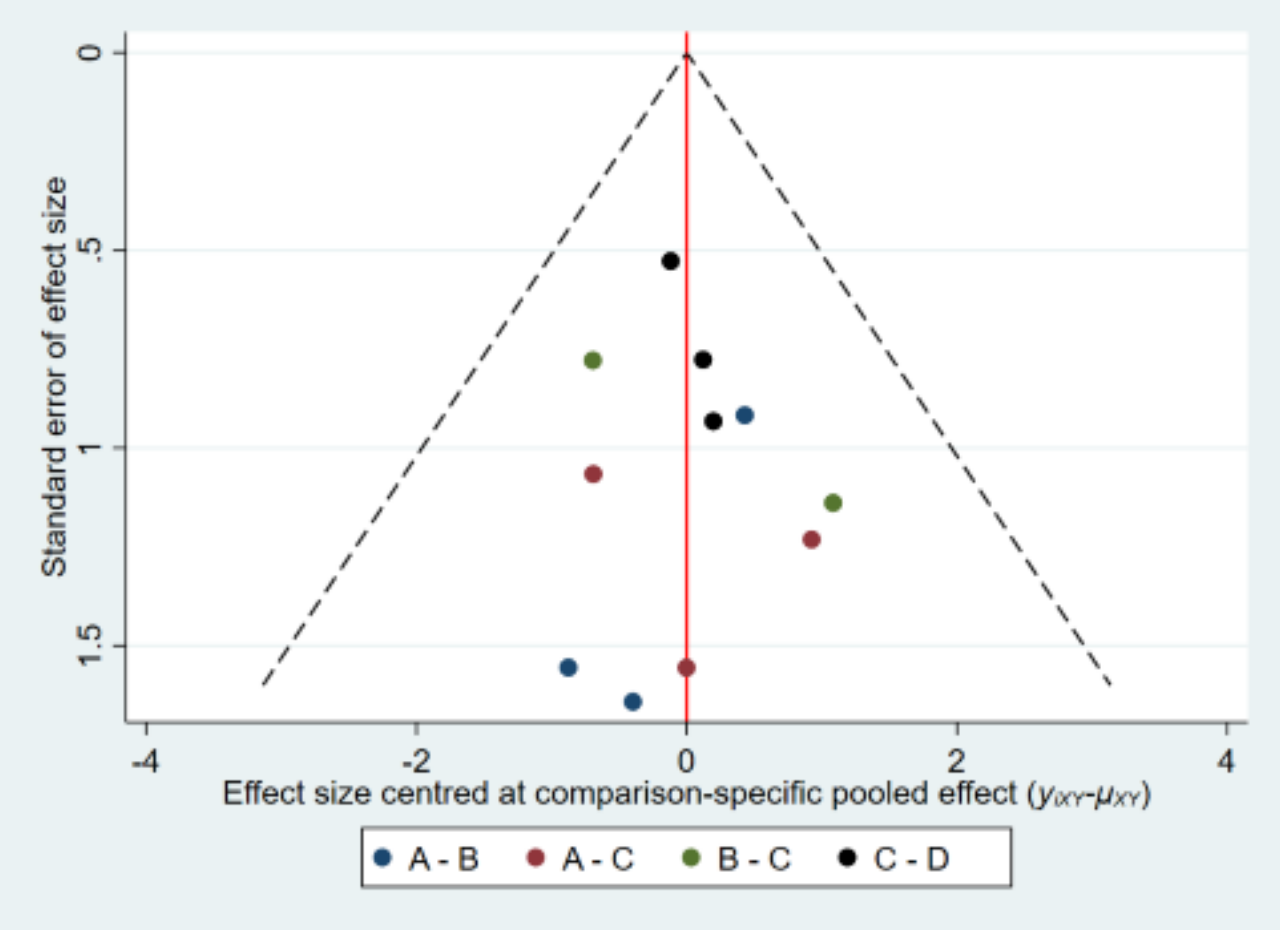


Figure 18. Comparison-adjusted funnel plot for multiple pregnancy. (A: expectant management or IUI; B: OS; C: OS-IUI; D: IVF/ICSI.)



Results of pairwise meta-analyses (Analysis 1.2) are consistent with those in the network meta-analysis.

Clinical pregnancy

Twenty-three RCTs reporting on 3792 couples were included in the network meta-analysis of clinical pregnancy (Agarwal 2004; Arcaini 1996; Arici 1994; Bensdorp 2015; Bhattacharya 2008; Crosignani 1991; Custers 2011; Deaton 1990; Farquhar 2017; Fisch 1989; George 2006; Glazener 1990; Guzick 1999; Harrison 1983; Ho 1998; Janko 1998; Karlstrom 1993; Kirby 1991; Leanza 2014; Martinez 1990; Melis 1995; Nandi 2017; Steures 2006). The network plot for clinical pregnancy is presented in Figure 19. Results of the network meta-analysis are shown in Figure 20.

Figure 19. Network plot for clinical pregnancy. Each node represents an intervention, and the size of each node is proportional to the number of trials reporting such intervention. The widths of the lines are proportional to the numbers of trials comparing each pair of interventions.

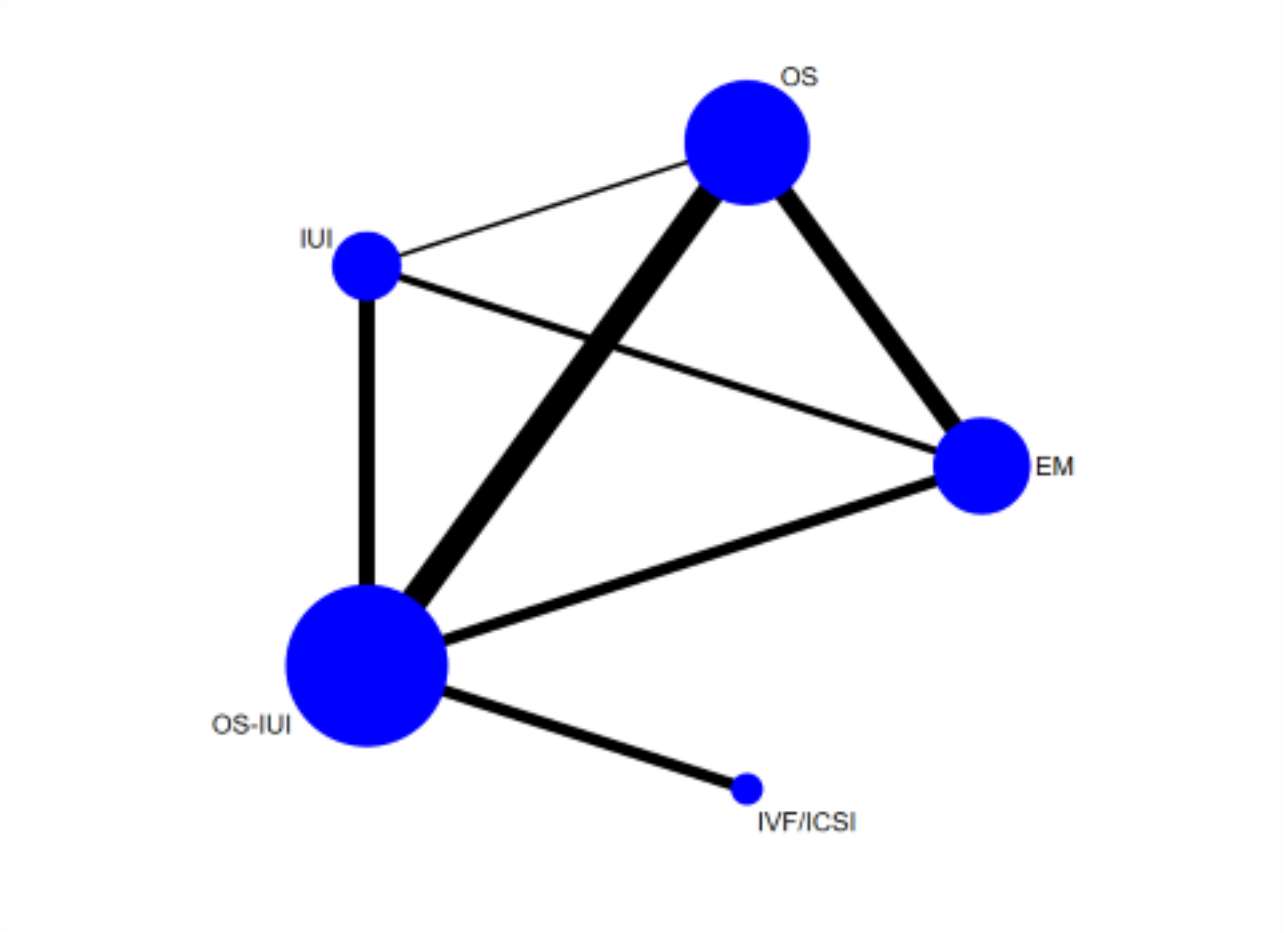
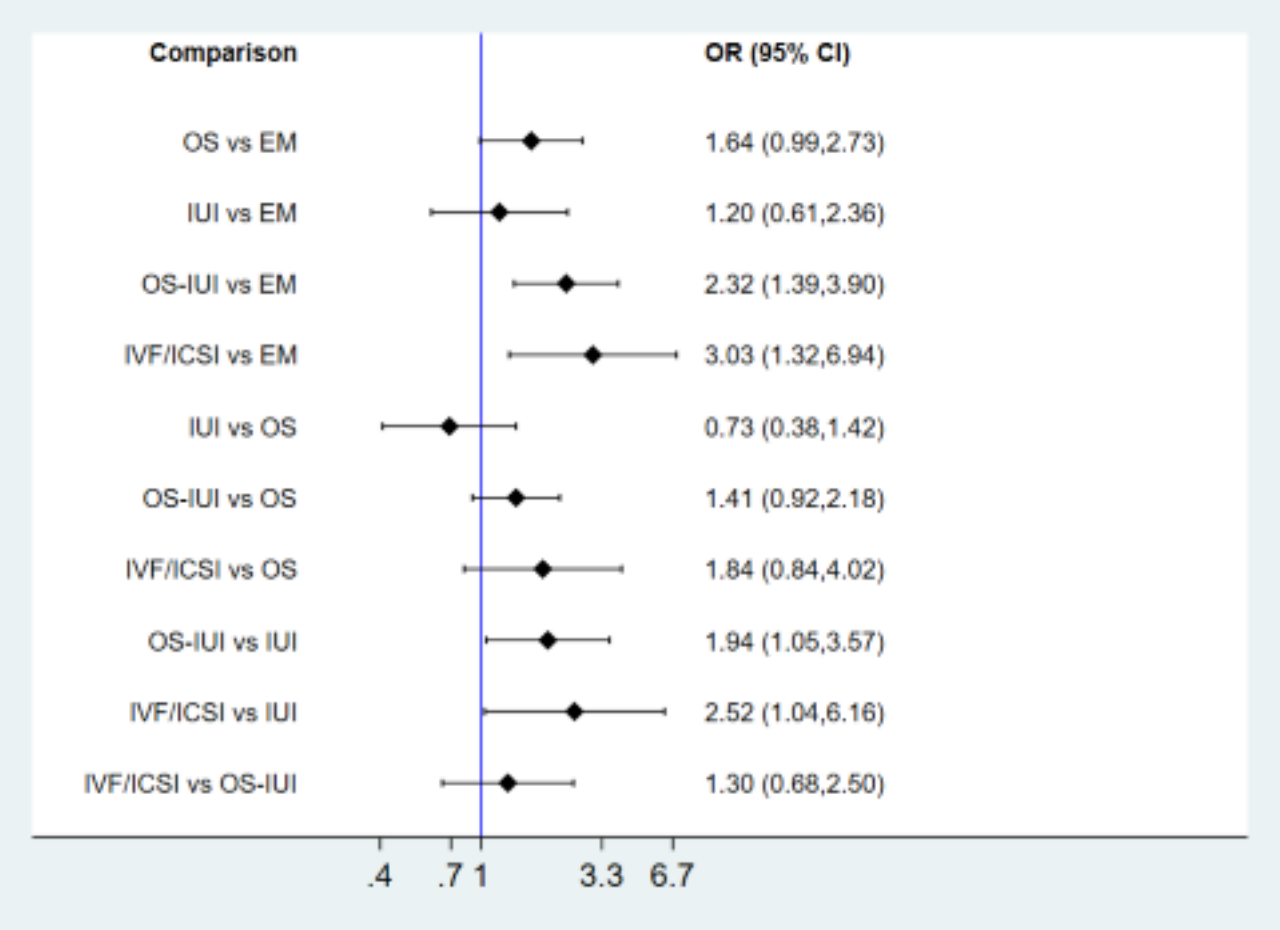


Figure 20. Network meta-analysis for clinical pregnancy. Each diamond represents the estimate summary odds ratio for each comparison; each horizontal line represents the confidence interval for each comparison; blue vertical line represents line of no effect (odds ratio = 1). Odds ratio greater than 1 favours the first intervention; odds ratio less than 1 favours the second intervention.



Compared to expectant management, OS-IUI or IVF/ICSI increased the odds of live birth (OR 2.32, 95% CI 1.39 to 3.90; low-certainty evidence; OR 3.03, 95% CI 1.32 to 6.94; low-certainty evidence). There was insufficient evidence of a difference between OS and expectant management (OR 1.64, 95% CI 0.99 to 2.73; very-low-certainty evidence) or between IUI and expectant management (OR 1.20, 95% CI 0.61 to 2.36; low-certainty evidence). These findings suggest that if the chance of clinical pregnancy following expectant management is assumed to be 16.4%, the chance following OS, IUI, OS-IUI, and IVF/ICSI would be 15.5% to 33.7%, 10.2% to 30.5%, 20.5% to 42.0%, and 19.7% to 56.3%, respectively.

Compared to OS, IVF/ICSI increased the odds of clinical pregnancy (OR 1.84, 95% CI 1.40 to 4.02; low-certainty evidence). There was insufficient evidence of a difference between IUI or OS-IUI and expectant management (OR 0.73, 95% CI 0.38 to 1.42; very low-certainty evidence; OR 1.41, 95% CI 0.92 to 2.18; very low-certainty evidence). Compared to IUI, OS-IUI or IVF/ICSI increased the odds of clinical pregnancy (OR 1.94, 95% CI 1.05 to 3.57; very low-certainty evidence; OR 2.52, 95% CI 1.04 to 6.16; low-certainty evidence). Evidence of a difference between IVF/ICSI and OS-IUI for clinical pregnancy was insufficient (OR 1.30, 95% CI 0.68 to 2.50; low-certainty evidence).

There was no evidence of global inconsistency (P = 0.23), but local inconsistency was detected in the comparison between IUI and OS (P = 0.039). Therefore, the certainty of evidence in this comparison was downgraded due to incoherence. Cumulative rankograms illustrate the cumulative probability per rank for each treatment in terms of clinical pregnancy (Figure 21). The comparison-adjusted funnel plot seems symmetrical, implying the absence of small study effects in this network (Figure 22). The SUCRA values for expectant management, OS, IUI, OS-IUI, and IVF/ICSI were 7.8%, 48.4%, 23.3%, 78.8%, and 91.7%, respectively. This suggests that IVF/ICSI was is more likely to result in more clinical pregnancies than the other interventions, followed by OS-IUI, OS, IUI, and expectant management.

Figure 21. Cumulative rankograms of interventions for clinical pregnancy. Each cumulative rankogram illustrates the cumulative probability of each ranking (from the best to the worst rank) for each intervention in terms of clinical pregnancy.

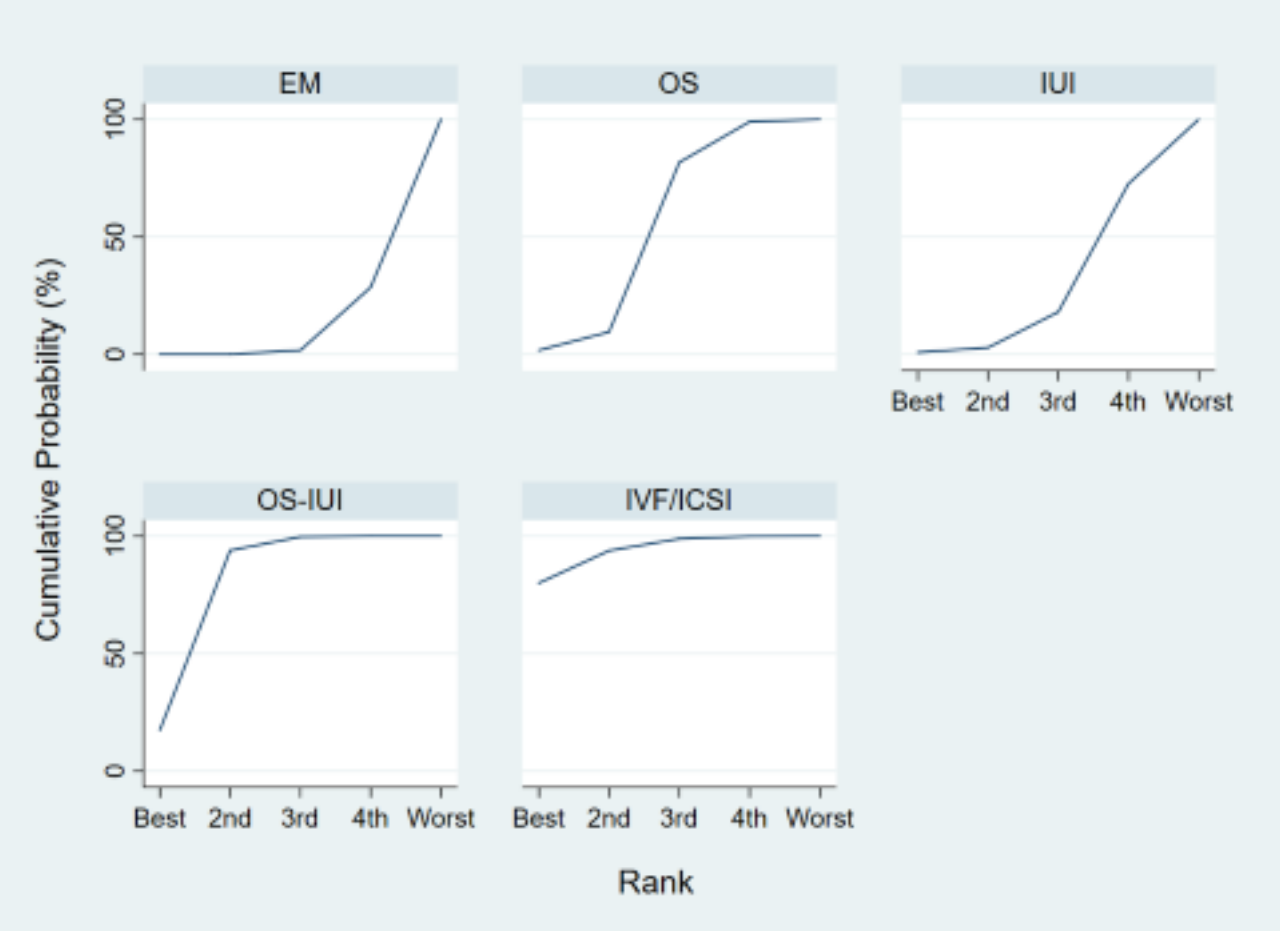
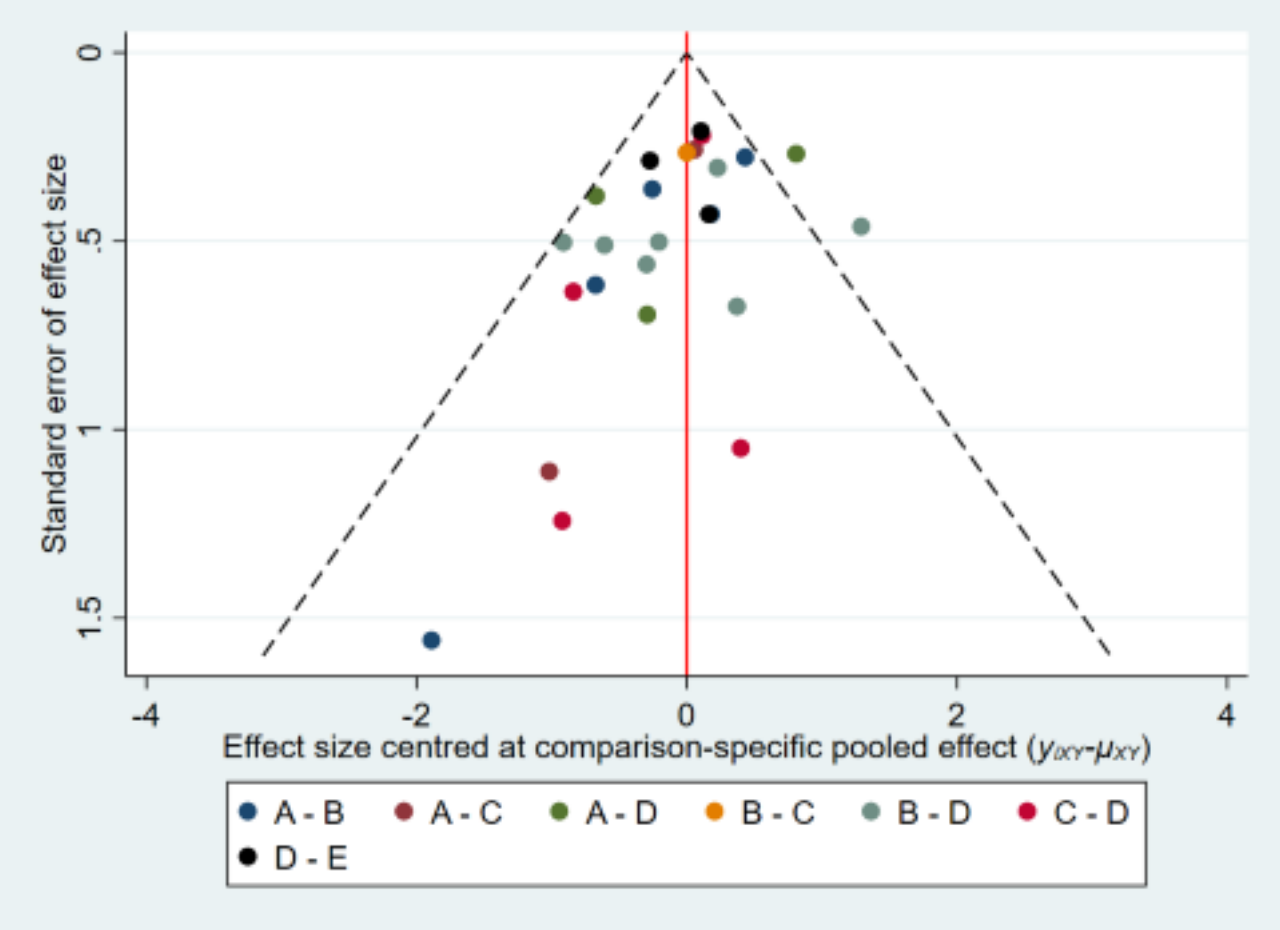


Figure 22. Comparison-adjusted funnel plot for clinical pregnancy.(A: expectant management; B: OS; C: IUI; D: OS-IUI; E: IVF/ICSI.)



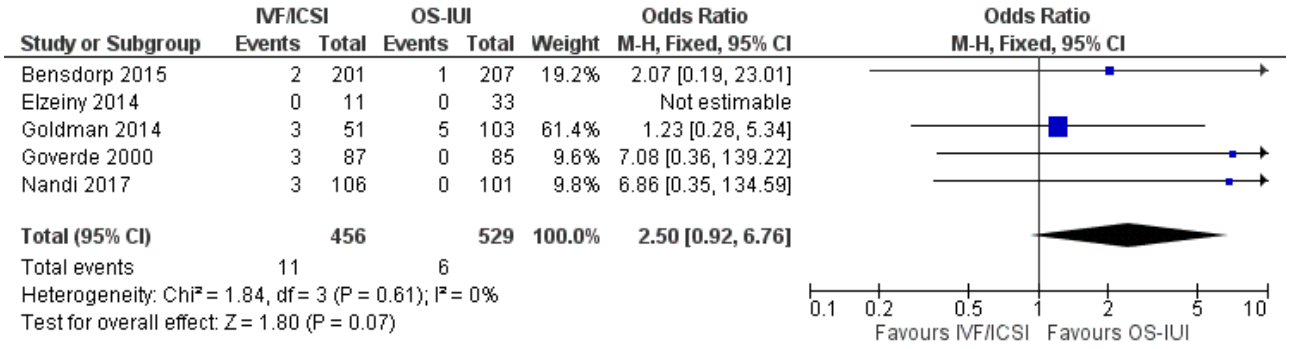
Results of pairwise meta-analyses were consistent with those in the network meta-analysis (Analysis 1.3) .

OHSS

Eight studies reported moderate/severe OHSS. Four studies reported zero events in both groups (Deaton 1990; Elzeiny 2014; Ho 1998; Melis 1995). We did not perform network meta-analysis given the extremely low event rates for some interventions.

Five studies compared IVF/ICSI versus OS-IUI (Bensdorp 2015; Elzeiny 2014; Goldman 2014; Goverde 2000; Nandi 2017). Pooled analysis showed insufficient evidence of a difference between IVF/ICSI and OS-IUI (OR 2.50, 95% CI 0.92 to 6.76; 5 studies; 985 women; moderate-certainty evidence; Figure 23). This suggests that if the chance of moderate/severe OHSS following OS-IUI is assumed to be 1.1%, the chance following IVF/ICSI would be between 1.0% and 7.2%.

Figure 23. Forest plot of comparison: 2 Pairwise meta-analysis for OHSS, outcome: 2.5 IVF/ICSI vs OS-IUI.



DISCUSSION

Summary of main results

This systematic review and network meta-analysis compared the effectiveness and safety of in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI), ovarian stimulation (OS)-intrauterine insemination (IUI), IUI, OS, and expectant management with each other in couples with unexplained infertility. There was insufficient evidence of differences in terms of live birth between expectant management and the other four interventions. Compared to expectant management or IUI, OS may increase the odds of multiple pregnancy, and OS-IUI probably increases the odds of multiple pregnancy. Evidence of differences between IVF/ICSI and expectant management for multiple pregnancy was insufficient. There was also insufficient evidence of a difference in moderate or severe ovarian hyperstimulation syndrome (OHSS) between IVF/ICSI and OS-IUI. The overall certainty of the evidence was low to moderate, mainly due to imprecision and/or heterogeneity.

Overall completeness and applicability of evidence

Our population of interest consisted of couples with unexplained infertility. We used a relatively broad definition of unexplained infertility, including couples with mild endometriosis and mild male infertility (pre-wash total motile sperm count > 3 * 10^6) to increase the applicability of findings. As the distributions of potential effect modifiers showed similarities across different comparisons and the interventions of interest are jointly randomisable, the overall transitivity assumption in this network was valid. For IVF/ICSI, all RCTs including this arm applied single embryo transfer policy, which guarantees the clinical homogeneity of IVF/ICSI.

Current NICE 2013 guidelines do not recommend IUI, either with or without ovarian stimulation, for couples with unexplained infertility. Based on our systematic review, we would argue that OS-IUI still plays an important role in the treatment of unexplained infertility, especially for couples with poor prognosis of natural conception. Shared decision-making should consider not only effectiveness and safety, but also patient preferences and costs. Two economic evaluations found that OS-IUI resulted in lower cost per live birth than IVF/ICSI in couples with poor prognosis of natural conception and a median duration of infertility less than two years, which implies that OS-IUI is an important alternative to IVF/ICSI in these narrowly defined couples with unexplained infertility (Tjon-Kon-Fat 2015; van Rumste 2014).

Quality of the evidence

Overall certainty of the evidence was very low to moderate (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4). This was due mainly to lack of precision and/or the existence of heterogeneity. All comparisons had relatively few included studies with direct evidence, which explained the imprecision in these comparisons. The heterogeneity observed was most likely due to the heterogeneous nature of unexplained infertility, and some included RCTs focused on different subpopulations with unexplained infertility. For instance, Steures 2006 included only couples with an intermediate prognosis of natural conception based on the Hunault prediction model (Hunault 2004), and Farquhar 2017 included only couples with a poor prognosis. The result of network meta-analysis in the comparison of OS-IUI and expectant management was consistent with existing cohorts on unselected unexplained infertility (van Eekelen 2019), but the pooled result was not applicable to the two subpopulations with poor or intermediate prognoses, respectively.

The strengths of this systematic review include the extensive search strategy, use of indirect evidence, performance of sensitivity analyses, and application of Confidence in Network Meta-analysis (CINeMA) to evaluate the overall certainty of evidence in network meta-analysis. The current systematic review and network meta-analysis provided an overview of the evidence base in clinical management of unexplained infertility. Nevertheless, there are several limitations. Couples with unexplained infertility are a heterogeneous population, and various inclusion criteria were used. For instance, participants in the included studies may or may not have had a diagnostic laparoscopy before diagnosis of unexplained infertility. Next, some included studies focused on a subgroup of couples based on prognostic factors (e.g. Hunault prediction model as discussed above). Pooled results led to heterogeneity and imprecision in the evidence for these comparisons. Additionally, our primary effectiveness and safety outcomes live birth and multiple pregnancy were not reported in approximately half of the included trials. This explains in part the imprecision evident in some comparisons. Furthermore, as breakdown data for different subgroups were not available, our subgroup analysis on duration of infertility was based on different mean/median values; therefore these results should be interpreted with caution. A planned subgroup analysis on treatment-naive couples versus couples who had received prior treatment was not feasible in the network meta-analysis, as couples with various previous treatments were also allowed to be randomised to less invasive interventions, including expectant management in pragmatic RCTs. Last, about half of the included studies were published before 2000. Although IVF in different studies in this network meta-analysis appears similar, the intensive OS protocols and the relatively loose cancellation criteria used in old trials of OS and OS-IUI are not the same compared to recent ones, the latter of which led to fewer multiple pregnancies.

Potential biases in the review process

Given the extensive search strategy, including the electronic database search and the handsearch of relevant references, the chance of incomplete identification of studies was low. We did not identify small study effects in the main outcomes. Therefore, we concluded that no publication bias was evident. In addition, as live birth and/or multiple pregnancy was not reported in about half of the included studies, we could not rule out the possibility of reporting bias.

As indirect evidence does not involve new randomisation and therefore the validity of network meta-analysis relies on transitivity assumption, we assessed the transitivity assumption carefully before conducting this network meta-analysis and did not find evidence of intransitivity. However, we could not completely rule out the existence of intransitivity due to the small number of RCTs included in all comparisons and the lack of baseline information from old RCTs. We further evaluated inconsistency by using both global and local approaches. Statistical testing did not show evidence of inconsistency in networks of the main outcomes, but statistical testing for inconsistency could be underpowered

(Higgins 2012). The overall limitations in each comparison on different outcomes are reflected in the summary of finding tables.

Agreements and disagreements with other studies or reviews

A Cochrane Review on IUI for unexplained infertility found no conclusive evidence of a difference in live birth or multiple pregnancy for the comparison between IUI or OS-IUI versus expectant management (Veltman-Verhulst 2016). Our network meta-analysis showed consistent results on live birth with overlapping confidence intervals. Evidence on multiple pregnancy between OS-IUI versus expectant management or IUI in our network meta-analysis was based on moderate certainty, as the use of network meta-analysis increased the precision of the evidence.

Another Cochrane Review on IVF/ICSI for unexplained infertility found that IVF/ICSI may be associated with higher live birth rates than expectant management, but the overall certainty of evidence was very low (Pandian 2015). This conclusion was based on one RCT with small sample size and an intensive embryo transfer policy (up to four embryos in an unselected population) (Hughes 2004). This RCT was not included in the network meta-analysis due to the different embryo transfer policy used from current clinical practice. No direct evidence was available for the comparison between IVF/ICSI and expectant management. Indirect evidence arising from our network meta-analysis was insufficient to judge a difference in terms of effectiveness and safety.

AUTHORS' CONCLUSIONS

Implications for practice

We found insufficient evidence of differences in terms of live birth between expectant management and the other four interventions (OS, IUI, OS-IUI, and IVF/ICSI). Compared to expectant management/IUI, OS may increase the odds of multiple pregnancy, and OS-IUI probably increases the odds of multiple pregnancy. Evidence showing differences between IVF/ICSI and expectant management for multiple pregnancy was insufficient, as was evidence of a difference in moderate or severe OHSS between IVF/ICSI and OS-IUI.

Implications for research

Given the overall low certainty of evidence for most comparisons in this network meta-analysis, future RCTs comparing interventions for unexplained infertility are needed. A recent systematic review showed that existing RCTs in reproductive medicine are likely to be underpowered to detect plausible improvements in live birth rate (Stocking 2019), as clinically important differences between these interventions appear small. Therefore, accounting for prognostic factors is helpful in guiding the design in future research. As the prognosis of natural conception in unexplained infertility is predicable, the relative effects between expectant management and other interventions are expected to be larger in couples with poor prognosis. This was confirmed not only in our subgroup analysis, which showed different effects in couples with shorter and longer duration of infertility, but also in our sensitivity analysis, which showed large relative effects in couples with poor prognosis. Future RCTs should compare IVF or OS-IUI versus expectant management in couples with different prognoses to confirm the available evidence and to shape the clinical indications for IVF and IUI in unexplained infertility.

We need more studies comparing OS-IUI or IVF versus expectant management as well as studies comparing OS-IUI versus IVF to enable better fine-tuning of when to start treatment and what treatment to use. More specifically, in an OS-IUI protocol, gonadotropins with strict cancellation criteria and recently widely used medication such as letrozole should be tested. Studies comparing IVF versus other interventions should also address the use of the freeze-only strategy and the report of cumulative live birth rate.

Studies should include a cost-effectiveness analysis with a time horizon that allows multi-cycle treatment plus frozen-thawed cycles in cases of IVF, with live birth as the primary outcome.

Study investigators are advised to use cumulative live birth as the primary outcome. Cumulative live birth has been recognised as the current standard in outcome reporting (Gadalla 2018). The development of a core outcome set for infertility trials is under way (Duffy 2018). The use of core outcomes will standardise outcome reporting in future trials and will minimise outcome reporting bias.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Agarwal 2004 *{published data only}*

Agarwal S, Mittal S. A randomised prospective trial of intrauterine insemination versus timed intercourse in superovulated cycles with clomiphene. *Indian Journal of Medical Research* 2004;**120**(6):519-22.

Arcaini 1996 *{published data only}*

Arcaini L, Bianchi S, Baglioni A, Marchini M, Tozzi L, Fedele L. Superovulation and intrauterine insemination vs. superovulation alone in the treatment of unexplained infertility. A randomized study. *Journal of Reproductive Medicine* 1996;**41**(8):614-8.

Arici 1994 *{published data only}*

Arici A, Byrd W, Bradshaw K, Kutteh WH, Marshburn P, Carr BR. Evaluation of clomiphene citrate and human chorionic gonadotropin treatment: a prospective, randomized, crossover study during intrauterine insemination cycles. *Fertility & Sterility* 1994;**61**(2):314-8.

Bensdorp 2015 *{published data only}*

Bensdorp AJ, Slappendel E, Kok C, Oosterhuis J, Hoek A, Hompes P, et al. The INeS study: prevention of multiple pregnancies: a randomised controlled trial comparing IUI COH versus IVF e SET versus MNC IVF in couples with unexplained or mild male subfertility. *BMC Women's Health* 2009;**9**:35.

Bensdorp AJ, Tjon Kon Fat RI, Koks C, Oosterhuis GJE, Hoek A. Hompes PGA, et al. Preliminary comparative effectiveness of IVF with single embryo transfer or IVF in the modified natural cycle and IUI with hyperstimulation; a randomized trial (INeS trial). *Human Reproduction* 2013;**28(Suppl 1)**:i14-i17 O-037.

* Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PMM, Koks CAM, Oosterhuis GJE, et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. *BMJ (Online)* 2015;**350**:g7771. [DOI: http://dx.doi.org/10.1136/bmj.g7771]

Bhattacharya 2008 *{published data only}*

* Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C, Harrold A, et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. *BMJ* 2008;**337**(72):a716.

Wordsworth S, Buchanan J, Mollison J, Harrild K, Robertson L, Tay C, et al. Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?. *Human Reproduction* 2011;**26**(2):369-75.

Crosignani 1991 *{published data only}*

Crosignani P, Walters DE, Soliani A. The ESHRE multicentre trial on the treatment of unexplained infertility. *Fertility & Sterility* 1991;**54**:S61.

* Crosignani PG, Walters DE, Soliani A. The ESHRE multicentre trial on the treatment of unexplained infertility: a preliminary report. European Society of Human Reproduction and Embryology. *Human Reproduction* 1991;**6**(7):953-8.

Custers 2011 *{published data only}*

Custers I, Hompes P, Broekmans F, Kaaijk E, Oosterhuis JM, Mochtar M, et al. IVF with elective single embryo transfer versus IUI-COH in couples with unexplained subfertility and a poor prognosis: a multicentre RCT. *Human Reproduction.* 2009;**24 Suppl 1**:i76, O-188 Oral.

* Custers IM, Konig TE, Broekmans FJ, Hompes PG, Kaaijk E, Oosterhuis J, et al. Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. *Fertility & Sterility* 2011;**96**(5):1107-11.e1.

van Rumste MME, Custers IM, Koks CA, van Weering HGI, Beckers NGM, Scheffer GJ, et al. IVF with single embryo transfer versus iui with ovarian hyperstimulation in couples with unexplained subfertility, an economic analysis. *Human Reproduction* 2009;**24 Suppl 1**:i44, Abstract No: O-110 Oral.

Deaton 1990 *{published data only}*

Deaton JL, Gibson M, Blackmer KM, Nakajima ST, Badger GJ, Brumsted JR. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. *Fertility & Sterility* 1990;**54**(6):1083-8.

Elzeiny 2014 *{published data only}*

Elzeiny H, Garrett C, Toledo M, Stern K, McBain J, Baker HW. A randomised controlled trial of intra-uterine insemination versus in vitro fertilisation in patients with idiopathic or mild male infertility. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2014;**54**(2):156-61.

Farquhar 2017 *{published data only}*

Farquhar CM, Liu E, Armstrong S, Arroll N, Lensen S, Brown J. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial.. *Lancet* 2017;**391**(10119):441-50. [DOI: 10.1016/S0140-6736(17)32406-6]

Fisch 1989 *{published data only}*

Fisch P, Casper RF, Brown SE, Wrixon W, Collins JA, Reid RL, et al. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. *Fertility & Sterility* 1989;**51**(5):828-33.

George 2006 *{published data only}*

George K, George SS, Chandy A. A randomized controlled trial to evaluate the efficacy of clomiphene citrate in unexplained infertility. *Fertility and Sterility* 2006;**86 Suppl 2**:S100.

Glazener 1990 *{published data only}*

Glazener CM, Coulson C, Lambert PA, Watt EM, Hinton RA, Kelly NG, et al. Clomiphene treatment for women with unexplained infertility: placebo-controlled study of hormonal responses and conception rates. *Gynecological Endocrinology* 1990;**4**(2):75-83.

Goldman 2014 *{published data only}*

* Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL, Hornstein MD, et al. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). *Fertility & Sterility* 2014;**101**(6):1574-81.e1-2.

Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertility & Sterility* 2010;**94**(3):888-99.

Goverde 2000 *{published data only}*

Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. *Lancet* 2000;**355**(9197):13-8.

Guzick 1999 *{published data only}*

Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. *New England Journal of Medicine* 1999;**340**(3):177-83. [DOI: 10.1056/NEJM199901213400302]

Harrison 1983 *{published data only}*

Harrison R, O'Moore R. The use of clomiphene citrate with and without human chorionic gonadotropin. *Irish Medical Journal* 1983;**76**:273-4.

Ho 1998 *{published data only}*

Ho PC, Yeung WSB, So WWK, Lau EYL. A randomised trial comparing the efficacy of ovarian stimulation and intrauterine insemination versus ovarian stimulation alone in the treatment of male infertility and unexplained infertility. *British Journal of Obstetrics & Gynaecology* 1998;**105**(Suppl 17):43.

Hughes 2004 *{published data only}*

Hughes EG, Beecroft ML, Wilkie V, Burville L, Claman P, Tummon I, et al. A multicentre randomized controlled trial of expectant management versus IVF in women with Fallopian tube patency. *Human Reproduction (Oxford, England)* 2004;**19**(5):1105-9. [DOI: 10.1093/humrep/deh209]

Janko 1998 *{published data only}*

Janko P, Hruzik P, Pruzinec J, Saliba H, Zidzik J. Induction of ovulation with or without intrauterine insemination in cases of unexplained sterility. *Fertility and Sterility* 1998;**70**(3):S442.

Karlstrom 1993 *{published data only}*

Karlstrom PO, Bergh T, Lundkvist O. A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate. *Fertility & Sterility* 1993;**59**(3):554-9.

Kirby 1991 *{published data only}*

Kirby CA, Flaherty SP, Godfrey BM, Warnes GM, Matthews CD. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse. *Fertility & Sterility* 1991;**56**(1):102-7.

Leanza 2014 *{published data only}*

Leanza V, Coco L, Grasso F, Leanza G, Zarbo G, Palumbo M. Ovulation induction with clomiphene citrate for infertile couple. *Minerva Ginecologica* 2014;**66**(3):309-12.

Martinez 1990 *{published data only}*

Martinez AR, Bernardus RE, Voorhorst FJ, Vermeiden JP, Schoemaker J. Intrauterine insemination does and clomiphene citrate does not improve fecundity in couples with infertility due to male or idiopathic factors: a prospective, randomized, controlled study. *Fertility & Sterility* 1990;**53**(5):847-53.

Melis 1995 *{published data only}*

Melis GB, Paoletti AM, Ajossa S, Guerriero S, Depau GF, Mais V. Ovulation induction with gonadotropins as sole treatment in infertile couples with open tubes: a randomized prospective comparison between intrauterine insemination and timed vaginal intercourse. *Fertility & Sterility* 1995;**64**(6):1088-93.

Nandi 2017 *{published data only}*

* Nandi A, Bhide P, Hooper R, Gudi A, Shah A, Khan K, et al. Intrauterine insemination with gonadotropin stimulation or in vitro fertilization for the treatment of unexplained subfertility: a randomized controlled trial. *Fertility & Sterility* 2017;**107**(6):1329-35.e2.

Nandi A, Gudi A, Shah A, Hooper R, Khan K, Homburg R. Controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) vs. In Vitro fertilization (IVF) for the first line treatment of unexplained subfertility - a randomised controlled trial. *Human Reproduction* 2016;**31 Suppl 1**:i70-i71 Abstract no: O-167.

Steures 2006 *{published data only}*

Steures P, Van der Steeg JW, Hompes PGA, Bossuyt PMM, Habbema JDF, Eijkemans MJC, et al. Effectiveness of intrauterine insemination with ovarian hyperstimulation in couples with an unexplained moderately reduced fertility. *21st Annual Meeting of the European Society of Human Reproduction and Embryology, Copenhagen, Denmark, 19-22 June 2005* 2005;**20**(Suppl 1):i113.

Steures P, van der Steeg JW, Hompes PG, Bossuyt PM, van der Veen F, Habbema JD, et al. [Intra-uterine insemination with controlled ovarian hyperstimulation compared to an expectant management in couples with unexplained subfertility and an intermediate prognosis: a randomised study]. *Nederlands Tijdschrift voor Geneeskunde* 2008;**152**(27):1525-31.

* Steures P, van der Steeg JW, Hompes PG, Habbema JD, Eijkemans MJ, Broekmans FJ, et al. Collaborative Effort on the Clinical Evaluation in Reproductive Medicine. Intrauterine insemination with controlled ovarian hyperstimulation

versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. *Lancet* 2006;**368**(9531):216-21.

References to studies excluded from this review

Buvat 1993 *{published data only}*

Buvat J, Buvat Herbaut M, Marcolin G, Guittard C, Herbaut M, Verbecq P. Ovarian hyperstimulation and insemination vs IVF in unexplained infertility: results of randomized trial (poster). *Contraception, Fertilite, Sexualite* 1993;**21**:432.

Chung 1995 *{published data only}*

Chung CC, Fleming R, Jamieson ME, Yates RW, Coutts JR. Randomized comparison of ovulation induction with and without intrauterine insemination in the treatment of unexplained infertility. *Human Reproduction* 1995;**10**(12):3139-41.

Fujii 1997 *{published data only}*

Fujii S, Fukui A, Fukushi Y, Kagiya A, Sato S, Saito Y. The effects of clomiphene citrate on normally ovulatory women. *Fertility & Sterility* 1997;**68**(6):997-9.

Goldman 2010 *{published data only}*

Goldman MB, Regan MM, Alper MM, Thornton KL, Reindollar RH. Pregnancy rates across multiple treatment cycles: data from the fast track and standard treatment (FASTT) trial. *Fertility and Sterility* 2010;**94 Suppl 1**(4):S1 Abstract no. O-01.

Gregoriou 1995 *{published data only}*

Gregoriou O, Vitoratos N, Papadias C, Konidaris S, Gargaropoulos A, Louridas C. Controlled ovarian hyperstimulation with or without intrauterine insemination for the treatment of unexplained infertility. *International Journal of Gynaecology & Obstetrics* 1995;**48**(1):55-9.

Leanza 2014a *{published data only}*

Leanza V, Coco L, Grasso F, Leanza G, Zarbo G, Palumbo M. Unexplained infertility and ovulatory induction with menopausal gonadotropins. *Minerva Ginecologica* 2014;**66**(3):303-7.

Martinez 1991 *{published data only}*

Martinez AR, Bernardus RE, Voorhorst FJ, Vermeiden JP, Schoemaker J. Pregnancy rates after timed intercourse or intrauterine insemination after human menopausal gonadotropin stimulation of normal ovulatory cycles: a controlled study. *Fertility & Sterility* 1991;**55**(2):258-65.

Melis 1987 *{published data only}*

Melis G, Paoletti A, Strigini F, Fabris F, Canale D, Fioretti P. Pharmacologic induction of multiple follicular development improves the success rate of artificial insemination with husband's semen in couples with male-related or unexplained infertility. *Fertility & Sterility* 1987;**47**:441-5.

Murdoch 1991 *{published data only}*

Murdoch AP, Harris M, Mahroo M, Williams M, Dunlop W. Gamete intrafallopian transfer (GIFT) compared with intrauterine insemination in the treatment of unexplained infertility. *British Journal of Obstetrics & Gynaecology* 1991;**98**(11):1107-11.

Nulsen 1993 *{published data only}*

Nulsen JC, Walsh S, Dumez S, Metzger DA. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. *Obstetrics & Gynecology* 1993;**82**(5):780-6.

Prentice 1995 *{published data only}*

Prentice A, Sacks GP, Morton NC, Deary AJ, Smith SK. Controlled ovarian stimulation (superovulation) and intrauterine insemination for the treatment of unexplained and minor male factor infertility. *Human Reproduction (Oxford, England)* 1995;**10**:112.

Reindollar 2010 *{published data only}*

Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertility & Sterility* 2010;**94**(3):888-99.

Shokeir 2006 *{published data only}*

Shokeir TA. Tamoxifen citrate for women with unexplained infertility. *Archives of Gynecology & Obstetrics* 2006;**274**(5):279-83.

Soliman 1993 *{published data only}*

Soliman S, Daya S, Collins J, Jarrell J. A randomized trial of in vitro fertilization versus conventional treatment for infertility. *Fertility and Sterility* 1993;**59**(6):1239-44.

Tjon Kon Fat 2014 *{published data only}*

Tjon-Kon-Fat, R, Bensdorp, A. J, Mol, B. W. J, van der Veen, F, van Wely, M. The natural conception rate in couples with unexplained or mild male subfertility scheduled for treatment with IVF-SET, IVF-MNC or IUI-COH (INeS trial). *Human Reproduction* 2014;**29 suppl 1**:i214 Abstract no: P-234.

Zayed 1997 *{published data only}*

Zayed F, Lenton EA, Cooke ID. Comparison between stimulated in-vitro fertilization and stimulated intrauterine insemination for the treatment of unexplained and mild male factor infertility. *Human Reproduction* 1997;**12**(11):2408-13.

Zikopoulos 1993 *{published data only}*

Zikopoulos K, West CP, Thong PW, Kacser EM, Morrison J, Wu FC. Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility. *Human Reproduction* 1993;**8**(4):563-7.

Zolghadri 2012 *{published data only}*

Zolghadri J, Younesi M, Tabibi A, Khosravi D, Behdin S, Vafayee H. Comparison of intrauterine insemination with timed intercourse method in controlled ovarian hyperstimulation. *Iranian Journal of Reproductive Medicine* 2012;**10**:42.

References to ongoing studies

NCT01992731 *{published data only}*

NCT01992731. IUI vs. IVF/ICSI in Women Aged 38-42 Years: A Prospective Randomized Controlled Trial [IUI vs. IVF/ICSI in Women Aged 38-42 Years: A Prospective Randomized Controlled Trial]. clinicaltrials.gov/ct2/show/NCT01992731 (first posted 25 November 2013).

NCT02001870 *{published data only}*

NCT02001870. Comparison of the Efficiency of Intra-uterine Insemination and in Vitro Fertilization in Women Over 37 Years (AMPAGE) [Comparison of the Efficiency of Intra-uterine Insemination and in Vitro Fertilization in Women Over 37 Years (AMPAGE)]. clinicaltrials.gov/ct2/show/NCT02001870 (first posted 5 December 2013).

NCT02461173 *{published data only}*

NCT02461173. Stimulated Intrauterine Insemination Cycles and Unstimulated Intrauterine Insemination Cycles in Couples With Unexplained Infertility [Comparison Between Stimulated Intrauterine Insemination Cycles and Unstimulated Intrauterine Insemination Cycles in Couples With Unexplained Infertility]. clinicaltrials.gov/ct2/show/NCT02461173 (first posted 3 June 2015).

NCT03455426 *{published data only}*

NCT03455426. Intrauterine Insemination With Letrozole Versus Intrauterine Insemination in Natural Cycle. A Randomised Controlled Trial [Intrauterine Insemination With Letrozole Versus Intrauterine Insemination in Natural Cycle. A Randomised Controlled Trial]. clinicaltrials.gov/ct2/show/NCT03455426 (first posted 6 March 2018).

NTR5599 *{published data only}*

NTR5599. Intrauterine Insemination for Unexplained or Mild Male Subfertility [Intrauterine Insemination for Unexplained or Mild Male Subfertility]. trialregister.nl/trialreg/admin/rctview.asp?TC=5599 2016; Vol. (registered 18 December 2015).

Additional references

ASRM 2006

American Society for Reproductive Medicine. Effectiveness and Treatment for Unexplained Infertility. The practice committee of the American Society for Reproductive Medicine 2006.

Athaullah 2002

Athaullah N, Proctor M, Johnson N. Oral versus injectable ovulation induction agents for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003052]

Boivin 2007

Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human Reproduction* 2007;**22**:1506-12.

Brandes 2010

Brandes M, Hamilton CJCM, de Bruin JP, Nelen WLDM, Kremer JAM. The relative contribution of IVF to the total ongoing pregnancy rate in a subfertile cohort. *Human Reproduction* 2010;**25**:118-26.

Brandes 2011

Brandes M, Hamilton CJCM, van der Steen JOM, de Bruin JP, Bots RSGM, Nelen WLDM, et al. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. *Human Reproduction* 2011;**26**:360-8.

Chaimani 2013

Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS ONE* 2013;**8**(10):e76654.

Chaimani 2015

Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. *Stata Journal* 2015;**15**(4):905-50.

CINeMA 2017 [Computer program]

Institute of Social and Preventive Medicine, University of Bern 2017. Available from cinema.ispm.ch. CINeMA: Confidence in Network Meta-Analysis [Software].. Institute of Social and Preventive Medicine, University of Bern 2017. Available from cinema.ispm.ch, 2017.

Datta 2016

Datta J, Palmer MJ, Tanton C, Gibson LJ, Jones KG, Macdowall W, et al. Prevalence of infertility and help seeking among 15 000 women and men. *Human Reproduction* 2016;**31**(9):2108-18.

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;**29**(7-8):932-44.

Duffy 2018

Duffy JMN, Bhattacharya S, Curtis C, Evers JLH, Farquharson RG, et al. A protocol developing, disseminating and implementing a core outcome set for infertility. *Human Reproduction Open* 2018;**2018**(3):hoy007.

Gadalla 2018

Gadalla MA, Wang R, van Wely M, Mol BWJ. How should we report outcomes in reproductive medicine?. *Ultrasound in Obstetrics and Gynecology* 2018;**51**(1):7-9. [DOI: 10.1002/uog.18969]

Gnoth 2003

Gnoth C. Time to pregnancy: results of the German prospective study and impact of the management of infertility. *Human Reproduction* 2003;**18**:1959-66.

Gunn 2016

Gunn DD, Bates GW. Evidence-based approach to unexplained infertility: a systematic review. *Fertility and Sterility* 2016;**105**(6):1566-74.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2012

Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98-110.

Huang 2018

Huang S, Wang R, Li R, Wang H, Qiao J, Mol BWJ. Ovarian stimulation in infertile women treated with the use of intrauterine insemination: a cohort study from China. *Fertility and Sterility* 2018;**109**(5):872-8. [PUBMED: 29778386]

Hughes 2010

Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD000057.pub2]

Hull 1985

Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA, et al. Population study of causes, treatment, and outcome of infertility. *British Medical Journal (Clinical Research Ed.)* 1985;**291**:1693-7.

Hunault 2004

Hunault CC, Habbema JD, Eijkemans MJ, Collins JA, Evers JL, te Velde ER. Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. *Human Reproduction* 2004;**19**(9):2019-26.

Hunault 2005

Hunault CC, Laven JS, van Rooij IA, Eijkemans MJ, te Velde ER, Habbema JD. Prospective validation of two models predicting pregnancy leading to live birth among untreated subfertile couples. *Human Reproduction* 2005;**20**(6):1636-41.

Kamphuis 2014

Kamphuis EI, Bhattacharya S, van der Veen F, Mol BW, Templeton A, Evidence Based IVFG. Are we overusing IVF?. *BMJ* 2014;**348**:g252.

Kandavel 2018

Kandavel V, Cheong Y. Does intra-uterine insemination have a place in modern ART practice?. *Best Practice & Research: Clinical Obstetrics & Gynaecology* 2018;**53**(11):3-10. [DOI: 10.1016/j.bpobgyn.2018.08.003]

Mathur 2005

Mathur R, Evbuomwan I, Jenkins J. Prevention and management of ovarian hyperstimulation syndrome. *Current Obstetrics and Gynaecology* 2005;**15**:132-8.

NICE 2013

Fertility Guideline. National Institute for Health and Care Excellence 2013.

NVOG 2010

Guideline: unexplained subfertility [Richtlijn: Onverklaarde subfertiliteit]. Dutch Society of Obstetrics and Gynaecology (NVOG) 2010.

Palermo 1992

Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992;**340**:17-8.

Pandian 2015

Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD003357.pub4]

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163–71.

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;**9**(7):e99682.

Steptoe 1978

Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet* 1978;**2**:366.

Stocking 2019

Stocking K, Wilkinson J, Lensen S, Brison DR, Roberts SA, Vail A. Are interventions in reproductive medicine assessed for plausible and clinically relevant effects? A systematic review of power and precision in trials and meta-analyses. *Human Reproduction* 2019;**34**(4):659-65.

Tjon-Kon-Fat 2015

Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PM, Koks C, Oosterhuis GJ, Hoek A, et al. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation?. *Human Reproduction* 2015;**30**(10):2331-9.

van Eekelen 2017

van Eekelen R, Scholten I, Tjon-Kon-Fat RI, van der Steeg JW, Steures P, van Wely M, et al. Natural conception: repeated predictions over time. *Human Reproduction* 2017;**32**(2):346-53.

van Eekelen 2019

van Eekelen R, van Geloven N, van Wely M, McLernon DJ, Mol F, Custers IM, et al. Is IUI with ovarian stimulation effective in couples with unexplained subfertility?. *Human Reproduction* 2019;**34**(1):84-91.

van Rumste 2014

van Rumste MM, Custers IM, van Wely M, Koks CA, van Weering HG, Beckers NG, et al. IVF with planned single-embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility: an economic analysis. *Reproductive Biomedicine Online* 2014;**28**(3):336-42. [PUBMED: 24456703]

Veltman-Verhulst 2016

Veltman-Verhulst SM, Hughes E, Olugbenga Ayeleke R, Cohlen BJ. Intra-uterine insemination for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2016, Issue 2. [DOI: 10.1002/14651858.CD001838.pub5]

White 2015

White IR. Network meta-analysis. *Stata Journal* 2015;**15**(4):951-85.

Zegers-Hochschild 2017

Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. *Human Reproduction* 2017;**32**(9):1786-801.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agarwal 2004

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS • *Female age*: 28.83 ± 4.76 years (mean ± SD) • *Duration of infertility*: 4.93 ± 3.27 years (mean ± SD) OS-IUI • *Female age*: 29.52 ± 3.65 years (mean ± SD) • *Duration of infertility*: 4.91 ± 2.72 years (mean ± SD) **Sample size:** OS (n = 69); OS-IUI (n = 44) **Included criteria:** couples with unexplained infertility: biphasic basal body temperature charts; in-phase late luteal endometrial biopsy; normal serum levels of thyroid, prolactin, luteinising hormone, and follicle-stimulating hormone; hysterosalpingogram indicating normal uterine contour and laparoscopy indicating bilateral tubal patency; absence of pelvic adhesions; and endometriosis. All men had normal values on at least 2 standard semen analyses (sperm concentration > 20 million/mL, > 50% motile, and > 50% morphologically normal spermatozoa) and a positive post-coital test. Tests for immunological causes of infertility for both partners revealed negative results (antisperm antibodies) **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** OS • *Description*: clomiphene citrate 50 to 150 mg orally from day 3 to 7 of menstrual cycle depending on response. Follicular monitoring was done by serial vaginal ultrasonography beginning day 10 until demonstration of ovulation. Human chorionic gonadotropin (hCG) 10,000 IU intramuscular was administered when not more than 4 leading follicles > 16 mm were seen. Couples were advised to have intercourse 36 to 40 hours after administration of hCG OS-IUI

Agarwal 2004 *(Continued)*

- *Description*: clomiphene citrate 50 to 150 mg orally from day 3 to 7 of menstrual cycle depending on response. Follicular monitoring was done by serial vaginal ultrasonography beginning day 10 until demonstration of ovulation. hCG 10,000 IU intramuscular was administered when not more than 4 leading follicles > 16 mm were seen. IUI was performed 36 to 40 hours later. Sperm cells present in 90% fraction were used after 2 washes to remove the Percoll. Culture media used were Ham's F10 (SIGMA, USA) enriched with 7.5% patient's serum or 1% human serum albumin. A volume of 0.3 to 0.4 mL of the preparation was taken for IUI with an IUI cannula used for the procedure. The woman was instructed to lie in supine/lateral position for 30 minutes after the procedure

Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** Council of Scientific and Industrial Research, New Delhi, India **Country:** India **Setting:** Gynecological Outpatients of All India Institute of Medical Sciences (AIIMS), New Delhi **Author's name:** Sonika Agarwal **Institution:** Department of Obstetrics Gynaecology, All India Institute of Medical Sciences, New Delhi, India **Email:** agarwalsonika@hotmail.com
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 140 couples were divided into two groups using random number table, 70 in each group and followed over three years" Judgement comment: random numbers table used
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blind not likely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Twenty six women in group B and one in group A did not have complete follow up and were thus excluded from the analysis" Judgement comment: 26/70 in OS-IUI group and 1/70 in OS group lost to follow-up
Selective reporting (reporting bias)	High risk	Judgement comment: outcomes for the 2 groups (live birth, miscarriage, and multiple pregnancy) not reported separately
Other bias	Low risk	Judgement comment: no other sources of bias detected

Arcaini 1996

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS • *Female age*: 33.4 ± 4.7 years (mean ± SD) • *Duration of infertility*: 47 (28 ± SD) months OS-IUI • *Female age*: 34.6 (4.9 ± SD) years • *Duration of infertility*: 50 (19 ± SD) months **Sample size:** OS (n = 32); OS-IUI (n = 36) **Included criteria:** unexplained infertility diagnosed after normal results were obtained from the following tests: basal body temperature measurements and endometrial biopsy in the luteal phase, hysterosalpingography, post-coital test, and at least 2 semen analyses for the partner. Laparoscopy showed a normal pelvis in all patients **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** OS • *Description*: CC 100 mg/d from day 3 to 7 of the cycle and hMG 1 to 3 ampoules/d from day 8 of the cycle until development of 2 or more follicles (maximum 6) with diameter > 17 mm. hCG 10,000 IU was administered when 17beta E2 levels were > 200 pg/mL/follicle but not over a total of 2000 pg/mL, and when the lead follicles had diameter > 17 mm. Intercourse was recommended 24 and 48 hours after hCG administration. Three to five cycles of treatment, preferably consecutive, were planned OS-IUI • *Description*: CC 100 mg/d from day 3 to 7 of the cycle and hMG 1 to 3 ampoules/d from day 8 of the cycle until development of 2 or more follicles (maximum 6) with diameter > 17 mm. hCG 10,000 IU was administered when 17beta E2 levels were > 200 pg/mL/follicle but not over a total of 2000 pg/mL, and when the lead follicles had diameter > 17 mm. IUI was performed 24 and 48 hours after hCG administration. Three to five cycles of treatment, preferably consecutive, were planned
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** NA **Country:** Italy **Setting:** Infertility Unit of the Modern Medical Center, Milan, Italy **Authors name:** Luisa Arcaini, Luigi Fedele* **Institution:** Department of Obstetrics and Gynecology, L. Mangiagalli, University of Milan, Milan, Italy **Email:** NA
Notes	
Risk of bias	

Arcaini 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding not likely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 14/68 (20.5%) lost to follow-up
Selective reporting (reporting bias)	High risk	Judgement comment: outcomes for the 2 groups (live birth/ongoing pregnancy, miscarriage, and multiple pregnancy) not reported separately
Other bias	Low risk	Judgement comment: no sources of bias detected

Arici 1994

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over Only data for the first cycle (before cross-over) were extracted
Participants	**Baseline characteristics** Overall • *Female age*: 32.3 years (mean) • *Duration of infertility*: 3.5 years (mean) **Sample size:** IUI (n = 16); OS-IUI (n = 10) **Included criteria:** for unexplained infertility, all couples exhibited normal semen analysis, negative antisperm antibodies, normal hysterosalpingogram, regular ovulatory cycles (by luteal phase P levels and/or in-phase endometrial biopsy), and normal laparoscopic findings. Five patients with surgically treated minimal endometriosis without pelvic adhesive disease were included in this diagnostic group **Excluded criteria:** all patients positive for sperm antibodies by immunobead testing were excluded. Couples unwilling to be randomised were also excluded from the study **Pretreatment:** NA
Interventions	**Intervention characteristics** IUI

Arici 1994 *(Continued)*

- *Description*: the natural cycle group underwent urinary LH timed IUI during an unstimulated natural cycle. Urine samples were collected twice daily, in the evening and as the second voided morning sample, and quantitative urinary LH measurements were performed using an immunofluorometric assay (Delphia; LKB-WAUAC Pharmacia, Turku, Finland). Intrauterine insemination was performed on the day of the LH peak and the next day when possible

OS-IUI

- *Description*: 50 mg CC/d between days 5 and 9 of the menstrual cycle. An injection of 10,000 U 1 M hCG was administered when 1 or more follicles reached 18 mm mean diameter as determined by US. A single IUI was performed 32 hours after hCG injection

Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** NA **Country:** USA **Setting:** tertiary academic medical centre **Author's name:** Aydin Arici **Institution:** Department of Obstetrics and Gynecology, Yale University School of Medicine **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "couples were randomized using a computer-generated random numbers table to one of the two study groups"
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding not likely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: original report included 2 subgroups of participants: male infertility and unexplained infertility. Data for participants lost to follow-up not reported separately
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth and multiple pregnancy not reported
Other bias	Unclear risk	Judgement comment: no sufficient information to judge baseline characteristics

Bensdorp 2015

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS-IUI • *Female age*: 34 ± 3.67 years (mean ± SD) • *Duration of infertility*: 2.30 (1.82 to 3.13) years (median, IQR) IVF/ICSI • *Female age*: 33 ± 3.39 years (mean ± SD) • *Duration of infertility*: 2.13 (1.73 to 3.01) years (median, IQR) **Sample size:** OS-IUI (n = 207); IVF/ICSI (n = 201) **Included criteria:** couples seeking fertility treatment after at least 12 months of unprotected intercourse were eligible. All couples underwent basic fertility investigations, which included semen analysis, evaluation of ovulation, and tubal patency testing (Chlamydia antibody test, hysterosalpingography, or laparoscopy). Inclusion criteria were age of female partner between 18 and 38 years, unfavourable prognosis for natural conception, and diagnosis of unexplained or mild male subfertility. We classified couples as having unexplained subfertility when fertility investigations showed at least 1 patent fallopian tube, an ovulatory menstrual cycle, and a normal semen analysis (pre-wash total motile sperm count > 10 million). We considered couples who qualified for intrauterine insemination with donor sperm after at least 6 cycles of artificial intracervical insemination with donor sperm to have unexplained subfertility for the purpose of this study. Mild male subfertility was diagnosed when semen analysis showed a pre-wash total motile sperm count between 3 and 10 million (according to Dutch guidelines). We defined an unfavourable prognosis for natural conception as a probability of natural conception within the next 12 months of < 30%, as calculated through the validated synthesis model of Hunault. This model encompasses female age, duration of subfertility, whether subfertility is primary or secondary, percentage of motile progressive sperm, and referral status. It is readily available for the use of all clinicians (www.freya.nl/web_bereken/bereken.php) **Excluded criteria:** anovulation, double-sided tubal disease, severe endometriosis, premature ovarian failure, known endocrine disorders (such as Cushing's syndrome or adrenal hyperplasia) **Pretreatment:** none
Interventions	**Intervention characteristics** OS-IUI • *Description*: intrauterine insemination with controlled ovarian hyperstimulation: (1) hyperstimulation from cycle day 3 or 4; start with 100 mg clomiphene citrate or subcutaneous injections of 75 IU FSH; (2) monitoring of follicular growth by transvaginal ultrasound; (3) induction of final oocyte maturation with 5000 IU of hCG when ≥ 1 follicle has diameter of 17 or 18 mm; (4) IUI 36 hours thereafter • Cancel criteria: hCG administration and IUI withheld with > 3 follicles with diameter of 16 mm or > 5 follicles with diameter of 12 mm IVF/ICSI • *Description*: in vitro fertilisation with single embryo transfer: (1) downregulation with GnRH agonist in long/short protocol or fixed start antagonist protocol; stimulation start dose 150 IU FSH; (2) ultrasound monitoring according to local protocol; (3) ovulation induction with 10,000 IU hCG until ≥ 2 follicles > 18 mm; (4) oocyte retrieval 36 hours thereafter; (5) embryo transfer day 2, 3, or 4; (6) cryopreservation of non-transferred good quality embryos (1 embryo will be transferred per freeze-thaw cycle if it is of good quality) • Cancel criteria: ovarian hyperstimulation syndrome, non-response
Outcomes	*Clinical pregnancy*

Bensdorp 2015 *(Continued)*

	Live birth *Multiple pregnancy* *OHSS*
Identification	**Sponsorship source:** the study was supported by a grant from ZonMW, the Dutch Organization for Health Research and Development (120620027), and a grant from Zorgverzekeraars Nederland, the Dutch Association of Healthcare Insurers (09-003) **Country:** Netherlands **Setting:** 17 fertility clinics in Netherlands **Authors' names:** A.J. Bensdorp, M. van Wely* **Institution:** Centre for Reproductive Medicine, Academic Medical Centre, University of Amsterdam, 1100DD Amsterdam, Netherlands **Email:** m.vanwely@amc.nl
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with an online randomisation program, using biased coin minimisation, stratified for study centre"
Allocation concealment (selection bias)	Low risk	Quote: "minimisation, stratified for study centre. A web based program generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither the recruiters nor the trial project group could access the randomisation sequence. " Judgement comment: a web-based programme generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither the recruiters nor the trial project group could access the randomisation sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "blinding was not possible owing to the nature of the interventions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding not likely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: IVF (SET): 2/201 lost to follow-up; IVF (NC): 3/194 lost to follow-up; OS-IUI: 1/207 lost to follow-up
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Bhattacharya 2008

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** EM • *Female age*: 32 ± 3.4 years (mean ± SD) • *Duration of subfertility (months)*: 30 (25 to 38) months (median, IQR) OS • *Female age*: 32 ± 3.5 years (mean ± SD) • *Duration of subfertility (months)*: 30 (24 to 38) months (median, IQR) IUI • *Female age*: 32 ± 3.7 years (mean ± SD) • *Duration of subfertility (months)*: 30 (25 to 40) months (median, IQR) **Sample size:** EM (n = 193); OS (n = 194); IUI (n = 193) **Included criteria:** at least 2 years of infertility, bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography), ovulation demonstrated by appropriately timed mid-luteal progesterone, and normal semen variables (according to World Health Organization criteria). Also couples with minimum sperm motility of 20% or minimal endometriosis (rAFS stage 1) **Excluded criteria:** NA **Pretreatment:** none
Interventions	**Intervention characteristics** EM • *Description*: 6 months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse, but no specific measures such as basal temperature charts or luteinising hormone kits were recommended OS • *Description*: 50 mg (starting dose) CC from day 2 to 6 of each treatment cycle. Couples were advised to have intercourse on days 12 to 18 of the cycle. If 3 or more ovarian follicles were detected by scan in the first cycle, the cycle was cancelled and the couple was advised to avoid intercourse. In the next cycle, women who were overstimulated on the first cycle started on a reduced dose of clomiphene (25 mg) and were monitored in the same way as they would be for a first cycle (i.e. scan on day 12 and blood test for progesterone on day 21) with a further reduction to alternate days of 25 mg offered in the next cycle if necessary IUI • *Description*: monitor urinary luteinising hormone concentrations from day 12 of the cycle. A single insemination was performed 20 to 30 hours after an endogenous surge was detected
Outcomes	*Live birth* *Clinical pregnancy* *Multiple pregnancy* *OHSS*

Bhattacharya 2008 *(Continued)*

Identification	**Sponsorship source:** Chief Scientist Office, Scotland **Country:** UK **Setting:** 4 teaching hospitals and a district general hospital in Scotland **Author's name:** S. Bhattacharya **Institution:** Department of Obstetrics and Gynaecology, University of Aberdeen **Email:** s.bhattacharya@abdn.ac.uk
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement comment: central telephone randomisation system used
Allocation concealment (selection bias)	Low risk	Quote: "research nurses enrolled participants at each centre and assigned them to their groups using a central telephone randomisation system based in Aberdeen (the coordinating centre)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Non-blinding not likely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: lost to follow-up (EM: 0, OS: 2, IUI: 2)
Selective reporting (reporting bias)	Low risk	Judgement comment: all outcomes prespecified and adequately reported
Other bias	Low risk	Judgement comment: no other bias detected

Crosignani 1991

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over (after the first cycle)
Participants	**Baseline characteristics** Overall • *Female age*: NA • *Duration of infertility*: NA **Sample size:** OS (n = 73); OS-IUI (n = 64); IVF/ICSI (n = 30)

Crosignani 1991 *(Continued)*

	Included criteria: (a) women were to be < 38 years of age and must have experienced > 36 months of infertility before study entry; (b) only women with at least 1 macroscopically normal tubo-ovarian unit, as identified by a recent diagnostic laparoscopy, were included; (c) there must have been evidence of the occurrence of spontaneous ovulation in 2 recent cycles, as judged by plasma progesterone levels in the luteal phase; (d) it was necessary for semen to be classed as 'normal' by WHO criteria; (e) it was mandatory for patients to refrain from sexual activity for 6 days before and 3 days after treatments; (f) there must have been a period of at least 2 months without treatment for infertility before study entry **Excluded criteria:** NA **Pretreatment:** no
Interventions	**Intervention characteristics** OS • *Description*: NA OS-IUI • *Description*: NA IVF/ICSI • *Description*: NA
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** Ares-Serono (Geneva) **Country:** France, Greece, Italy, Germany, Belgium, Sweden, Norway, Finland, Austria, and Netherlands **Setting:** 19 fertility centres in Europe **Authors' names:** P.G. Crosignani, D.E. Walters* **Institution:** Department of Obstetrics and Gynaecology, University of Milan, Milan, Italy **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details of sequence generation at each centre not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details of allocation concealment at each centre not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible because of the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes

Crosignani 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: details not reported
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth and multiple pregnancy not reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Custers 2011

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS-IUI • *Female age*: 34.0 (2.9) years • *Duration of infertility*: 2.2 (1.8) years IVF/ICSI • *Female age*: 33.6 (3.0) years • *Duration of infertility*: 2.3 (1.9) years **Sample size:** OS-IUI (n = 58); IVF/ICSI (n = 58) **Included criteria:** couples were invited to participate if they were diagnosed with unexplained or mild male subfertility. Couples had to have poor fertility prospects as calculated by the validated model of Hunault. Poor fertility prospects were defined as a chance of natural conception of 30% within 12 months. All couples had undergone a basic fertility workup according to the guidelines of the Dutch Society of Obstetrics and Gynecology. This workup included medical history, cycle monitoring, post-coital test, semen analysis, and assessment of tubal patency. Mild male subfertility was defined as a total motile count (TMC) of 3 to 10 × 10^6 spermatozoa/mL. Unexplained subfertility was defined as TMC > 10 × 10^6 spermatozoa/mL and exclusion of a cervical factor **Excluded criteria:** other causes of subfertility, including severe male subfertility, cervical factor, and polycystic ovary syndrome; female age > 38 years; prior treatment within this subfertility episode. Age limit was based on concerns that IUI-COS may compromise pregnancy rates in older women **Pretreatment:** none detected
Interventions	**Intervention characteristics** OS-IUI • *Description*: in couples allocated to receive IUI-COS, women underwent ovarian stimulation with 50 to 75 IU rFSH (Puregon; Organon) in a low-dose step-up protocol to achieve the growth of 1 to (maximally) 3 dominant follicles. In case the cycle was monofollicular, the amount of rFSH was raised in the subsequent cycle. Cycles with 1 dominant follicle (R15 mm) and at least 1 more follicle > 10 mm at the time of hCG administration were considered multi-follicular. In case more than 3 dominant follicles were present, the cycle was cancelled. Ovulation was induced with 5000 or 10,000 IU of hCG (Pregnyl). Semen samples were processed within 1 hour of ejaculation by density-gradient centrifugation followed by washing with culture medium. The volume of semen that was inseminated varied between 0.2 mL and 1.0 mL. Women were inseminated 36 to 40 hours after hCG administration IVF/ICSI

Custers 2011 *(Continued)*

- *Description*: patients allocated to receive IVF-eSET underwent controlled ovarian hyperstimulation after downregulation with the GnRH agonist triptorelin (Ferring) in a long protocol with a midluteal start. Controlled ovarian hyperstimulation was started with 100 to 150 U recombinant FSH (rFSH). Treatment was continued until at least 3 follicles > 18 mm had developed. Ovulation was induced by 10,000 IU hCG (Pregnyl; Organon), and cumulus–oocyte complexes were recovered by transvaginal ultrasound–guided retrieval 36 hours thereafter. Embryos were scored with the use of validated morphological scoring criteria at the time of fertilisation (pronuclear morphology) and daily until the time of transfer. Embryos were assessed for their morphology daily by an embryologist/IVF technician using an Olympus IX71 inverted microscope equipped with Relief Contrast optics at a magnification of 320, or a similar kind of microscope. On day 3, 1 embryo was selected for transfer if 1 or more embryos of good quality were available. In case no good-quality embryos were available, 2 embryos were transferred. Non-transferred good-quality embryos were cryopreserved on the fourth day (conventional slow freezing). When implantation was not successful or early miscarriage occurred, the frozen embryos were thawed and transferred. Again, only 1 embryo was transferred per freeze–thaw cycle if it was of good quality

Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy*
Identification	**Sponsorship source:** Organon, Oss, Netherlands. **Country:** Netherlands **Setting:** 3 academic and 6 teaching hospitals in Netherlands **Author's name:** Inge M. Custers **Institution:** Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center, Room H4-213, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands **Email:** i.m.custers@amc.uva.nl
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "couples who gave informed consent were randomized by a central Internet-based randomization stratified for center"
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: zero lost to follow-up

Custers 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Deaton 1990

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Female age*: 33 (4.0) years • *Duration of infertility*: 3.5 (1.7) years **Sample size:** EM (n = 28); OS-IUI (n = 23) **Included criteria:** couples with unexplained infertility or surgically corrected endometriosis **Excluded criteria:** women with tubal disease **Pretreatment:** NA
Interventions	**Intervention characteristics** EM • *Description*: during the 4 control cycles, the couple was instructed to have intercourse during the periovulatory period. The BBT chart or luteinising hormone (LH) kit was analysed after each cycle to ensure that intercourse was appropriately timed. No other adjuvant therapy was used during the control cycles. Women exhibiting an anovulatory cycle at any time during the study were excluded from the analysis OS-IUI • *Description*: treatment cycles: treatment consisted of CC 50 mg orally on cycle days 5 through 9. If a subject's cycle length was 27 days, then the CC was given on days 4 through 8. Morning ultrasound for folliculogenesis was performed during the first cycle on or about day 12. Timing of the ultrasound in future cycles was planned based on the response in the first cycle. Assuming follicular growth of 2 mm/d, an intramuscular injection of human chorionic gonadotropin (hCG) 10,000 U was administered on the evening when the lead follicle was estimated to be at least 18 mm. Thirty-six hours after hCG injection, a semen sample for IUI was obtained. After liquefaction, the ejaculate was placed in 10 cc warmed (38℃) Ham's F-10 (GIBCO, Grand Island, NY) and centrifuged at 1000 × g for 5 minutes. The supernatant was then discarded, and the pellet was resuspended in roughly 200 µL. Sperm suspension was introduced into the uterine cavity via a no. 5 paediatric feeding tube
Outcomes	*Clinical pregnancy* *Multiple pregnancy* *OHSS* *Ongoing pregnancy*
Identification	**Sponsorship source:** American College of Obstetricians and Gynecologists, Washington, DC; Mead Johnson Laboratories, Evansville, IN

Deaton 1990 *(Continued)*

	Country: USA
	Setting: University of Vermont College of Medicine
	Authors' names: Jeffrey L. Deaton, John R. Brumsted
	Institution: Department of Obstetrics and Gynecology, University of Vermont, Given C-252, Burlington, VT 05405
	Email: NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 16/67 participants excluded from analysis due to anovulation, poor semen quality, or inability to follow the treatment protocol. Of the remaining 51 participants, 6 couples did not complete treatment because of illness or relocation. 4/51 dropped out before cross-over
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth not reported
Other bias	Unclear risk	Judgement comment: insufficient data to make a judgement

Elzeiny 2014

Methods	**Study design:** randomised controlled trial
	Study grouping: parallel group
Participants	**Baseline characteristics**
	IVF/ICSI
	• *Female age*: 34 (3.5) years • *Duration of infertility*: 3.1 (1.3) years
	OS-IUI
	• *Female age*: 33 (4.2) years

Elzeiny 2014 *(Continued)*

- *Duration of infertility*: 3.2 (2.5) years

Sample size: IVF/ICSI (n = 11); OS-IUI (n = 33)

Included criteria: eligible participants were adults, had primary or secondary infertility of at least 1 year's duration, with evidence of ovulation and tubal patency, and were 18 to 42 years of age if female and 18 to 60 years of age if male

Excluded criteria: IUI or IVF treatment in previous 12 months, coital disorder, untreated ovulatory disorders, or endometriosis (American Fertility Society criteria grade 2 to 4), tubal obstruction, abnormal semen analyses (concentration $20*10^6$/mL, progressive motility 25%, abnormal morphology > 95% or positive sperm antibodies), or any contraindication for multiple pregnancy

Pretreatment: NA

Interventions	**Intervention Characteristics** IVF/ICSI • *Description*: all female participants received the same ovarian stimulation protocol using recombinant FSH 112.5 IU/d (Gonal-F; Serono East Frenchs Forest, Australia) starting from cycle day 3. Transvaginal ultrasound was performed on day 8 of the cycle and was repeated every 2 to 3 days if necessary. When ultrasound revealed follicles reaching a mean diameter of 14 mm, 250 g per day of GnRH antagonist Cetrorelix (Serono, East Frenchs Forest, Australia) was given to prevent premature ovulation and was repeated if necessary to avoid weekend oocyte retrieval. To minimise complications of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy, only women who had an ultrasound scan indicating that there would be either 2 or 3 preovulatory follicles (> 16 mm) at the time of hCG injection were randomised 3 to 1 to IUI or IVF. Final oocyte maturation was induced with 250 g of recombinant hCG (Ovidrel, Serono, East Frenchs Forest, Australia) when follicles had reached 18 mm in mean diameter, and IUI or IVF was scheduled 36 hours later. For IVF, oocyte retrieval was performed 36 hours after hCG administration under light sedation using transvaginal ultrasound, and groups of 2 or 3 oocytes were cultured with 0.29 10^6/mL motile sperm in 0.5 mL of Quinn's Advantage Sequential Medium. Embryo transfer of 1 or 2 embryos at cleavage stage, according to patient preference, was performed using a soft catheter (Cook Ireland Ltd, Limerick, Ireland). Embryos were selected for transfer on cell number and morphological grade. Supernumerary embryos were cryopreserved for subsequent transfer OS-IUI • *Description*: all female participants received the same ovarian stimulation protocol using recombinant FSH 112.5 IU/d (Gonal-F; Serono East Frenchs Forest, Australia) starting from cycle day 3. Transvaginal ultrasound was performed on day 8 of the cycle and was repeated every 2 to 3 days if necessary. When ultrasound revealed follicles reaching a mean diameter of 14 mm, 250 g per day of GnRH antagonist Cetrorelix (Serono, East Frenchs Forest, Australia) was given to prevent premature ovulation and was repeated if necessary to avoid weekend oocyte retrieval. To minimise complications of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy, only women who had an ultrasound scan indicating that there would be either 2 or 3 preovulatory follicles (> 16 mm) at the time of hCG injection were randomised 3 to 1 to IUI or IVF. Final oocyte maturation was induced with 250 g of recombinant hCG (Ovidrel, Serono, East Frenchs Forest, Australia) when follicles had reached 18 mm in mean diameter and IUI or IVF was scheduled 36 hours later. For IUI, fresh semen was collected after 2 days' abstinence and when liquefied was prepared using colloidal silica density gradient and made up to a final volume of 0.6 mL. An aliquot of 0.1 mL was used for analysis to determine motile sperm concentration, and 0.5 mL was used for insemination. Insemination was performed using an intrauterine insemination catheter (Cook Ireland Ltd., Limerick, Ireland)
Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy* *OHSS*

Elzeiny 2014 *(Continued)*

Identification	**Sponsorship source:** Serono (Geneva, Switzerland) and Melbourne IVF (Melbourne, AUSTRALIA) supported this trial financially **Country:** Australia **Setting:** a tertiary level fertility centre at the Royal Women's Hospital in Melbourne **Author's name:** Hossam ELZEINY **Institution:** Reproductive Services, Royal Women's Hospital, Carlton; Melbourne IVF, 320 Victoria Parade, East Melbourne, Vic 3002, Australia **Email:** Hossam.elzeiny@mivf.com.au
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated, adaptive-biased coin randomisation schedule"
Allocation concealment (selection bias)	Low risk	Quote: "allocation was concealed through the use of sequentially numbered opaque sealed envelopes and was held by the research trial manager and opened after the clinician indicated two or three follicles"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 1/44 not included in the analysis
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Farquhar 2017

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** EM • *Female age*: 33.6 (3.7) years • *Duration of infertility*: median IQR 46.0 (27.8 to 60.0) months

Farquhar 2017 *(Continued)*

	OS-IUI • *Female age*: 34.4 (3.5) years • *Duration of infertility*: 41.0 (31.0 to 60.0) months **Sample size:** EM (n = 100); OS-IUI (n = 101) **Included criteria:** we included women younger than 42 years with body mass index < 35 kg/m² and unexplained infertility, which was defined as normal ovulation (or normal with ovarian stimulation), bilateral patent fallopian tubes as determined by laparoscopy or hysterosalpingography, normal semen analysis (progressive motility ≥ 32% and concentration ≥ 15 million per mL), and a prediction score of natural conception leading to live birth in the next year < 30%. We used the validated Hunault prediction model for natural conception, which includes age, length of infertility, any previous pregnancies, source of referral, and sperm motility. We included women with mild endometriosis (diagnosed by laparoscopy), polycystic ovarian syndrome according to the Rotterdam criteria (providing ovulation was confirmed with or without ovarian stimulation for at least six cycles), and previous IUI or IVF cycles **Excluded criteria:** couples requiring donor sperm **Pretreatment:** NA
Interventions	**Intervention characteristics** EM • *Description*: couples assigned to EM were followed up for 3 cycles. They were advised to be sexually active around the likely time of ovulation and were provided with a diary to record the first day of each menstrual cycle and dates of sexual activity. Women in the EM group who had anovulatory polycystic ovary syndrome continued with their ovulation induction OS-IUI • *Description*: in the IUI with ovarian stimulation group, women received oral clomiphene citrate (Merck Serono; 50 to 150 mg, days 2 to 6) or oral letrozole (Douglas Pharmaceuticals; 2.5 to 7.5 mg, days 2 to 6) for ovarian stimulation according to patient response. Choice of ovarian stimulation was made by the clinic. When 1 to 3 follicles were present, IUI was performed by injecting the prepared sample of 0.5 mL sperm into the uterus. Oestradiol and luteinising hormone were measured on day 7. Serial ultrasound started when oestradiol was higher than 400 pmol/L in the first cycle and if clinically indicated on subsequent cycles. Daily luteinising hormone tracking started when the leading follicle was 14 mm or larger in diameter, or when oestradiol reached 400 pmol/L. When 1 to 3 follicles were present, IUI was performed approximately 24 hours after the luteinising hormone surge or 36 hours after a human chorionic gonadotropin trigger injection. Ultrasound generally was not used in the second or third cycle unless the oestradiol level was ≥ 2000 pmol/L. Letrozole cycles were monitored with both oestradiol levels and ultrasound. The semen sample was prepared using density gradients of 45% and 90%, and following centrifugation, the sample was washed in 3 mL of culture media and was resuspended in 0.5 mL of culture media. A TomCat catheter (Santesel, Turkey) was used for a single insemination. The prepared sperm sample of 0.5 mL was injected into the uterus. Luteal support was not routinely given. If 7 days after insemination, the progesterone level was < 20 pmol/L, utrogestan vaginal pessaries 200 mg 3 times a day were started. Cycles were cancelled if there was no response (no rise in oestradiol or development of follicles) or if there were more than 3 follicles (in which case women were requested to avoid unprotected intercourse). The cancelled cycle was replaced by a further cycle with appropriate dose adjustment
Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy*
Identification	**Sponsorship source:** Auckland Medical Research Foundation, Evelyn Bond Fund of Auckland District Health Board, Mercia Barnes Trust of Royal Australian, and New Zealand College of Obstetricians and

Farquhar 2017 *(Continued)*

	Gynaecologists, Maurice and Phyllis Paykel Trust, and The Nurture Foundation for Reproductive Research **Country:** New Zealand **Setting:** 2 fertility clinics in New Zealand **Author's name:** Cynthia M. Farquhar **Institution:** Department of Obstetrics and Gynaecology, University of Auckland, Auckland 1101, New Zealand **Email:** c.farquhar@auckland.ac.nz
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "we used a computer-generated randomisation sequence, prepared by an independent statistician, to randomly assign women (1:1) to three cycles of IUI with ovarian stimulation or three cycles of EM in blocks of four, six, and ten, without stratification"
Allocation concealment (selection bias)	Low risk	Quote: "allocations were concealed in sequentially numbered, sealed, opaque envelopes, which were opened by the study coordinator at the University of Auckland research department after verification of the inclusion criteria and obtaining written informed consent from each participant"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the participating couple and the clinicians were informed of treatment allocation" Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no data were missing for any of the pregnancy, livebirth, or neonatal outcomes" Judgement comment: zero lost to follow-up
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Fisch 1989

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall

Fisch 1989 *(Continued)*

- *Female age*: 30.3 (3) years
- *Duration of infertility*: 4.3 (1.4) years

Sample size: OS (n = 76); EM (n = 72)

Included criteria: unexplained infertility; primary infertility of 2 or more years' duration; normal history and physical examination; proven ovulation by regular cycles and biphasic basal body temperature charts, serum progesterone (P) > 10 ng/mL in the midluteal phase, or an in-phase, secretory endometrial biopsy in the late luteal phase; normal hysterosalpingogram; normal laparoscopy done within the last 2 years confirming bilateral tubal patency and no other pelvic pathology; normal serum prolactin; ≥ 2 normal semen analyses fitting the following criteria: volume > 1 cc, count ˜20 × 10^6 sperm/cc, morphology > 60% normal, motility > 50%

Excluded criteria: NA

Pretreatment: NA

Interventions	**Intervention characteristics** OS • *Description*: group 3 patients were given CC tablets (Serophene, Serono, Randolph, MA) 100 mg (2 tablets) on cycle day 5 to 9 with saline injections as in group 1. Group 4 patients were given CC and hCG injections with dosage and schedule as noted previously EM • *Description*: group 1 patients were given a placebo (2 tablets) taken by mouth on cycle day 5 to 9 followed by saline injections given intramuscularly (IM) on cycle days 19, 22, 25, and 28. Group 2 patients were given placebo tablets as described above with hCG injections (APL; Ayerst Pharmaceuticals, Montreal, Quebec, Canada) 5000 IU given IM on cycle days 19, 22, 25, and 28
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** Medical Research Council of Canada, Ayerst Pharmaceutical Company, Pharmascience, Montreal, Quebec, Canada **Country:** Canada **Setting:** 5 Canadian university centres **Authors' names:** Patricia Fisch, Robert F. Casper* **Institution:** 6-240 EN, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada, M5G 2C4 **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using a computer-generated random number table"
Allocation concealment (selection bias)	Low risk	"assignment of code numbers and distribution of drugs was coordinated by one center"

Fisch 1989 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear whether outcome assessors were blinded, but this was unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22 of 177 couples excluded from analysis for the following reasons: 11 had incomplete data or missed tablets or injections, 7 dropped out, 2 had endometriosis found on review of their records, and 2 were found to have secondary infertility
Selective reporting (reporting bias)	Unclear risk	Live births in the 2 groups not reported separately
Other bias	Unclear risk	Insufficient information to make a judgement

George 2006

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Female age*: no difference between groups • *Duration of infertility*: NA **Sample size:** OS (n = 70); EM (n = 70) **Included criteria:** women with a diagnosis of unexplained infertility **Excluded criteria:** NA **Pretreatment:** no statistical difference between the 2 groups in terms of age, presence of medical complications, or side effects of the medication received
Interventions	**Intervention characteristics** OS • *Description*: women were instructed to take 2 tablets (100 mg CC) daily from the 2nd to the 6th day of the cycle and to present for a transvaginal ultrasound examination on day 12. If follicular development was adequate as determined by size > 18 mm, hCG 5000 units was administered in the morning and the couple was advised to have intercourse 34 to 36 hours later. If follicular growth was not adequate, ultrasound examination was carried out on an appropriate day, estimating a follicular growth pattern of 2 mm/d. Women so treated were instructed to start the next course of treatment on the 2nd day of the next cycle, if pregnancy did not occur. If a period was missed, they were asked to report for a pregnancy test and subsequently for a transvaginal ultrasound for confirmation of clinical pregnancy at 7 weeks' gestation. Three treatment cycles were planned and carried out, and women were followed up for a further 3 months EM

George 2006 *(Continued)*

- *Description*: women were instructed to take 2 tablets (placebo) daily from the 2nd to the 6th day of the cycle and to present for a transvaginal ultrasound examination on day 12. If follicular development was adequate as determined by size > 18 mm, hCG 5000 units was administered in the morning and the couple was advised to have intercourse 34 to 36 hours later. If follicular growth was not adequate, ultrasound examination was carried out on an appropriate day, estimating a follicular growth pattern of 2 mm/d. Women so treated were instructed to start the next course of treatment on the 2nd day of the next cycle, if pregnancy did not occur. If a period was missed, they were asked to report for a pregnancy test and subsequently for a transvaginal ultrasound for confirmation of clinical pregnancy at 7 weeks' gestation. Three treatment cycles were planned and carried out, and women were followed up for a further 3 months

Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy*
Identification	**Sponsorship source:** no funding **Country:** India **Setting:** single centre **Author's name:** K. George **Institution:** Christian Medical Coll, Vellore, India **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "(computer generated in blocks of 5)"
Allocation concealment (selection bias)	Low risk	Quote: "opening consecutively numbered opaque envelopes" Judgement comment: concealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "neither the physician [nor] the patients were aware of the contents of the treatment packets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: not sure whether outcomes assessors were blinded, but this was unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: not reported in the abstract
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Unclear risk	Judgement comment: insufficient information to make a judgement

Glazener 1990

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Female age*: median 28 years (range 19 to 44) • *Duration of infertility*: median 28 months (12 to 102) **Sample size:** OS (n = 109); EM (n = 105) **Included criteria:** at least 1 year's infertility, with the following provisions. All women had normal menstrual cycles (21 to 35 days), normal serum prolactin and thyroid hormone levels, normal coital frequency (at least twice weekly), and normal post-coital sperm-mucus penetration. Those who failed to conceive within a few months had a laparoscopy to exclude pelvic disease and tubal damage. A blood sample was taken at the midluteal phase in 3 cycles for serum progesterone measurement (timing checked retrospectively as occurring 5 to 10 days before the next menstrual period) **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** OS • *Description*: clomiphene (Clomid, Merrell) 100 mg on days 2 to 6 of the menstrual cycle for 3 cycles, crossing over to the alternative treatment for a further 3 cycles. Only the first 3 cycles were included EM • *Description*: matched placebos were given on days 2 to 6 of the menstrual cycle for 3 cycles, crossing over to the alternative treatment for a further 3 cycles
Outcomes	*Clinical pregnancy* *Multiple pregnancy*
Identification	**Sponsorship source:** South Western Regional Health Authority Medical Research Committee for support for Dr. Glazener; Dr. H.C. Masheter of Merrell Pharmaceuticals Ltd., for the supply of clomiphene and matching placebo **Country:** UK **Setting:** single centre **Author's name:** C.M.A. Glazener **Institution:** Health Services Research Unit, University of Aberdeen **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Glazener 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: double-blind study but unclear whether outcome assessors were blinded; unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: outcome of 1 participant of 109 in CC group not reported
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth not reported
Other bias	High risk	Judgement comment: in methods, it was reported that 118 patients were recruited. However, in results, it was reported that 105 patients were treated with placebo and 109 with clomiphene

Goldman 2014

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS-IUI • *Female age*: 40.3 (1.3) years • *Duration of infertility*: NA IVF/ICSI • *Female age*: 39.9 (1.4) years • *Duration of infertility*: NA **Sample size:** OS-IUI (n = 103); IVF/ICSI (n = 51) **Included criteria:** couples in which the woman was 38 to 42 years of age and sought care for unexplained infertility from August 2004 to November 2009 at Boston IVF and from November 2008 to November 2009 at Brigham and Women's Hospital were screened. Eligibility criteria included 6 months of attempted conception; at least 1 ovary and ipsilateral patent fallopian tube confirmed by hysterosalpingogram or laparoscopy; regular menstrual cycles of 21 to 45 days; and no pelvic pathology, ectopic pregnancy, or previous infertility treatment (except up to 3 cycles of clomiphene without IUI). Acceptable ovarian reserve was demonstrated by a clomiphene challenge test (100 mg clomiphene on cycle days 5 to 9; FSH value 15 mIU/mL on cycle days 3 and 10; and oestradiol value 100 pg/mL on cycle day 3). Normal prolactin and thyroid-stimulating hormone levels and body mass index (BMI) ≤ 38 in the woman, and sperm concentration ≥ 15 million total motile sperm or ≥ 5 million total motile sperm at reflex IUI preparation in partner required. Only the first 2 cycles were included

Goldman 2014 *(Continued)*

	Excluded criteria: NA **Pretreatment:** no previous infertility treatment (except up to three cycles of clomiphene without IUI)
Interventions	**Intervention characteristics** OS-IUI • *Description*: treatment with CC was 100 mg orally daily for 5 days starting between cycle days 3 and 5, with serial ultrasound monitoring beginning between cycle days 10 and 12 and luteinising hormone (LH) home monitoring beginning on cycle day 11. One IUI was performed either the day after the LH surge was detected or 36 to 40 hours after subcutaneous/intramuscular (SC/IM) administration of 10,000 IU of human chorionic gonadotropin (hCG) when the lead follicle was R18 mm, whichever came first. If pregnancy was not achieved after 2 treatment cycles, patients proceeded to IVF IVF/ICSI • *Description*: patients randomised to the immediate IVF arm initiated therapy with an IVF protocol consisting of 21 days of an oral contraceptive followed by a microdose leuprolide acetate protocol (40 mg SC twice/d until hCG injection) with a starting dose of twice-daily gonadotropins (300 IU FSH in the morning and 150 IU human menopausal gonadotropin (hMG) in the afternoon) for 3 days beginning on day 3 or 4 of leuprolide acetate. Adjustments to gonadotropin dosage were determined by oestradiol monitoring and ultrasound; 10,000 IU hCG was given SC or IM when the lead follicle was R17 mm and at least 3 follicles were R15 mm in size. Oocyte retrieval was performed 36 hours after hCG administration, and embryos were routinely transferred on day 3. The number of embryos transferred was based on American Society for Reproductive Medicine (ASRM) guidelines for day 3 embryo transfers (6). Standardised cancellation criteria and low response protocols were used. Intracytoplasmic sperm injection (ICSI) was used only after failed fertilisation or when10 million total motile sperm were available at IVF. Preimplantation genetic diagnosis (3.6% of cycles) and assisted embryo hatching (one-third of cycles) were performed when considered necessary. Patients in all arms who did not become clinically pregnant after 2 treatment cycles continued with the IVF protocol up to a maximum of 6 IVF cycles, usually 4 fresh and 2 thaw cycles, if available
Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy* *OHSS*
Identification	**Sponsorship source:** supported by the National Institutes of Health Eunice Kennedy Shriver, National Institute of Child Health and Human Development (grant R01-HD44547) **Country:** USA **Setting:** academic medical centres and private infertility centre in a state with mandated insurance coverage (Boston IVF and Brigham and Women's Hospital) **Author's name:** Marlene B. Goldman **Institution:** Department of Obstetrics and Gynecology and Community and Family Medicine, Geisel School of Medicine at Dartmouth and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire **Email:** marlene.b.goldman@dartmouth.edu
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Goldman 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was performed using permuted blocks of varying sizes, stratified by the woman's age" Judgement comment: but details of sequence generation were not reported
Allocation concealment (selection bias)	Low risk	Quote: "the allocation sequence was generated by an independent biostatistician and was implemented by an epidemiologist"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "neither the patients nor their providers were blind to their treatment assignment" Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all clinical investigators were blinded to the outcome determinations"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: 6/154 with incomplete outcome data
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Goverde 2000

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** IUI • *Female age*: 31.61 (3.73) years • *Duration of infertility*: 3.88 (1.71) years OS-IUI • *Female age*: 31.73 (3.92) years • *Duration of infertility*: 4.20 (1.87) years IVF/ICSI • *Female age*: 32.06 (4.20) years • *Duration of infertility*: 4.45 (2.82) years **Sample size:** IUI (n = 86); OS-IUI (n = 85); IVF/ICSI (n = 87) **Included criteria:** couples who had been affected by idiopathic subfertility for at least 3 years, or by male subfertility for at least 1 year, were eligible for the study **Excluded criteria:** if woman had cycle disorders, untreated endometriosis (American Fertility Society criteria grade 2 to 4), or bilateral occluded tubes, or if a semen sample yielded fewer than 1 million progressively motile spermatozoa after processing by Percoll 40/80 gradient centrifugation; if more than 20% of spermatozoa carried antibodies as tested with an immunobead test after Percoll processing, or

Goverde 2000 *(Continued)*

if more than 50% of spermatozoa had no acrosome. Patients had undergone extensive investigation of infertility including a basal body temperature chart, a late luteal-phase endometrial biopsy, a post-coital test, a hysterosalpingogram, a diagnostic laparoscopy, and ≥ 2 semen analyses. Couples were diagnosed as having idiopathic subfertility if no abnormality was found during the full infertility investigation. Male subfertility was diagnosed if ≥ 3 of 5 semen analyses showed a total motile sperm count of fewer than 20 million progressively motile spermatozoa in the ejaculate, and if the remainder of the infertility investigation revealed no additional abnormalities. In both groups of patients, semen processing by Percoll 40/80 gradient centrifugation yielded a minimum of 1 million progressively motile spermatozoa at least once

Pretreatment: none detected

Interventions	**Intervention characteristics** IUI • *Description*: for IUI in a spontaneous cycle, a single IUI was done 20 to 30 hours after the endogenous luteinising-hormone surge was detected with a urinary semi-quantitative monoclonal-antibody-based kit with a detection level of 40 IU (OvuQuick, Quidel, San Diego, CA, USA). Patients tested their urine samples twice daily (second morning void and between 1800 hours and 1900 hours) starting on an individually calculated cycle day. A maximum of 0.5 mL suspension of processed spermatozoa was introduced into the uterine cavity with a catheter 10 cm in length (International Medical, Zutphen, Netherlands). Patients were tested for pregnancy if menstruation had not started on the 15th day after insemination OS-IUI • *Description*: for IUI in a mildly hyperstimulated cycle, a low dose of follicle-stimulating hormone was given to achieve the growth of 2 to 3 dominant follicles before administration of human chorionic gonadotropin (to optimise the pregnancy rate while preventing a high multiple pregnancy rate). Multi-follicular growth was defined as growth of more than 1 follicle with a diameter ≥ 14 mm on the day of administration of human chorionic gonadotropin. Baseline pelvic ultrasonography was done at cycle day 3 to exclude ovarian cysts larger than 20 mm. When this point had been established, patients injected themselves intramuscularly with 1 ampoule (75 IU) follicle-stimulating hormone (Metrodin, Ares Serono, Geneva, Switzerland) daily until transvaginal ultrasonography showed ≥ 1 follicle with diameter 18 mm. Patients tested their urine twice daily (morning and evening void) for the occurrence of a luteinising-hormone surge. In the event of such a surge, 10,000 IU human chorionic gonadotropin (Profasi, Ares Serono) was given as soon as possible, and a single IUI was done 20 to 30 hours after detection of the surge. When no luteinising-hormone surge was detected in the presence of at least 1 follicle with diameter of 18 mm or more, 10,000 IU human chorionic gonadotropin was given intramuscularly, and a single IUI was done 40 to 42 hours later. Administration of human chorionic gonadotropin was withheld and IUI was not done when more than 3 follicles with diameter of at least 18 mm, or more than 6 follicles with diameter of at least 14 mm, were present. The daily dose of follicle-stimulating hormone was increased by 0.5 ampoules in every subsequent cycle when the dose of the previous cycle had resulted in monofollicular growth. Patients were tested for pregnancy if menstruation had not started on the 15th day after insemination IVF/ICSI • *Description*: a standard IVF procedure was carried out as described by Roseboom and colleagues. Women aged 38 years or younger underwent controlled ovarian hyperstimulation with a “long” protocol with gonadotropin-releasing hormone agonist (Decapeptyl, Ferring, Copenhagen, Denmark). Gonadotropins were given at a daily dose of 2 to 3 ampoules (150 to 225 IU) of human menopausal gonadotropin (Pergonal, Ares Serono) or follicle-stimulating hormone, depending on patient age or previous response to gonadotropins. In women older than 38 years, a “short” stimulation protocol was applied. In both protocols, gonadotropin-releasing hormone agonists and gonadotropins were discontinued if transvaginal ultrasonography showed the presence of at least 1 follicle with diameter of at least 18 mm and a minimum of 3 follicles of at least 16 mm in diameter. 35 hours before follicle aspiration, 10,000 IU human chorionic gonadotropin was given unless the serum oestradiol concentration exceeded 20,000 nmol/L. Follicular aspiration guided by transvaginal ultrasonography was done under systemic analgesia (7.5 mg diazepam orally and 50 mg pethidine hydrochloride intramuscularly), and all follicles present were aspirated. Retrieved oocytes were cultured in Earls' +

Goverde 2000 *(Continued)*

	medium (Sigma, St. Louis, MO, USA), and was inseminated with Percoll-processed spermatozoa 42 hours after the human chorionic gonadotropin injection. We transferred a maximum of 2 pre-embryos in women 35 years of age or younger, and 3 pre-embryos in women older than 35 years, 48 to 72 hours after oocyte retrieval. The luteal phase was supported by 3 doses of progesterone (200 mg; Progestan, Nourypharma, Oss, Netherlands) intravaginally daily from the day of oocyte retrieval, or, in the case of breakthrough bleeding, before the 13th day of the luteal phase under progesterone treatment, by 1500 IU human chorionic gonadotropin (Pregnyl, Organon, Oss, Netherlands) intramuscularly every 48 hours, starting from the second day after oocyte retrieval until a pregnancy test was done at the 15th day after oocyte retrieval
Outcomes	*Live birth* *OHSS* *Multiple pregnancy*
Identification	**Sponsorship source:** this work was financially supported by the Health Insurance Executive Board, Amstelveen, Netherlands **Country:** Netherlands **Setting:** single centre **Author's name:** Angelique J. Goverde **Institution:** Department of Obstetrics and Gynaecology, University Hospital Vrije Universiteit **Email:** aj.goverde@azvu.nl
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomisation schedule"
Allocation concealment (selection bias)	Low risk	Quote: "administered by numbered masked and sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 13/86, 14/85, and 37/87 participants withdrew during the study in IUI, OS-IUI, and IVF groups, respectively. Breakdown data unclear in unexplained infertility
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Guzick 1999

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** IUI • *Female age*: 32 (4) years • *Duration of infertility*: 46 (31) months OS-IUI • *Female age*: 32 (4) years • *Duration of infertility*: 42 (26) months **Sample size:** IUI (n = 234); OS-IUI (n = 231) **Included criteria:** females younger than 40 years of age; negative pregnancy test; normal pelvis and uterine cavity*; "in-phase" endometrial biopsy; negative serum antisperm antibody test; normal serum follicle-stimulating hormone and thyrotropin values on days 1 to 5 of cycle; length of 2 of the 3 most recent menstrual cycles between 24 and 40 days; history of infertility for > 1 year. Males younger than 55 years of age; negative serum antisperm antibody test; presence of any motile sperm on screening semen analysis; history of infertility for > 1 year **Excluded criteria:** females with previous use of in vitro fertilisation or other assisted reproductive technology; previous treatment with gonadotropins; previous intrauterine insemination with current partner; history of chronic disease; history of chemotherapy or radiation to the abdomen or pelvis; history of tubal surgery; extensive tubal adhesions; endometriosis of more than stage II; history of myomectomy, ovarian cystectomy, or unilateral oophorectomy. Males with previous use of in vitro fertilisation or other assisted reproductive technology; previous intrauterine insemination; history of vasovasostomy; varicocelectomy within 6 months before study; history of pelvic node dissection **Pretreatment:** no pretreatment
Interventions	**Intervention characteristics** IUI • *Description*: women who were not assigned to superovulation underwent insemination timed to spontaneous ovulation. Four days before the expected time of ovulation, women began daily testing of their second morning urine specimen for luteinising hormone, using a qualitative kit (OvuQuick, Quidel, San Diego, CA) OS-IUI • *Description*: 150 IU follicle-stimulating hormone was administered intramuscularly daily from day 3 through day 7. On day 8, ultrasonography was repeated and serum oestradiol measured. Daily administration of follicle-stimulating hormone was continued, with the dose adjusted if necessary, until ≥ 2 follicles reached > 18 mm (average 2 dimensions) and the serum oestradiol concentration ranged from 500 to 3000 pg/mL (1835 to 11,010 pmol/L). Once these criteria were met, treatment with follicle-stimulating hormone was discontinued and 10,000 IU human chorionic gonadotropin (Profasi, Serono Laboratories) was administered intramuscularly. A single insemination was performed 36 to 40 hours later
Outcomes	*Clinical pregnancy* *Live birth*

Guzick 1999 *(Continued)*

Identification	**Sponsorship source:** supported in part by Cooperative Agreements with the National Institute of Child Health and Human Development (U10 HD26975, U10HD26981, U10 HD27006, U10 HD27009, U10 HD27001, U10HD27049, U10 HD33172, and U10 HD33173) and by Serono Laboratories **Country:** USA **Setting:** 10 clinical sites **Authors' names:** David S. Guzick, Sandra Ann Carson* **Institution:** Dr. Carson at Baylor College of Medicine, Department of Obstetrics and Gynecology, 6550 Fannin #801, Houston, TX 77030 **Email:** scarson@bcm.tmc.edu
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: "randomisation was carried out with use of a permuted block procedure, stratified according to center", but details of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding mentioned and seemed impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: although there were 22 (9%) in the IUI group and 50 (22%) in the OS- IUI group, withdrawal from the study led to numbers of participants with unknown pregnancy outcomes of 1 and 2 in IUI and OS-IUI groups, respectively
Selective reporting (reporting bias)	Unclear risk	Judgement comment: data for multiple pregnancy in each group not available
Other bias	Low risk	Judgement comment: no other sources of bias detected

Harrison 1983

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Female age*: 29.3 (26 to 41) years

Harrison 1983 *(Continued)*

- *Duration of infertility*: 5.4 (2 to 14) years
- *Primary infertility (%)*: 20/30
- *Previous treatments*: initially, clomiphene citrate was given at a dosage of 100 mg daily for 4 days from day 3 of the cycle to all patients for 3 cycles

Sample size: EM (n = 15); OS (n = 15)

Included criteria: unexplained infertility: semen analysis, post-coital test, hysterosalpingogram, laparoscopy, immunological tests, and plasma hormone profile (FSH, LH, oestradiol, prolactin, and progesterone) had been found normal. All women had 3 cycles of CC before randomisation

Excluded criteria: NA

Pretreatment: NA

Interventions	**Intervention characteristics** EM • *Description*: 15 were scheduled to take Clomid 100 mg daily for 4 days from day 3 of the cycle plus self-administered 5000 IU hCG IM on day 12 of the cycle for 6 cycles. This was to be followed by 6 cycles of placebo, identically dosed as the clomid, with again 5000 IU hCG IM on day 12 OS • *Description*: the other 15 patients were given the same regimen but in reverse order
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** Merrell U.K., Ltd. **Country:** Ireland **Setting:** Rotunda or St. James's Infertility Clinics **Author's name:** Robert F. Harrison **Institution:** Rotunda Hospital, Dublin **Email:** NA **Address:** Rotunda Hospital, Dublin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: placebo-controlled study
Blinding of outcome assessment (detection bias)	Low risk	Judgement comment: placebo-controlled study; objective outcomes used

Harrison 1983 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data presented
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth and multiple pregnancy not reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Ho 1998

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Female age*: NA • *Duration of infertility*: NA **Sample size:** OS (n = 45); OS-IUI (n = 45) **Included criteria:** couples presenting with subfertility due to subnormal semen or unexplained infertility **Excluded criteria:** NA **Pretreatment:** unclear
Interventions	**Intervention characteristics** OS • *Description*: women were treated with 3 cycles of ovarian stimulation with human menopausal gonadotropin (hMG) alone. Couples were asked to have vaginal intercourse after administration of human chorionic gonadotropin (hCG) OS-IUI • *Description*: women were treated with 3 cycles of IUI after the same regimen of ovarian stimulation with hMG
Outcomes	*Clinical pregnancy* *OHSS* *Multiple pregnancy*
Identification	**Sponsorship source:** NA **Country:** Hong Kong, China **Setting:** single centre **Author's name:** P.C. Ho **Institution:** Department of Obstetrics and Gynecology, University of Hong Kong, Hong Kong, China

Ho 1998 *(Continued)*

	Email: NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding not likely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth not reported
Other bias	Unclear risk	Judgement comment: insufficient information to make a judgement

Hughes 2004

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** EM • *Female age*: 33.1 (3.7) years • *Duration of infertility*: 58 (33) months IVF/ICSI • *Female age*: 32.9 (3.2) years • *Duration of infertility*: 54 (24) months **Sample size:** EM (n = 27); IVF/ICSI (n = 24) **Included criteria:** duration of subfertility > 2 years, defined as no live birth during that time; no previous IVF treatment; female age 18 ± 39 years; willingness to commence either IVF within 6 weeks of allocation or a 3-month period of observation without intervention; day 3 serum FSH level > 15 IU/L or standard level for inclusion in an individual centre's IVF programme, whichever level was lower; semen analysis available within last 6 months showing an adequate number of sperm to perform ICSI; ev-

Hughes 2004 *(Continued)*

	idence of Fallopian tube patency, based on a hysterosalpingogram (HSG) or laparoscopy (only data for unexplained infertility were included) **Excluded criteria:** women with bilateral Fallopian tube occlusion confirmed by HSG or laparoscopy; use of donor sperm; need for sperm recovery procedures; concurrent serious medical illnesses that could be a relative contraindication to IVF **Pretreatment:** All couples had exhausted appropriate lower intensity treatment options, such as ovulation induction and intrauterine insemination.
Interventions	**Intervention characteristics** EM • *Description*: 90 days of observation with no treatment: no medications that might reduce spontaneous conception were allowed, such as commencement of GnRH analogue pretreatment for subsequent IVF IVF/ICSI • *Description*: patient's first ever cycle of IVF treatment: similar IVF techniques were used across centres. All programmes used "long protocol" GnRH analogue suppression followed by recombinant FSH as a prelude to oocyte retrieval and IVF. Drugs and dosages used for each patient's stimulation were recorded, along with the numbers of oocytes retrieved and embryos produced, quality of individual embryos, day of transfer, and number and quality of embryos transferred and frozen. Oocyte retrieval was carried out under vaginal ultrasound guidance, and no centre transferred more than 4 embryos per cycle. The day of embryo transfer was not standardised and ranged between day 3 and day 5 post retrieval. Medication was begun within 42 days of randomisation to ensure that all embryo transfers occurred within 90 days - the same period of observation used in the control group
Outcomes	*Live birth* *Clinical pregnancy*
Identification	**Sponsorship source:** NA **Country:** Canada **Setting:** 5 Canadian fertility clinics **Author's name:** E.G. Hughes **Institution:** Department of Obstetrics and Gynecology, McMaster University Medical Centre, 1200 Main Street West, Room 4D14, Hamilton, ON L8N 3Z5, Canada **Email:** hughese@mcmaster.ca **Address:** Department of Obstetrics and Gynecology, McMaster University Medical Centre, 1200 Main Street West, Room 4D14, Hamilton, ON L8N 3Z5, Canada
Notes	Breakdown outcome data of unexplained infertility were extracted from a Cochrane Review (Pandian 2015)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Random allocation was based on a blocked schedule using numbered, sealed, opaque envelopes. Randomization was stratified by centre" Judgement comment: but details of random sequence generation not available

Hughes 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Judgement comment: numbered sealed opaque envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: outcome data of all participants reported
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Janko 1998

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS • *Female age*: NA • *Duration of infertility*: NA OS-IUI • *Female age*: NA • *Duration of infertility: NA* **Sample size:** OS (n = 36); OS-IUI (n = 36) **Included criteria:** couples with a history of more than 3 years of unexplained subfertility **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** OS • *Description*: stimulation of follicular growth + timed intercourse. OS with 10 ampoules Pergonal or Humegon and timing with hCG Pregnyl 10,000 IU for up to 3 cycles OS-IUI • *Description*: stimulation of follicular growth + IUI. OS with 10 ampoules Pergonal or Humegon and timing with hCG Pregnyl 10,000 IU for up to 3 cycles

Janko 1998 *(Continued)*

Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** NA **Country:** Slovakia **Setting:** not reported **Author's name:** P. Janko **Institution:** Department of Gynaecology and Obstetrics, Postgraduate Medidcal School, Limbovn 5, Bratislava 883 07, Slovakia **Email:** NA **Address:** Limbova 5, Bratislava 833 07, Slovakia
Notes	*Noor Danhof* on 4 June 2018, 19:25 **Outcomes** A 19.5% per patient, B 29.4% per patient

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: not reported; blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: unblinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: details not available
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth and multiple pregnancy not reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Karlstrom 1993

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall

Karlstrom 1993 *(Continued)*

- *Female age*: 21 to 38 years
- *Duration of infertility*: 2 to 14 years

Sample size: OS (n = 47); OS-IUI (n = 32)

Included criteria: couples with unexplained infertility including cases with minimal or mild endometriosis according to the American Fertility Society score: (1) duration of the infertility should be at least 2 years; (2) no previous treatment with hMG and/or insemination; (3) woman should be 39 years of age and should have regular ovulatory menstrual cycles with maximum length of 35 days; (4) normal sperm sample according to the World Health Organization criteria and a swim-up test in hyaluronic acid (Sperm Select; Kabi Pharmacia, Uppsala, Sweden; Select Medical Systems, Williston, VT) using 1-mL aliquot of semen should result in at least 0.5×10^6/mL progressive motile sperm; (5) laparoscopy and HSG should reveal patent tubes without any adhesions; (6) normal PCT (> 3 progressive motile sperm per high power field)

Excluded criteria: NA

Pretreatment: NA

Interventions	**Intervention characteristics** OS • *Description*: CC or hMG: CC (Pergotime; Serono, Jerusalem, Israel) at a daily dosage of 100 mg was given orally for 5 days starting on days 3 to 5 of the cycle; hMG (Pergonal; Serono, Aubonne, Switzerland) was started at 2 ampoules (150 IU) on days 2 to 4 of the menstrual cycle. Couples were instructed to have intercourse at night the day of the LH surge and the next day. When ovulation occurred during weekends, couples were instructed to have intercourse and in the analysis were transferred to the group treated with CC only. In the group treated with hMG only, couples were instructed to have intercourse the 2 following nights after hCG injection. When ovulation occurred during weekends, couples were instructed to have intercourse, and in the analysis, they were transferred to the group treated with hMG only OS-IUI • *Description*: CC or hMG: CC (Pergotime; Serono, Jerusalem, Israel) at a daily dosage of 100 mg was given orally for 5 days starting on days 3 to 5 of the cycle; hMG (Pergonal; Serono, Aubonne, Switzerland) was started at 2 ampoules (150 IU) on days 2 to 4 of the menstrual cycle. Daily administration of hMG continued until the leading follicle reached an average diameter ≥ 17 mm or until detection of a luteinising hormone (LH) surge in serum or urine. Ovulation was induced by an injection of 10,000 IU of human chorionic gonadotropin (hCG, Profasi; Serono) the day after the last hMG injection. IUI was performed 36 to 41 hours after hCG administration. In cases with endogenous LH surge, hCG was given the same day and insemination was performed the day after. In the group treated with hMG only, couples were instructed to have intercourse the 2 following nights after hCG injection. When ovulation occurred during weekends, couples were instructed to have intercourse, and in the analysis, they were transferred to the group treated with hMG only
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** supported by grant no. B91-17X-03495-20A from The Swedish Medical Research Council, Stockholm, Sweden **Country:** Sweden **Setting:** Departments of Obstetrics and Gynecology, Central Hospital, Vasteras and Aka-demiska Hospital, Uppsala University, Uppsala, Sweden **Author's name:** Per-Olof Karlstrom **Institution:** Department of Obstetrics and Gynecology, Central Hospital, S-721 89 Viis-teras, Sweden **Email:** NA

Karlstrom 1993 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: this is a factorial design; study authors reported only withdrawals in CC and hMG groups, respectively. Unclear how many in OS and OS-IUI groups withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth not reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Kirby 1991

Methods

Study design: randomised controlled trial

Study grouping: parallel group

Participants

Baseline characteristics

EM

- *Female age*: NA
- *Duration of infertility*: NA

IUI

- *Female age*: NA
- *Duration of infertility*: NA

Sample size: EM (n = 53); IUI (n = 69)

Included criteria: couples included in this trial had at least 2 years of infertility and gave informed consent to participate in the trial. All males except those in the semen defect groups had normal spermiograms on at least 2 occasions. A normal spermiogram consisted of > 40 × 10^6 sperm/mL, > 45% progressive motility, and > 40% normal morphology. This corresponds to the 15th percentile of a reference population of all men who approached our clinic as potential semen donors. Tubal patency was assessed by laparoscopic tubal dye insufflation, whereas ovulation and cycle endocrinology were assessed in tracking cycles before treatment. Couples selected for the trial had no identifiable cause of in-

Kirby 1991 *(Continued)*

	fertility (unexplained group) or a single identified cause. The latter categories included cervical mucus hostility, moderate semen defect, and severe semen defect **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** EM • *Description*: patients were requested to have intercourse approximately 40 hours after the start of the endogenous LH rise IUI • *Description*: inseminations were performed in the periovular period. Serum LH, oestradiol, and progesterone were assessed during this period, and inseminations were timed for 40 hours after the start of the endogenous LH rise
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** supported in part by grant 850294 from the National Health and Medical Research Council of Australia, Canberra, Australia **Country:** Australia **Setting:** clinical infertility service **Authors' names:** Christine A. Kirby; Colin D. Matthews* **Institution:** Department of Obstetrics and Gynaecology, The University of Adelaide, The Queen Elizabeth Hospital **Email:** NA **Address:** Department of Obstetrics and Gynaecology, The University of Adelaide, The Queen Elizabeth Hospital, Woodville, South Australia 5011, Australia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias)	Unclear risk	Judgement comment: details not reported

Kirby 1991 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Judgement comment: protocol not available; live birth and multiple pregnancy not reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Leanza 2014

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Female age*: 25 to 45 years • *Duration of infertility*: > 3 years **Sample size:** IUI (n = 34); OS-IUI (n = 34) **Included criteria:** sterility for longer than 3 years, no severe male factors, no tubal damage, moderate oligoasthenospermia, minimal endometriosis, cervical factor, luteal phase defect **Excluded criteria:** chronic vaginal infection, liver disease, ovarian cyst, 45 years old, uterine malformation, chronic disease **Pretreatment:** NA
Interventions	**Intervention characteristics** IUI • *Description*: CC: 50 mg per day from day 3 to day 8 of cycle. Once the leading follicle reached 19 to 20 mm, a slot of hCG was done, after 36 to 40 hours, IUI was carried out OS-IUI • *Description*: assumed placebo (multi-vitamin) from day 3 to day 8 of cycle. Once the leading follicle reached 19 to 20 mm, a slot of hCG was done, after 36 to 40 hours, IUI was carried out
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** NA **Country:** Italy **Setting:** University of Catania **Authors' names:** V. Leanza, F. Grasso **Institution:** Department of Surgery, Obstetrics and Gynecology, University of Catania **Email:** federicagrasso88@gmail.com
Notes	
Risk of bias	

Leanza 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 9 couples excluded from the analysis
Selective reporting (reporting bias)	Unclear risk	Judgement comment: protocol not available; live birth not reported
Other bias	Unclear risk	Judgement comment: Insufficient information to make a judgement

Martinez 1990

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Female age*: 32.1 ± 4.1 years • *Duration of infertility*: 6.5 ± 3.1 years **Sample size:** EM (n = 10); OS (n = 10); IUI (n = 10); OS-IUI (n = 10) **Included criteria:** male or idiopathic factor infertility **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** EM • *Description*: timed intercourse was advised between 16 and 28 hours after detection of the first positive LH colour test OS • *Description*: 100 mg of CC for a period of 5 days starting on cycle day 3. Timed intercourse was advised between 16 and 28 hours after detection of the first positive LH colour test

Martinez 1990 *(Continued)*

	IUI • *Description*: intrauterine insemination was performed between 16 and 28 hours after detection of the first positive LH colour test. Only 1 single IUI per treatment cycle was performed OS-IUI • *Description*: 100 mg of CC for a period of 5 days starting on cycle day 3. Timed intercourse was advised between 16 and 28 hours after detection of the first positive LH colour test. Intrauterine insemination was performed between 16 and 28 hours after detection of the first positive LH colour test. Only 1 single IUI per treatment cycle was performed
Outcomes	*Clinical pregnancy*
Identification	**Sponsorship source:** Organon International, Oss, Netherlands **Country:** Netherlands **Setting:** single centre **Author's name:** Antonio R. Martinez **Institution:** Department of Obstetrics and Gynecology, Free University Hospital **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no withdrawal in the first cycle
Selective reporting (reporting bias)	Unclear risk	Judgement comment: live birth and multiple pregnancy not reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Melis 1995

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS • *Age*: 34.8 (5.3) years • *Duration of infertility*: 50.6 (13.8) months OS-IUI • *Age*: 33.3 (4.5) years • *Duration of infertility*: 52.1 (11.2) months **Sample size:** OS (n = 93); OS-IUI (n = 91) **Included criteria:** unexplained and mild male factor-related infertility. All couples underwent evaluation that included at least 2 semen analyses with andrological evaluation, female endocrine profile (FSH, LH, PRL, and T assay during the very early follicular phase), ovulation assessment (P and PRL assays during luteal phase), endometrial biopsy, transvaginal ultrasonography, post-coital test, hysterosalpingogram, and diagnostic laparoscopy. All couples had undergone 3 cycles of induction of ovulation with clomiphene citrate (CC) associated with timed vaginal intercourse and 3 cycles of induction of ovulation with CC associated with IUI without conceiving before being enrolled in this trial **Excluded criteria:** couples with severe male factor-related infertility (sperm concentration 10*10^6/mL, progressive motility 15%, total motility 30%, and normal morphology 30%), tubal damage, anovulatory cycle, polycystic ovary disease, hyperprolactinaemia, uterine fibroids, and endometriosis were treated according to their pathology and were not considered eligible for the study **Pretreatment:** no significant difference was present between baseline characteristics
Interventions	**Intervention characteristics** OS • *Description*: ovulation induction with gonadotropins was obtained by administering purified FSH (Metrodin; Serono, Rome, Italy), starting with a daily dose of 3 ampoules from the 3rd day of the cycle. During treatment with exogenous gonadotropins, pelvic ultrasonography, to determine the number and diameter of ovarian follicles, and blood samples for E2 rapid assay (Medical System, Genova, Italy) were obtained every other day until the mean diameter of the dominant follicles reached 12 mm and E2 plasma levels reached 300 pg/mL (conversion factor to SI unit, 3.671). Thereafter, both examinations were performed daily. The dose of FSH was adjusted according to ultrasonic and endocrine monitoring. Treatment was discontinued when E2 plasma levels reached 800 to 1500 pg/mL and there were at least 2 follicles with a mean diameter of 16 mm. Cycles were cancelled if E2 plasma level was > 1500 pg/mL. Human chorionic gonadotropin (10,000 IU Profasi; Serono) was administered 36 hours after the last injection of FSH. First timed intercourse was suggested 12 hours after hCG administration, whereas IUI was performed 30 to 36 hours after hCG administration. In both timed vaginal intercourse and IUI groups, patients were requested to avoid intercourse from 4 days before the expected time of ovulation until either timed intercourse or IUI was indicated OS-IUI • *Description*: OS protocol was the same as that in the OS group. Intrauterine insemination was performed using a Frydman catheter. The cervix was exposed with a bivalve speculum and the tip of the catheter was passed into the uterus until it lay about 0.5 cm from the top of the uterine cavity in the fundal region. The in vitro-prepared sperm was expelled gently and the catheter subsequently was withdrawn
Outcomes	*Clinical pregnancy*

Melis 1995 *(Continued)*

	Live birth *Multiple pregnancy* *OHSS*
Identification	**Sponsorship source:** NA **Country:** Italy **Setting:** single centre: Infertility Centre of Department of Obstetrics and Gynecology of the University of Cagliari, Cagliari, Italy **Author's name:** Gian Benedetto Melis **Institution:** Department of Obstetrics and Gynecology, University of Cagliari, Cagliari, Italy **Email:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: details not reported
Allocation concealment (selection bias)	Low risk	Quote: "numbered sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not possible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: 16/184 lost to follow-up
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Unclear risk	Judgement comment: insufficient information to judge

Nandi 2017

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** OS-IUI

Nandi 2017 *(Continued)*

- *Female age*: 32 (30 to 35) years
- *Duration of infertility*: 23.7 (3.4) months

IVF/ICSI

- *Female age*: 32.5 (30-35) years
- *Duration of infertility*: 23.5 (2.9) months

Sample size: OS-IUI (n = 101); IVF/ICSI (n = 106)

Included criteria: eligible participants were couples with primary or secondary subfertility of minimum 1 year's duration, where the female partner was between 23 and 37 years of age, body mass index (BMI) was 19 to 30, with a regular menstrual cycle of 21 to 35 days, day 2 FSH 10 IU/L, and confirmed bilateral patent tubes. A midluteal serum P level was used to confirm ovulation. The male partner with normal semen parameters (i.e. sperm density > 15 million/mL, progressive motility > 40%, and normal forms > 4% (World Health Organization criteria), or total progressive motile sperm count > 5 million) was included in the trial

Excluded criteria: couples not fulfilling the inclusion criteria, with known uterine anomaly or physical disability, or having difficulty in achieving vaginal intercourse, and couples using donor sperm or previous fertility treatment like IUI or IVF. Those with confirmed endometriosis of grade II to IV were also excluded from the trial. However, routine laparoscopy was not performed in all cases to diagnose endometriosis. Self-funded patients were excluded from the trial due to lack of research funding

Pretreatment: No pretreatment

Interventions

Intervention characteristics

OS-IUI

- *Description*: COH was performed with daily SC injections of 75 IU FSH (Fostimon, a highly purified urofollitropin, Pharmasure) starting from days 2 to 5 of the menstrual cycle onward. When at least 2 follicles with diameter of 17 to 18 mm were present, final oocyte maturation was induced by SC administration of 250 mg hCG (Ovitrelle, Merck Serono), and 24 hours later, IUI was performed. IfR3 follicles of R14 mm developed, then the cycle was cancelled by withholding hCG and IUI and recommending avoiding sexual intercourse due to risk of multiple pregnancies. Semen samples were processed within 1 hour of ejaculation using density gradient centrifugation followed by washing with culture medium. Single insemination was done by the nurse or an on-duty doctor

IVF/ICSI

- *Description*: in the IVF group, women underwent downregulation with GnRH agonist in a long protocol, starting on day 21 of the previous cycle. COH was started with FSH (either hMGs or recombinant FSH) with a dose ranging from 150 to 450 IU depending on the woman's ovarian reserve (as tested by anti-mullerian hormone level, basal antral follicle count, and day 2FSH level) and decided by the attending clinician. When most follicles were R18 mm, ovulation was triggered with 250 mg recombinant hCG (Ovitrelle, Merck Serono), and cumulus-oocyte complexes were retrieved by transvaginal ultrasound-guided oocyte retrieval 36 hours later. Women who were deemed high risk for ovarian hyperstimulation syndrome (OHSS) (anti-mullerian hormone > 25 pmol/L, antral follicle count > 20) underwent a GnRH antagonist protocol for stimulation when COH was achieved with low-dose FSH (150 IU) and starting GnRH antagonist on day 6 of stimulation. Ovulation was induced by GnRH agonist (Buserelin 0.5 mg SC), and oocyte retrieval was performed after 36 hours. If > 20 oocytes were collected, embryos were frozen and transferred at a later date in a frozen embryo replacement cycle. In that case, the first frozen ET cycle was considered as the first cycle and was included in the analysis. We did not collect data for additional frozen ET cycles, as this was not in our study design. For the frozen ET cycle, downregulation was achieved with GnRH agonist starting from day 21 of the previous cycle followed by endometrial preparation with daily E2 valerate of 8 mg for 10 to 14 days, or until endometrial thickness > 8 mm was achieved. If at least 1 top-grade embryo was available, then only 1 embryo was transferred on day 3 or day 5. If no top-grade embryos were available, couples were given the option to transfer up to 2 embryos. Luteal phase support was provided with P vaginal pessaries (Cyclogest 400 mg twice daily, Actavis UK, Ltd.). For frozen ET cycle or GnRH agonist trigger cycle where a fresh

Nandi 2017 *(Continued)*

	embryo was transferred daily, E2 valerate of 8 mg and P gel (Crinone gel, Allergan) were given in addition to P vaginal pessaries for luteal support
Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy* *OHSS*
Identification	**Sponsorship source:** this trial had no funding **Country:** UK **Setting:** single centre **Author's name:** Anupa Nandi **Institution:** Fertility Unit, Homerton University Hospital, London, UK **Email:** anupa.nandi@gmail.com
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomization procedure was followed"
Allocation concealment (selection bias)	Low risk	Quote: "allocation concealment was achieved by using individual, consecutively numbered opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "due to the nature of the trial, blinding was not possible"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "this is unlikely to affect the outcome of the trial, as the outcome was objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: outcome data of all participants reported
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcome reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

Steures 2006

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Steures 2006 *(Continued)*

Participants	**Baseline characteristics** EM • *Female age*: 33 (3.1) years • *Duration of infertility*: 1.9 (0.5) years OS-IUI • *Female age*: 33 (2.4) years • *Duration of infertility*: 2.0 (0.5) years **Sample size:** EM (n = 126); OS-IUI (n = 127) **Included criteria:** couple had not conceived after at least a year of frequent unprotected intercourse; the woman was younger than 39 years; and the woman had a regular menstrual cycle. Couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy within the next 12 months were eligible for this study. The basic fertility assessment included medical history, cycle monitoring, semen analysis, post-coital test, and investigation of tubal function **Excluded criteria:** NA **Pretreatment:** NA
Interventions	**Intervention characteristics** EM • *Description*: couples assigned expectant management were followed up until an ongoing pregnancy occurred, or for 6 months if no pregnancy occurred. If a pregnancy miscarried, follow-up continued until the next pregnancy or the end of 6 months. Hysterosalpingography or laparoscopy was allowed in these 6 months OS-IUI • *Description*: women started daily subcutaneous injections of follicle-stimulating hormone (Gonal F (Serono Benelux, The Hague, Netherlands) or Puregon (Organon, Oss, Netherlands)) or human menopausal gonadotropin (Menopur (Ferring, Hoofddorp, Netherlands)) in mean doses of 75 IU, ranging from 37 IU to 150 IU, until transvaginal sonography showed at least 1 follicle ≥ 16 mm in diameter. Ovulation was then induced with 5000 IU or 10,000 IU of human chorionic gonadotropin (Pregnyl (Organon)), and women were inseminated 36 to 40 hours later. We withheld human chorionic gonadotropin and intrauterine insemination if there were more than 3 follicles with diameter ≥ 16 mm, or 5 with diameter ≥ 12 mm. We did not give luteal support. We processed semen samples within 1 hour of ejaculation by density-gradient centrifugation followed by washing with culture medium. The volume of semen that was inseminated varied between 0.2 mL and 1.0 mL. We did the insemination irrespective of the total motile count after preparation on the scheduled day
Outcomes	*Clinical pregnancy* *Live birth* *Multiple pregnancy* *OHSS*
Identification	**Sponsorship source:** this study was supported by grant 945/12/002 from ZonMW (Netherlands Organization for Health Research and Development, The Hague, Netherlands) **Country:** Netherlands **Setting:** 26 fertility centres in Netherland **Author's name:** Pieternel Steures

Steures 2006 *(Continued)*

Institution: Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam, Netherlands

Email: pn.steures@amc.uva.nl

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation sequence was computer generated in balanced block multiples of two or four, stratified by centre"
Allocation concealment (selection bias)	Low risk	Quote: "the sequence was concealed, and sealed opaque envelopes containing details of the treatment allocation were assembled by an independent person. Clinicians in the participating centres enrolled the couple and subsequently opened the next envelope. The inclusion was then confirmed to the trial coordinator by fax"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding impossible due to the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: non-blinding unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: OS-IUI: 3/127 lost to follow-up, EM: 2/126 lost to follow-up, 2 still pregnant
Selective reporting (reporting bias)	Low risk	Judgement comment: all relevant outcomes reported
Other bias	Low risk	Judgement comment: no other sources of bias detected

BBT: basal body temperature.
BMI: body mass index.
CC: clomiphene citrate.
EM: expectant management.
ET: embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotropin-releasing hormone.
hCG: human chorionic gonadotropin.
hMG: human menopausal gonadotropin.
HSG: hysterosalpingogram.
ICSI: intracytoplasmic sperm injection.
IQR: interquartile ratio.
IUI: intrauterine insemination.
IUI-COS: intrauterine insemination with controlled ovarian stimulation.
IVF: in vitro fertilisation.
LH: luteinising hormone.
NA: not applicable.
OHSS: ovarian hyperstimulation syndrome.
OS: ovarian stimulation.
PCT: post-coital test.
PRL: prolactin.
rAFS: The revised American Fertility Society classification system.

rFSH: recombinant follicle-stimulating hormone.
SD: standard deviation.
TMC: total motile count.
WHO: World Health Organization.

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

Study	Reason for exclusion
Buvat 1993	Interventions not of interest
Chung 1995	Interventions not of interest
Fujii 1997	Not a randomised controlled trial
Goldman 2010	Interventions not of interest
Gregoriou 1995	Cross-over trial but data before cross-over not available
Leanza 2014a	Interventions not of interest
Martinez 1991	Cross-over trial but data before cross-over not available
Melis 1987	Interventions not of interest
Murdoch 1991	Interventions not of interest
Nulsen 1993	Not a randomised controlled trial
Prentice 1995	Not a randomised controlled trial
Reindollar 2010	Interventions not of interest
Shokeir 2006	Interventions not of interest
Soliman 1993	Interventions not of interest
Tjon Kon Fat 2014	Not a randomised controlled trial
Zayed 1997	Not a randomised controlled trial
Zikopoulos 1993	Cross-over trial but data before cross-over not available
Zolghadri 2012	Irrelevant population: included women with PCOS and unexplained infertility; breakdown data not available. No response after study authors were contacted

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

NCT01992731

Trial name or title	IUI vs IVF/ICSI in Women Aged 38-42 Years: A Prospective Randomized Controlled Trial
Methods	Randomised controlled trial; parallel group
Participants	Sample size: 138

NCT01992731 *(Continued)*

	Inclusion criteria: women between 38 and 42 years of age; use of donor sperm or husband sperm reaching WHO criteria 2010 Exclusion criteria: tubal infertility (even 1 tube); major uterine or ovarian abnormalities; metabolic abnormalities
Interventions	3 consecutive gonadotropin-stimulated IUI cycles Intervention vs 1 IVF/ICSI with standard antagonist protocol
Outcomes	Primary outcome: cumulative ongoing pregnancy
Starting date	December 2014
Contact information	Michael De Brucker, MD Universitair Ziekenhuis Brussel, Jette, Belgium Telephone: 024776699 Email: mdebruck@vub.ac.be
Notes	First posted: 25 November 2013; last updated: 27 March 2015

NCT02001870

Trial name or title	Comparison of the Efficiency of Intra-uterine Insemination and In Vitro Fertilization in Women Over 37 Years (AMPAGE)
Methods	Randomised controlled trial; parallel group
Participants	Sample size: 600 Inclusion criteria: female between 37 and 42 years of age at the time of inclusion; infertility duration ≥ 12 months; normal tubes; no severe endometriosis, at least 1.5*10^6 motile spermatozoa to be inseminated; no previous ART attempt Exclusion criteria: tubal abnormalities; severe endometriosis; less than 1.5*10^6 motile spermatozoa to be inseminated; use of frozen sperm; presence of anti-spermatozoa antibodies
Interventions	IVF (experimental arm) vs IUI (control arm)
Outcomes	Primary outcome: delivery rate [Time frame: after 1 year of treatment] Secondary outcomes: multiple pregnancy rate [Time frame: after 1 year of treatment] Cost of treatment [Time frame: after 1 year of treatment] Adverse effects (hyperstimulation, infection) [Time frame: after 1 year of treatment]
Starting date	May 2014
Contact information	Jean PARINAUD, MD Univerisity Hospital, Toulouse, Midi-Pyrénnées, France, 31059 Telephone: 05 67 77 10 02 ext 33 Email: parinaud.j@chu-toulouse.fr Caroline PEYROT, CRA University Hospital, Toulouse, Midi-Pyrénnées, France, 31059

NCT02001870 *(Continued)*

	Telephone: 05 61 77 84 86 ext 33 Email: peyrot.c@chu-toulouse.fr
Notes	First posted: 5 December 2013; last update posted: 14 August 2018

NCT02461173

Trial name or title	Stimulated Intrauterine Insemination Cycles and Unstimulated Intrauterine Insemination Cycles in Couples With Unexplained Infertility
Methods	Randomised controlled trial; parallel group
Participants	Sample size: 450 Inclusion criteria: women 20 to 40 years of age; unexplained infertility Exclusion criteria: known allergy to FSH; diabetes; hypertension; known cardiac, renal, or liver disease
Interventions	OS-IUI: ovarian stimulation with hMG followed by IUI IUI: testing of urinary luteinising hormone followed by IUI Timed intercourse: testing of urinary luteinising hormone followed by intercourse
Outcomes	Primary outcome: ongoing pregnancy
Starting date	June 2015
Contact information	Abdel Gany Hassan, MRCOG, MD Cairo University Hospitals, Cairo, Egypt Telephone: 002 01017801604 Email: abdelgany2@gmail.com Nesreen A.A. Shehata, MD BeniSuef University Hospitals Telephone: +2001227866337, BeniSuef, Egypt Email: nesoomar@yahoo.com
Notes	First posted: 3 June 2015; last updated: 29 July 2016

NCT03455426

Trial name or title	Intrauterine Insemination With Letrozole Versus in Natural Cycle
Methods	Randomised controlled trial; parallel group
Participants	Sample size: 100

NCT03455426 *(Continued)*

	Inclusion criteria: being diagnosed with unexplained or mild male subfertility; ≥ 1-sided tubal patency, established according to local protocol; normal or mild impairment of semen quality defined as TMSC ≥ 3 million based on ≥ 1 semen analysis Exclusion criteria: women with double-sided tubal pathology; women with irregular cycles, PCOS, or other endocrine disorders; impaired semen quality: pre-wash TMSC < 3 million
Interventions	IUI with ovarian stimulation (letrozole) vs natural cycle IUI
Outcomes	Primary outcome: ongoing pregnancy leading to live birth
Starting date	March 2018
Contact information	Shuo Huang, PhD Peking University Third Hospital, Beijing, China Telephone: 86-13601203410 Email: homelyleaf@aliyun.com
Notes	First posted 6 March 2018; last updated 6 March 2018

NTR5599

Trial name or title	Intrauterine Insemination for Unexplained or Mild Male Subfertility - ex IUI
Methods	Randomised controlled trial, parallel group
Participants	Sample size: 1091 Inclusion criteria: 12 months of unprotected intercourse without conception; females between 18 and 42 years of age; regular ovulatory cycle and ≥ 1 patent fallopian tube. Male partner with no or mild impairment of semen quality with total motile sperm count (TMSC or VCM) > 3 million. Obtained written informed consent. 12-Month prognosis for natural conception (calculated according to the model of Hunault) ≤ 30%, or 12-month prognosis > 30% and returning after 6 months of expectant management without conception Exclusion criteria: IUI-OH with sperm donation; couples with medical contraindication for pregnancy; couples with previous ART in the current treatment episode
Interventions	Expectant management (experimental arm) vs OS-IUI (control arm)
Outcomes	Primary outcome: ongoing pregnancy leading to a live birth occurring within 6 months after randomisation Secondary outcomes: number of incomplete/cancelled cycles, clinical pregnancy, ongoing pregnancy, multiple pregnancy, ongoing multiple pregnancy, miscarriage, ectopic pregnancy, time to ongoing pregnancy, pregnancy outcomes, couples preference, quality of life, financial costs
Starting date	10 January 2016
Contact information	F. Mol Centrum voor Voortplantingsgeneeskunde Q3-119 Academisch Medisch Centrum Amsterdam, Netherlands Telephone: 020 5663557

NTR5599 *(Continued)*	
	Email: f.mol@amc.uva.nl
Notes	First posted: 18 December 2015; last updated: 30 April 2017

ART: assisted reproductive technology.
FSH: follicle-stimulating hormone.
hMG: human menopausal gonadotropin.
ICSI: intracytoplasmic sperm injection.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
OS: ovarian stimulation.
PCOS: polycystic ovarian syndrome.
TMSC: total motile sperm count.
VCM: total motile sperm count calculated as volume (in milliliters) × sperm concentration (10^6/mL) × percentage forward motility.
WHO: World Health Organization.

DATA AND ANALYSES

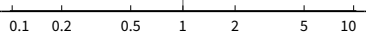
Comparison 1. Pairwise meta-analyses for live birth, multiple pregnancy, and clinical pregnancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 OS vs EM	2	527	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.49, 1.31]
1.2 IUI vs EM	1	386	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.87, 2.40]
1.3 OS-IUI vs EM	2	454	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.36, 9.90]
1.4 IUI vs OS	1	387	Odds Ratio (M-H, Random, 95% CI)	1.85 [1.09, 3.16]
1.5 OS-IUI vs OS	1	184	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.46, 1.67]
1.6 OS-IUI vs IUI	2	636	Odds Ratio (M-H, Random, 95% CI)	1.68 [1.14, 2.49]
1.7 IVF/ICSI vs OS-IUI	3	731	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.85, 1.57]
2 Multiple pregnancy	12		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 OS vs EM/IUI	3	934	Odds Ratio (M-H, Random, 95% CI)	2.04 [0.51, 8.24]
2.2 OS-IUI vs EM/IUI	4	676	Odds Ratio (M-H, Random, 95% CI)	5.04 [1.24, 20.49]
2.3 OS-IUI vs OS	2	274	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.12, 3.81]
2.5 IVF/ICSI vs OS-IUI	3	731	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.37, 1.73]
3 Clinical pregnancy	23		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 OS vs EM	6	939	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.82, 2.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 IUI vs EM	3	528	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.47]
3.3 OS-IUI vs EM	4	525	Odds Ratio (M-H, Random, 95% CI)	2.69 [0.96, 7.55]
3.4 IUI vs OS	2	407	Odds Ratio (M-H, Random, 95% CI)	1.69 [1.01, 2.82]
3.5 OS-IUI vs OS	8	763	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.73, 2.18]
3.6 OS-IUI vs IUI	4	579	Odds Ratio (M-H, Random, 95% CI)	2.56 [1.72, 3.80]
3.7 IVF/ICSI vs OS-IUI	3	731	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.95, 1.76]

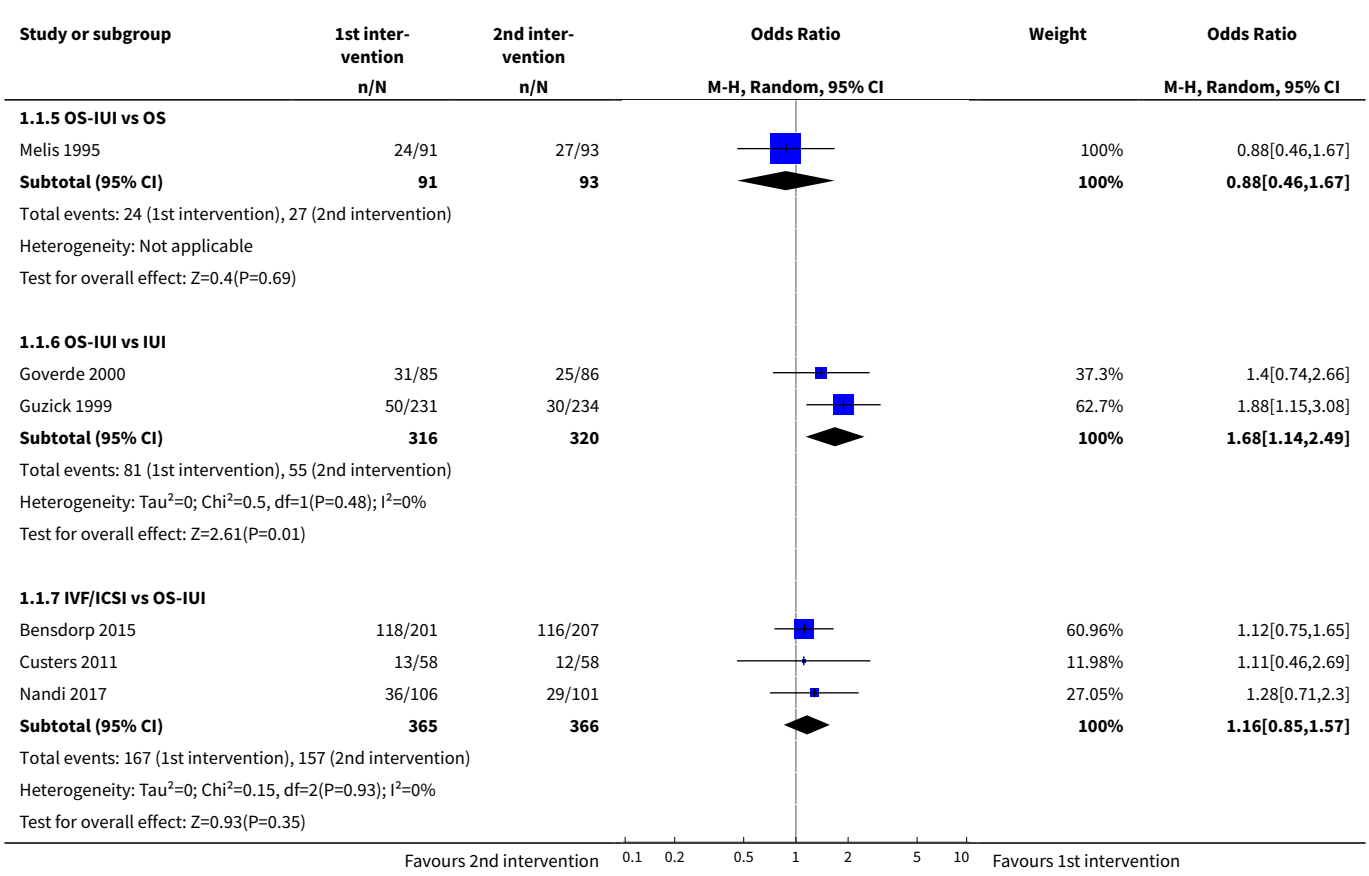
Analysis 1.1. Comparison 1 Pairwise meta-analyses for live birth, multiple pregnancy, and clinical pregnancy, Outcome 1 Live birth.

Study or subgroup	1st intervention n/N	2nd intervention n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 OS vs EM					
Bhattacharya 2008	26/194	32/193		74.89%	0.78[0.44,1.36]
George 2006	9/70	10/70		25.11%	0.89[0.34,2.33]
Subtotal (95% CI)	**264**	**263**		**100%**	**0.8[0.49,1.31]**
Total events: 35 (1st intervention), 42 (2nd intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					
1.1.2 IUI vs EM					
Bhattacharya 2008	43/193	32/193		100%	1.44[0.87,2.4]
Subtotal (95% CI)	**193**	**193**		**100%**	**1.44[0.87,2.4]**
Total events: 43 (1st intervention), 32 (2nd intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					
1.1.3 OS-IUI vs EM					
Farquhar 2017	31/101	9/100		48.67%	4.48[2,10.01]
Steures 2006	26/127	30/126		51.33%	0.82[0.45,1.49]
Subtotal (95% CI)	**228**	**226**		**100%**	**1.88[0.36,9.9]**
Total events: 57 (1st intervention), 39 (2nd intervention)					
Heterogeneity: Tau^2=1.31; Chi^2=11.04, df=1(P=0); I^2=90.94%					
Test for overall effect: Z=0.74(P=0.46)					
1.1.4 IUI vs OS					
Bhattacharya 2008	43/193	26/194		100%	1.85[1.09,3.16]
Subtotal (95% CI)	**193**	**194**		**100%**	**1.85[1.09,3.16]**
Total events: 43 (1st intervention), 26 (2nd intervention)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.26(P=0.02)					

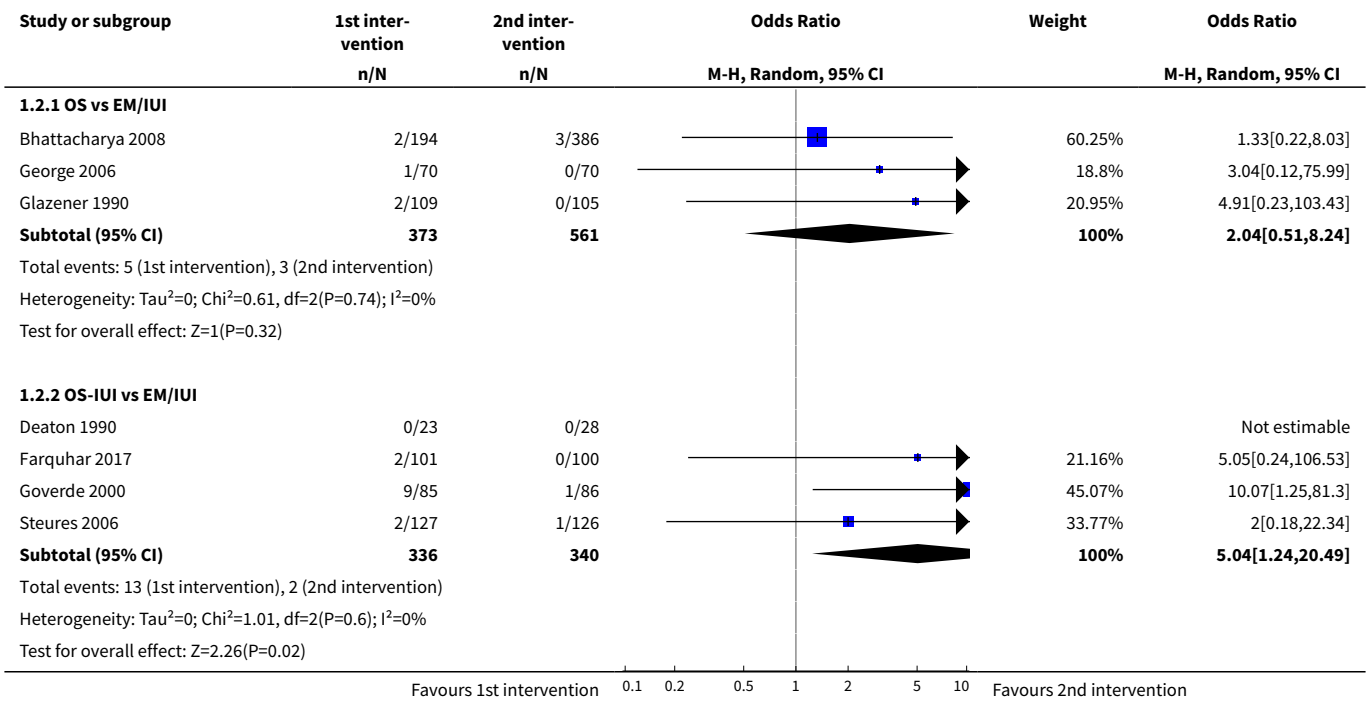


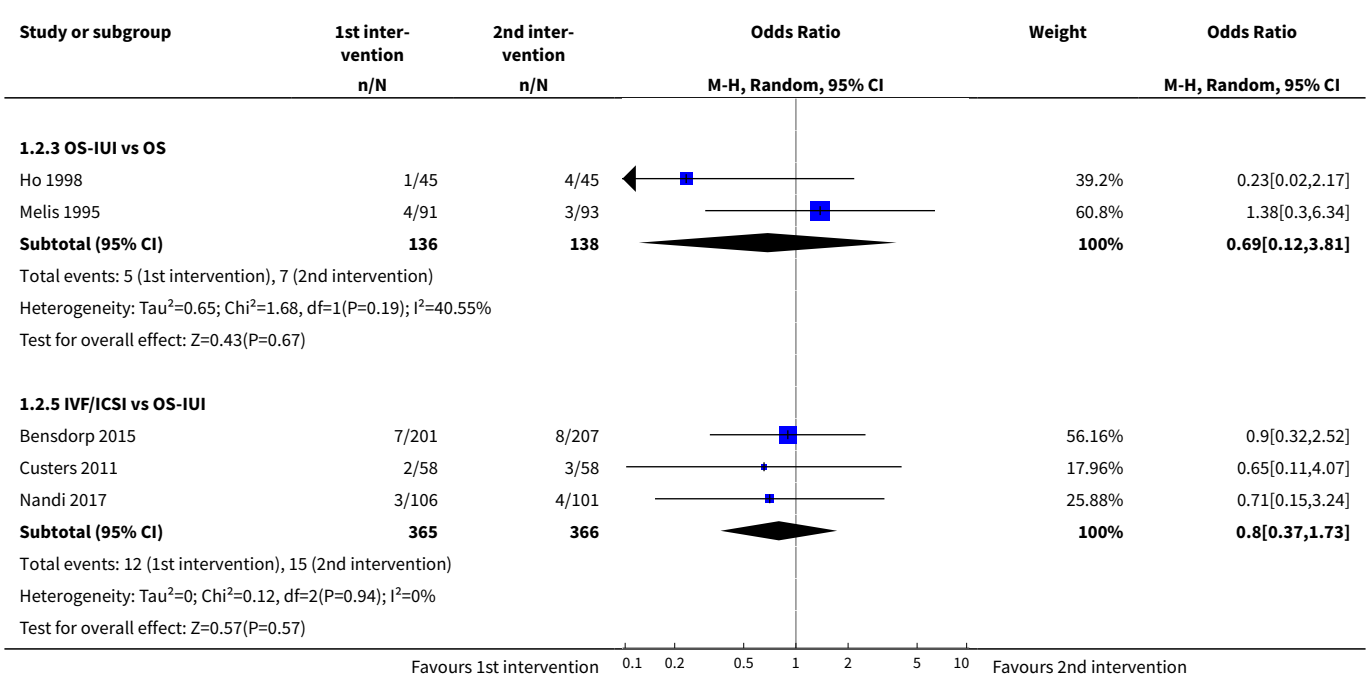
Favours 2nd intervention

Favours 1st intervention

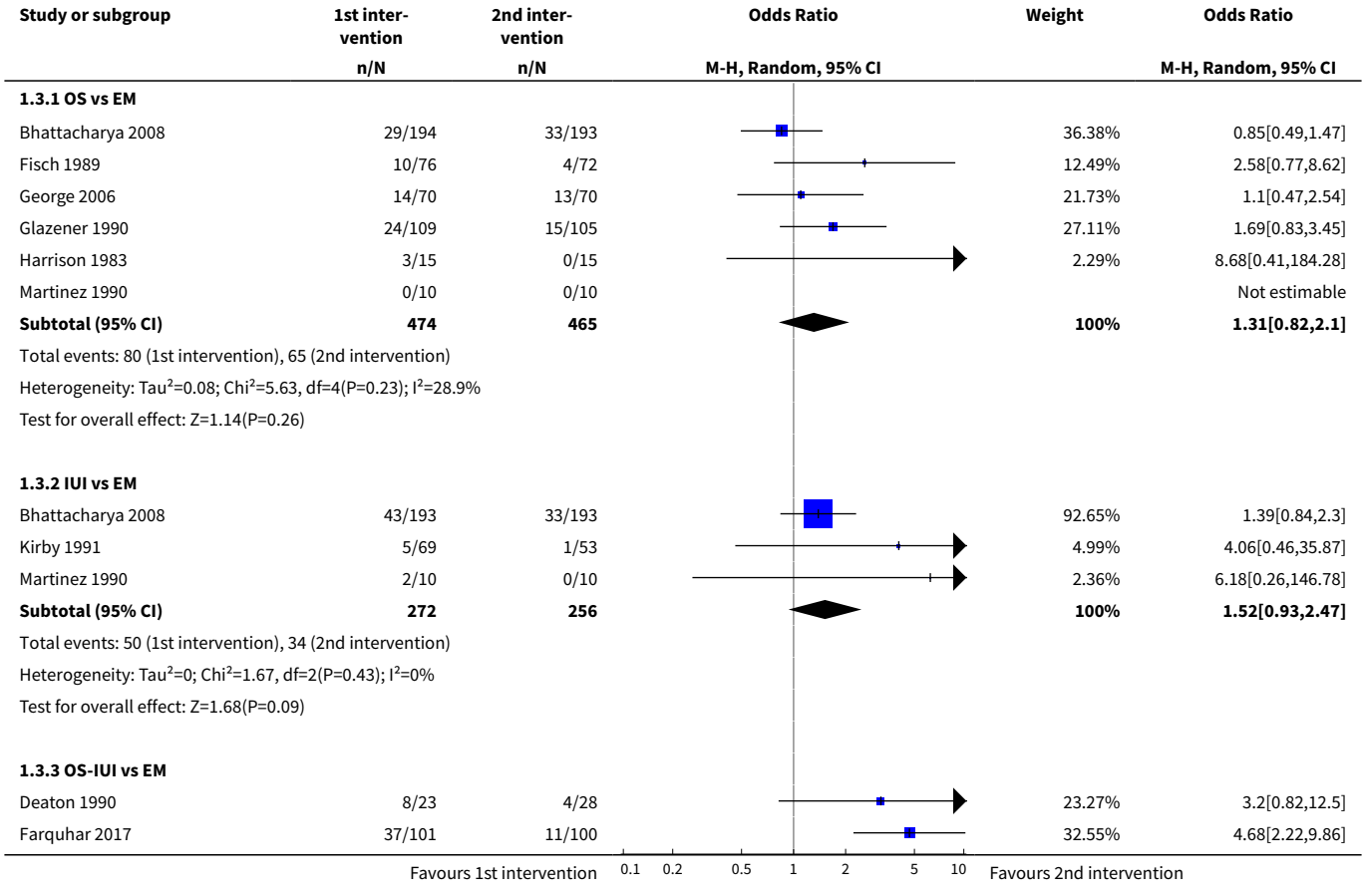


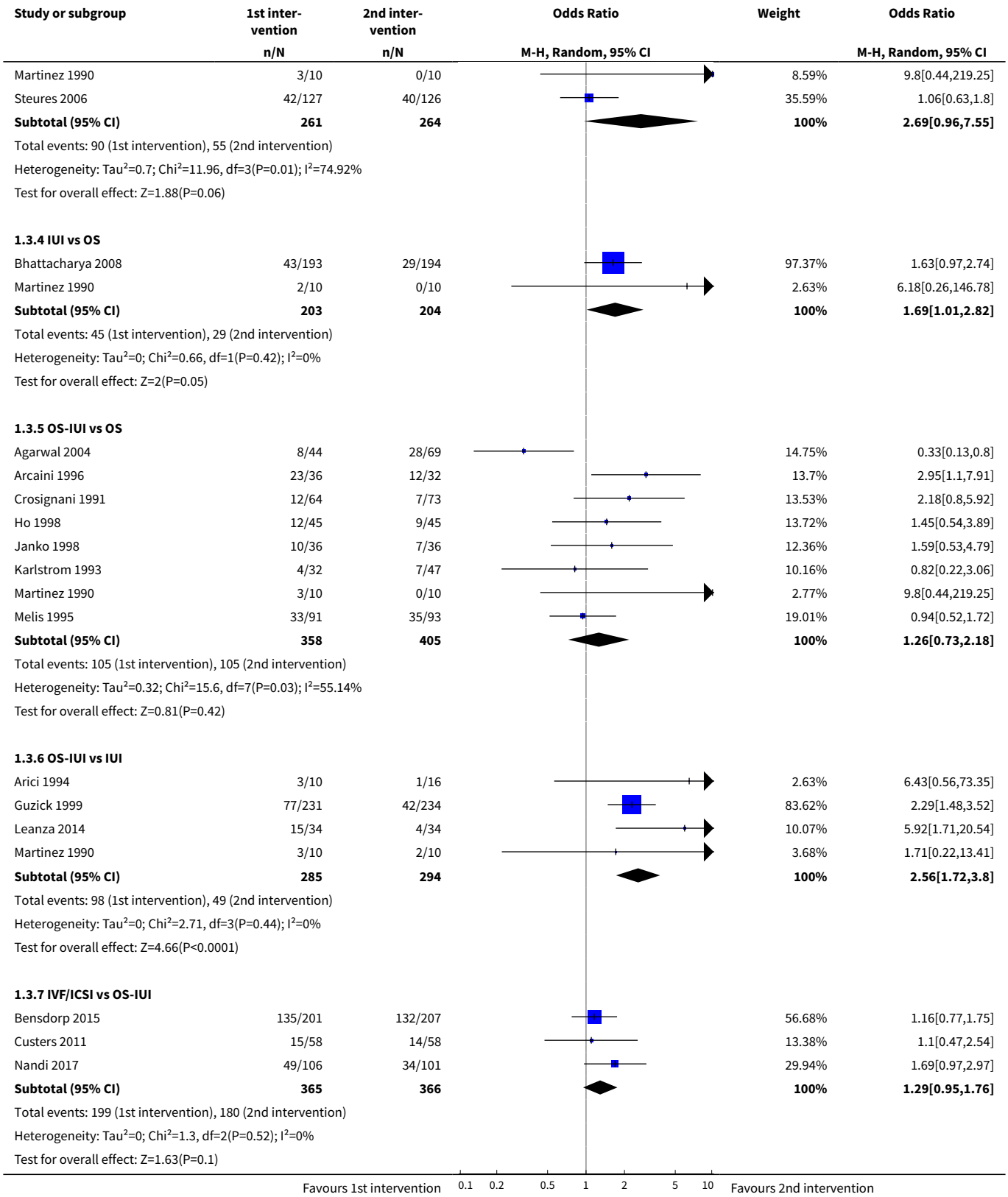
Analysis 1.2. Comparison 1 Pairwise meta-analyses for live birth, multiple pregnancy, and clinical pregnancy, Outcome 2 Multiple pregnancy.





Analysis 1.3. Comparison 1 Pairwise meta-analyses for live birth, multiple pregnancy, and clinical pregnancy, Outcome 3 Clinical pregnancy.



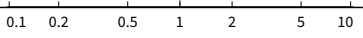


Comparison 2. Pairwise meta-analysis for OHSS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 OS-IUI vs EM	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 OS-IUI vs OS	2	274	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 OS-IUI vs IUI	1	171	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 IVF/ICSI vs IUI	1	173	Odds Ratio (M-H, Fixed, 95% CI)	7.17 [0.36, 140.84]
5 IVF/ICSI vs OS-IUI	5	985	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [0.92, 6.76]

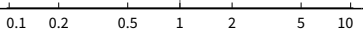
Analysis 2.1. Comparison 2 Pairwise meta-analysis for OHSS, Outcome 1 OS-IUI vs EM.

Study or subgroup	OS-IUI n/N	EM n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Deaton 1990	0/23	0/28			Not estimable
Total (95% CI)	**23**	**28**			**Not estimable**
Total events: 0 (OS-IUI), 0 (EM)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



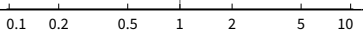
Analysis 2.2. Comparison 2 Pairwise meta-analysis for OHSS, Outcome 2 OS-IUI vs OS.

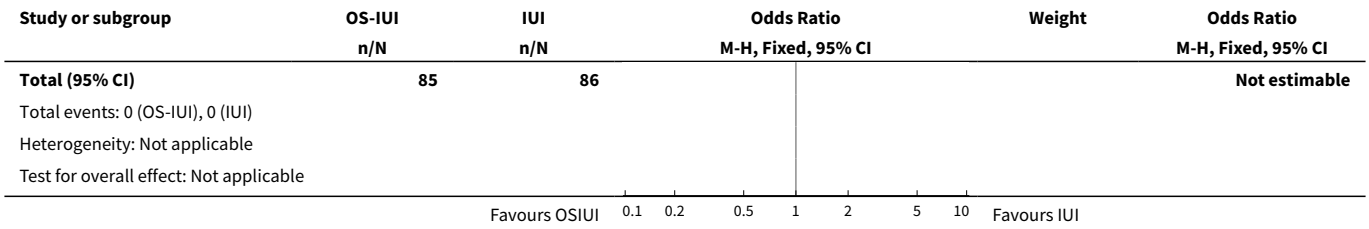
Study or subgroup	OS-IUI n/N	OS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ho 1998	0/45	0/45			Not estimable
Melis 1995	0/91	0/93			Not estimable
Total (95% CI)	**136**	**138**			**Not estimable**
Total events: 0 (OS-IUI), 0 (OS)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



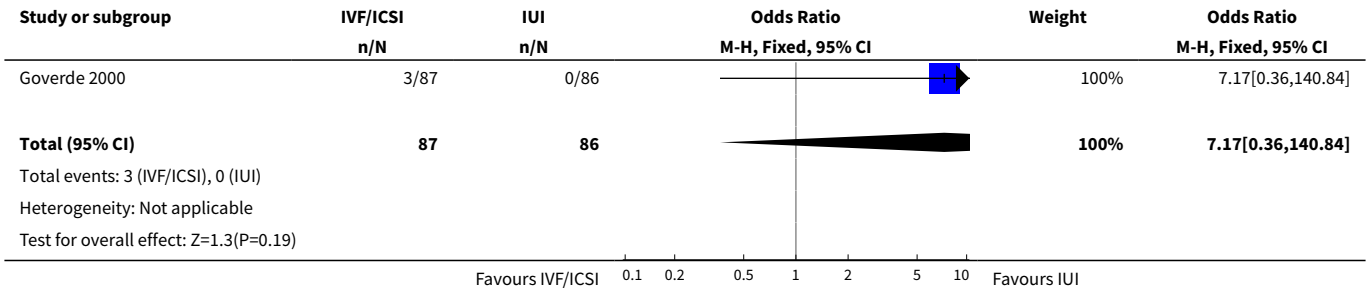
Analysis 2.3. Comparison 2 Pairwise meta-analysis for OHSS, Outcome 3 OS-IUI vs IUI.

Study or subgroup	OS-IUI n/N	IUI n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Goverde 2000	0/85	0/86			Not estimable

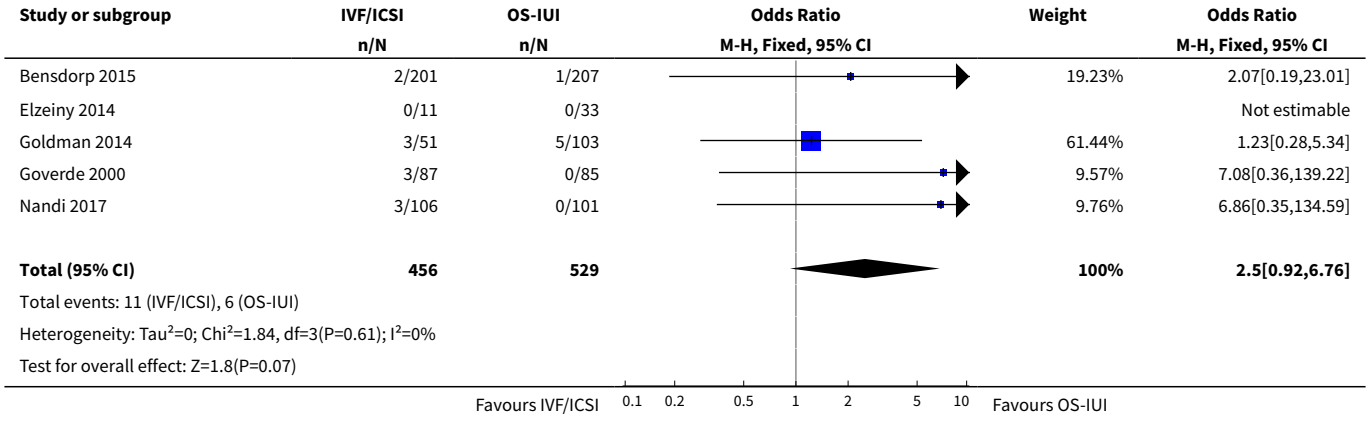




Analysis 2.4. Comparison 2 Pairwise meta-analysis for OHSS, Outcome 4 IVF/ICSI vs IUI.



Analysis 2.5. Comparison 2 Pairwise meta-analysis for OHSS, Outcome 5 IVF/ICSI vs OS-IUI.



Comparison 3. Data analyses of RCTs that were not included in the network meta-analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 IVF/ICSI vs EM	1	51	Odds Ratio (M-H, Random, 95% CI)	22.00 [2.56, 189.37]
1.2 IVF/ICSI vs IUI	1	173	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.79, 2.82]

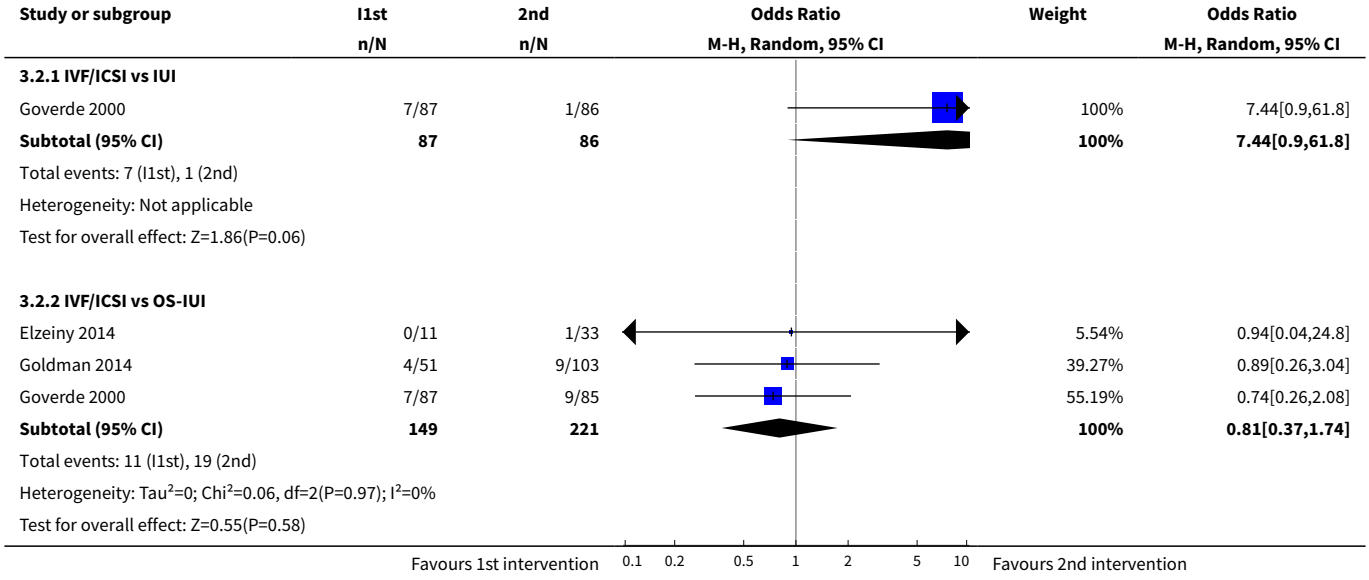
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 IVF/ICSI vs OS-IUI	3	370	Odds Ratio (M-H, Random, 95% CI)	2.23 [0.83, 5.98]
2 Multiple pregnancy	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 IVF/ICSI vs IUI	1	173	Odds Ratio (M-H, Random, 95% CI)	7.44 [0.90, 61.80]
2.2 IVF/ICSI vs OS-IUI	3	370	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.37, 1.74]
3 Clinical pregnancy	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 IVF/ICSI vs EM	1	51	Odds Ratio (M-H, Random, 95% CI)	8.00 [1.89, 33.85]
3.2 IVF/ICSI vs OS	1	103	Odds Ratio (M-H, Random, 95% CI)	2.36 [0.72, 7.72]
3.3 IVF/ICSI vs OS-IUI	3	292	Odds Ratio (M-H, Random, 95% CI)	2.61 [1.07, 6.37]

Analysis 3.1. Comparison 3 Data analyses of RCTs that were not included in the network meta-analysis, Outcome 1 Live birth.

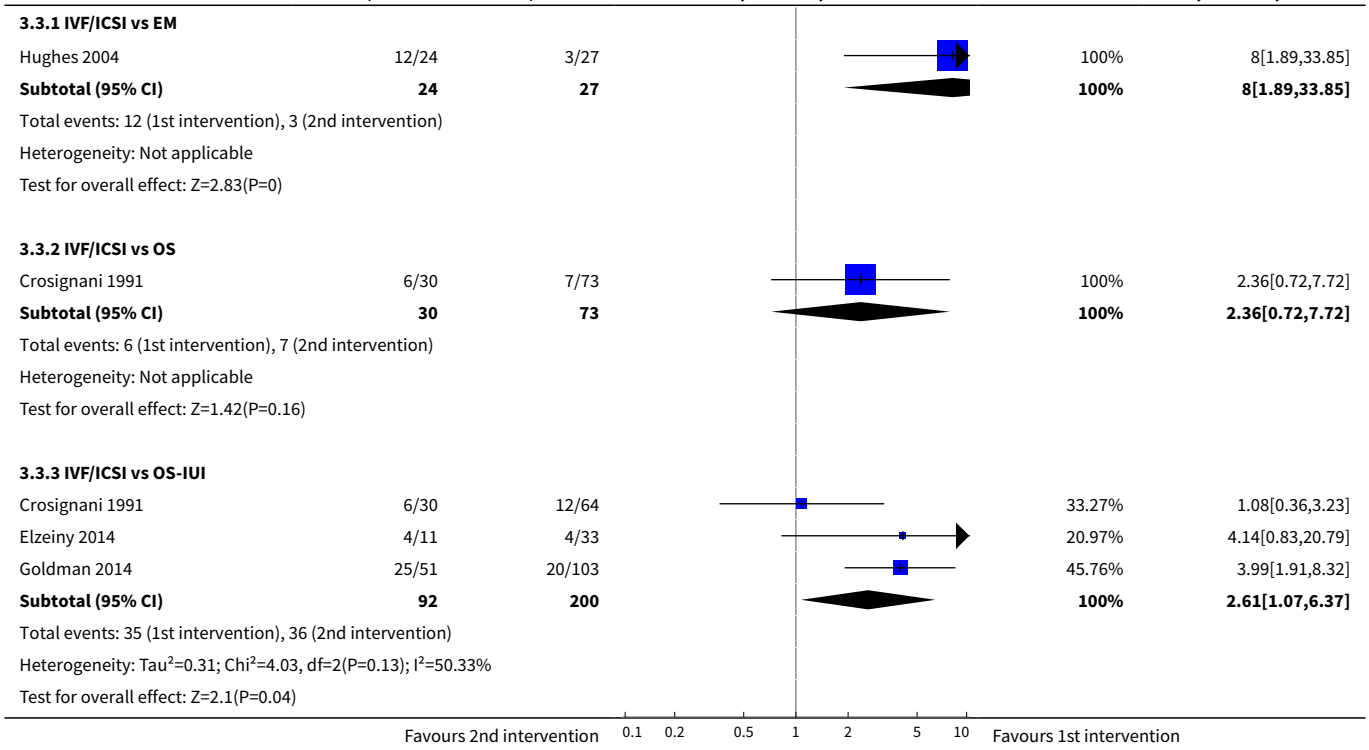
Study or subgroup	2nd intervention n/N	1st intervention n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 IVF/ICSI vs EM					
Hughes 2004	11/24	1/27		100%	22[2.56,189.37]
Subtotal (95% CI)	**24**	**27**		**100%**	**22[2.56,189.37]**
Total events: 11 (2nd intervention), 1 (1st intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.81(P=0)					
3.1.2 IVF/ICSI vs IUI					
Goverde 2000	33/87	25/86		100%	1.49[0.79,2.82]
Subtotal (95% CI)	**87**	**86**		**100%**	**1.49[0.79,2.82]**
Total events: 33 (2nd intervention), 25 (1st intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.23(P=0.22)					
3.1.3 IVF/ICSI vs OS-IUI					
Elzeiny 2014	4/11	2/33		17.98%	8.86[1.34,58.35]
Goldman 2014	16/51	15/103		38.72%	2.68[1.2,6]
Goverde 2000	33/87	31/85		43.31%	1.06[0.57,1.98]
Subtotal (95% CI)	**149**	**221**		**100%**	**2.23[0.83,5.98]**
Total events: 53 (2nd intervention), 48 (1st intervention)					
Heterogeneity: Tau²=0.49; Chi²=6.37, df=2(P=0.04); I²=68.62%					
Test for overall effect: Z=1.59(P=0.11)					

Favours 2nd intervention — Favours 1st intervention

Analysis 3.2. Comparison 3 Data analyses of RCTs that were not included in the network meta-analysis, Outcome 2 Multiple pregnancy.



Analysis 3.3. Comparison 3 Data analyses of RCTs that were not included in the network meta-analysis, Outcome 3 Clinical pregnancy.



APPENDICES

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

Searched 6 September 2018

Procite platform

Keywords CONTAINS "unexplained and endometriosis related infertility" or "unexplained infertility" or "unexplained subfertility" or "idiopathic infertility "or "idiopathic male infertility" or "idiopathic subfertility" or Title CONTAINS "unexplained and endometriosis related infertility" or "unexplained infertility" or "unexplained subfertility" or "idiopathic infertility" or "idiopathic male infertility" or "idiopathic subfertility" (374 hits)

Appendix 2. Cochrane Central Register of Studies Online (CRSO) search strategy

Searched 6 September 2018

CRSO web platform

#1 MESH DESCRIPTOR Infertility EXPLODE ALL TREES 2759

#2 unexplained:TI,AB,KY 1712

#3 idiopathic:TI,AB,KY 7295

#4 #2 OR #3 8953

#5 #1 AND #4 373

#6 (unexplain* adj5 infertil*):TI,AB,KY 483

#7 (unexplain* adj5 subfertil*):TI,AB,KY 74

#8 (idiopathic adj5 subfertil*):TI,AB,KY 11

#9 (idiopathic adj5 infertil*):TI,AB,KY 94

#10 (unknown adj5 subfertil*):TI,AB,KY 1

#11 (unknown adj5 infertil*):TI,AB,KY 1

#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 720

Appendix 3. MEDLINE search strategy

Searched from 1946 to 6 September 2018

Ovid platform

1 exp Infertility/ and unexplained.tw. (1901)
2 exp Infertility/ and idiopathic.tw. (1700)
3 (unexplain* adj5 infertil*).tw. (2090)
4 (unexplain* adj5 subfertil*).tw. (157)
5 (idiopathic adj5 subfertil*).tw. (74)
6 (idiopathic adj5 infertil*).tw. (1222)
7 (unknown adj3 infertil*).tw. (170)
8 (unknown adj3 subfertil*).tw. (11)
9 (unexplained adj3 steril*).tw. (56)
10 (idiopathic adj3 steril*).tw. (54)
11 (unknown adj3 steril*).tw. (48)
12 or/1-11 (4512)
13 exp Clomiphene/ (5115)
14 clomifene.tw. (127)
15 clomiphene.tw. (4875)
16 Serophene.tw. (4)
17 clomid.tw. (176)

18 selective estrogen receptor modulators/ or exp raloxifene hydrochloride/ or exp tamoxifen/ (21795)
19 selective estrogen receptor modulator*.tw. (2803)
20 (SERMs or SERM).tw. (2009)
21 (raloxifene or tamoxifen).tw. (23603)
22 or/13-21 (36987)
23 Aromatase Inhibitors/ (5733)
24 Aromatase inhibitor*.tw. (6687)
25 letrozole.tw. (2481)
26 (femara or anastrozole).tw. (1675)
27 (anti-?estrogen* or anti?estrogen*).tw. (8947)
28 or/23-27 (17912)
29 exp follicle stimulating hormone/ or exp follicle stimulating hormone, beta subunit/ or exp glycoprotein hormones, alpha subunit/ or exp menotropins/ or exp urofollitropin/ (38849)
30 Follicle Stimulating Hormone*.tw. (18222)
31 (FSH or rFSH or recFSH).tw. (33058)
32 (uFSH or rhFSH).tw. (233)
33 (hpFSH or pFSH).tw. (203)
34 (follitropin or Gonal F).tw. (705)
35 (menotropin* or menopur).tw. (207)
36 corifollitropin.tw. (90)
37 (urofollitropin or pergonal or bravelle* or follitrin).tw. (206)
38 Follistim*.tw. (12)
39 (Puregon or humegon or menogon).tw. (89)
40 human menopausal gonadotrop?in.tw. (1783)
41 growth hormone.tw. (53592)
42 HMG.tw. (13823)
43 gonadotrop?in*.tw. (60770)
44 or/29-43 (157278)
45 expectant management.tw. (2298)
46 watchful waiting.tw. (2284)
47 (watch and wait).tw. (750)
48 Coitus/ (7072)
49 coitus.tw. (2693)
50 intercourse.tw. (18110)
51 sex*.tw. (651487)
52 or/45-51 (662646)
53 exp Insemination, Artificial/ (11188)
54 intrauterine insemination*.tw. (2295)
55 artificial insemination*.tw. (6200)
56 superovulat*.tw. (3265)
57 IUI.tw. (1587)
58 or/53-56 (17342)
59 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (38494)
60 embryo transfer*.tw. (10716)
61 vitro fertili?ation.tw. (21146)
62 ivf.tw. (21404)
63 icsi.tw. (7513)
64 intracytoplasmic sperm injection*.tw. (6494)
65 (blastocyst adj2 transfer*).tw. (877)
66 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (63849)
67 assisted reproduct*.tw. (13076)
68 ovulation induc*.tw. (3941)
69 (ovar* adj2 stimulat*).tw. (6529)
70 ovarian hyperstimulation.tw. (4741)
71 COH.tw. (1579)
72 (ovar* adj2 induc*).tw. (3910)
73 (modified adj3 cycle*).tw. (560)
74 (natural adj3 cycle*).tw. (2396)
75 MNC IVF.tw. (23)
76 (NCIVF or NC-IVF).tw. (18)
77 unstimulated ivf.tw. (18)
78 (unstimulated adj2 in vitro fertili?ation).tw. (13)

79 (artificial adj3 cycle$).tw. (449)
80 or/59-79 (87813)
81 22 or 28 or 44 or 52 or 58 or 80 (914386)
82 12 and 81 (2487)
83 randomized controlled trial.pt. (467907)
84 controlled clinical trial.pt. (92625)
85 randomized.ab. (421185)
86 randomised.ab. (84107)
87 placebo.tw. (196867)
88 clinical trials as topic.sh. (184705)
89 randomly.ab. (296832)
90 trial.ti. (187190)
91 (crossover or cross-over or cross over).tw. (77604)
92 or/83-91 (1229120)
93 exp animals/ not humans.sh. (4493841)
94 92 not 93 (1131490)
95 82 and 94 (493)

Appendix 4. Embase search strategy

Searched from 1980 to 6 September 2018

Ovid platform

1 (exp infertility/ or exp infertility therapy/) and unexplained.tw. (3790)
2 (exp infertility/ or exp infertility therapy/) and idiopathic.tw. (3240)
3 (unexplain* adj5 infertil*).tw. (3122)
4 (unexplain* adj5 subfertil*).tw. (252)
5 (idiopathic adj5 subfertil*).tw. (89)
6 (idiopathic adj5 infertil*).tw. (1739)
7 (unknown adj3 infertil*).tw. (262)
8 (unknown adj3 subfertil*).tw. (14)
9 (unexplained adj3 steril*).tw. (59)
10 (idiopathic adj3 steril*).tw. (60)
11 (unknown adj3 steril*).tw. (56)
12 or/1-11 (7404)
13 exp clomifene/ (4436)
14 clomifene.tw. (215)
15 clomiphene.tw. (5229)
16 Serophene.tw. (194)
17 clomid.tw. (922)
18 exp selective estrogen receptor modulator/ (7325)
19 exp raloxifene/ (10783)
20 exp tamoxifen citrate/ or exp tamoxifen/ (58156)
21 selective estrogen receptor modulator*.tw. (3748)
22 (SERMs or SERM).tw. (2979)
23 (raloxifene or tamoxifen).tw. (33459)
24 or/13-23 (78982)
25 exp aromatase inhibitor/ (28231)
26 Aromatase inhibitor*.tw. (10361)
27 letrozole.tw. (4470)
28 (femara or anastrozole).tw. (3652)
29 (anti-?estrogen* or anti?estrogen*).tw. (10420)
30 or/25-29 (38435)
31 exp follitropin/ (48940)
32 exp human menopausal gonadotropin/ (8642)
33 exp urofollitropin/ (1649)
34 Follicle Stimulating Hormone*.tw. (18482)
35 (FSH or rFSH or recFSH).tw. (39571)
36 (uFSH or rhFSH).tw. (334)
37 (hpFSH or pFSH).tw. (207)
38 (follitropin or Gonal F).tw. (2940)
39 (menotropin* or menopur).tw. (773)

40 corifollitropin.tw. (190)
41 (urofollitropin or pergonal or bravelle* or follitrin).tw. (2034)
42 Follistim*.tw. (268)
43 (Puregon or humegon or menogon).tw. (2081)
44 human menopausal gonadotrop?in.tw. (1863)
45 growth hormone.tw. (55310)
46 HMG.tw. (17377)
47 gonadotrop?in*.tw. (61170)
48 or/31-47 (175256)
49 expectant management.tw. (3317)
50 watchful waiting.tw. (3340)
51 (watch and wait).tw. (1386)
52 exp coitus/ (5008)
53 coitus.tw. (2579)
54 intercourse.tw. (22847)
55 sex*.tw. (810058)
56 or/49-55 (823896)
57 exp artificial insemination/ (15778)
58 intrauterine insemination*.tw. (3376)
59 artificial insemination*.tw. (5478)
60 superovulat*.tw. (3537)
61 IUI.tw. (2883)
62 or/49-61 (843368)
63 exp fertilization in vitro/ (60536)
64 exp embryo transfer/ (27677)
65 exp intracytoplasmic sperm injection/ (18393)
66 embryo transfer*.tw. (16874)
67 vitro fertili?ation.tw. (27109)
68 ivf.tw. (35769)
69 icsi.tw. (14240)
70 intracytoplasmic sperm injection*.tw. (8545)
71 (blastocyst adj2 transfer*).tw. (1989)
72 exp infertility therapy/ (87213)
73 exp artificial insemination/ (15778)
74 exp ovulation induction/ (13068)
75 assisted reproduct*.tw. (19632)
76 ovulation induc*.tw. (5192)
77 (ovar* adj2 stimulat*).tw. (9965)
78 ovarian hyperstimulation.tw. (6858)
79 COH.tw. (2177)
80 (ovar* adj2 induc*).tw. (4609)
81 (modified adj3 cycle*).tw. (775)
82 (natural adj3 cycle*).tw. (3197)
83 MNC IVF.tw. (37)
84 (NCIVF or NC-IVF).tw. (47)
85 unstimulated ivf.tw. (30)
86 (unstimulated adj2 in vitro fertili?ation).tw. (18)
87 (artificial adj3 cycle$).tw. (528)
88 or/63-87 (122326)
89 24 or 30 or 48 or 56 or 62 or 88 (1159178)
90 Clinical Trial/ (939390)
91 Randomized Controlled Trial/ (506064)
92 exp randomization/ (79110)
93 Single Blind Procedure/ (32096)
94 Double Blind Procedure/ (148976)
95 Crossover Procedure/ (56068)
96 Placebo/ (307810)
97 Randomi?ed controlled trial$.tw. (183941)
98 Rct.tw. (29057)
99 random allocation.tw. (1783)
100 randomly.tw. (381272)
101 randomly allocated.tw. (30135)

102 allocated randomly.tw. (2330)
103 (allocated adj2 random).tw. (792)
104 Single blind$.tw. (21113)
105 Double blind$.tw. (182169)
106 ((treble or triple) adj blind$).tw. (803)
107 placebo$.tw. (269794)
108 prospective study/ (463707)
109 or/90-108 (2118634)
110 case study/ (55585)
111 case report.tw. (348767)
112 abstract report/ or letter/ (1017866)
113 or/110-112 (1413483)
114 109 not 113 (2069749)
115 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5490558)
116 114 not 115 (1926969)
117 12 and 89 and 116 (1070)

Appendix 5. PsycINFO search strategy

Searched from 1806 to 6 September 2018

Ovid platform

1 exp INFERTILITY/ and unexplained.tw. (40)
2 exp INFERTILITY/ and idiopathic.tw. (16)
3 (unexplain* adj5 infertil*).tw. (36)
4 (unexplain* adj5 subfertil*).tw. (2)
5 (idiopathic adj5 infertil*).tw. (18)
6 (unknown adj3 infertil*).tw. (10)
7 (unexplained adj3 steril*).tw. (1)
8 (idiopathic adj3 steril*).tw. (2)
9 (unknown adj3 steril*).tw. (2)
10 or/1-9 (71)
11 random*.ti,ab,hw,id. (181184)
12 trial*.ti,ab,hw,id. (166702)
13 controlled stud*.ti,ab,hw,id. (11453)
14 placebo*.ti,ab,hw,id. (38171)
15 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id. (27288)
16 (cross over or crossover or factorial* or latin square).ti,ab,hw,id. (27952)
17 (assign* or allocat* or volunteer*).ti,ab,hw,id. (152430)
18 treatment effectiveness evaluation/ (22271)
19 mental health program evaluation/ (2045)
20 exp experimental design/ (54262)
21 or/11-20 (480042)
22 10 and 21 (6)

Appendix 6. CINAHL search strategy

Searched from 1961 to 6 September 2018

Ebsco platform

#	Query	Results
S23	S10 AND S22	102
S22	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	1,255,308
S21	TX allocat* random*	9,041

(Continued)

S20	(MH "Quantitative Studies")	20,295
S19	(MH "Placebos")	10,838
S18	TX placebo*	52,082
S17	TX random* allocat*	9,041
S16	(MH "Random Assignment")	50,544
S15	TX randomi* control* trial*	153,119
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*))	972,401
S13	TX clinic* n1 trial*	227,640
S12	PT Clinical trial	86,040
S11	(MH "Clinical Trials+")	244,190
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	309
S9	TX(idiopathic N3 steril*)	2
S8	TX(unknown N3 subfertil*)	1
S7	TX(unknown N3 infertil*)	19
S6	TX(idiopathic N5 infertil*)	60
S5	TX(idiopathic N5 subfertil*)	5
S4	TX(unexplain* N5 subfertil*)	30
S3	TX (unexplain* N5 infertil*)	185
S2	(MM "Infertility") and TX idiopathic	64
S1	(MM "Infertility") and TX unexplained	147

CONTRIBUTIONS OF AUTHORS

RW, RIT, MJCE, PMMB, FvdV, SB, BWM, and MvW contributed to the study design and the original protocol. RW, NAD, RIT, and MvW collected the data. RW and MvW analysed the data. All review authors interpreted the data. RW wrote the first draft. All review authors revised the manuscript critically for important intellectual content and approved the final version.

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SB has not received money from any source to support the work leading up to this review. SB has received support for travel and accommodation for speaking at conferences. His institution and institutional colleagues have received support from pharmaceutical companies for educational activities such as hosting seminars and attending conferences. He receives an honorarium as Editor-in-Chief of *Human Reproduction Open*.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We replaced subfertility with infertility according to the latest version of the International Glossary on Infertility and Fertility Care (Zegers-Hochschild 2017). We excluded studies on modified natural cycle IVF as it is different from IVF with ovarian hyperstimulation.

We planned in the protocol to perform a sensitivity analysis by using alternative imputation strategies. However, for binary outcomes, it can be problematic to impute missing outcomes as events. Therefore, we did a sensitivity analysis by excluding missing outcome data as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*. We did not report the predictive interval in this network meta-analysis but used it when accessing heterogeneity for the overall certainty of evidence in CINeMA (CINeMA 2017; Salanti 2014).

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Rate; *Reproductive Techniques, Assisted; Birth Rate; Fertility Agents, Female [therapeutic use]; Fertilization in Vitro [methods]; Infertility, Female [etiology] [*therapy]; Network Meta-Analysis; Ovulation Induction [methods]; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic [methods]

MeSH check words

Female; Humans; Pregnancy