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[Intervention Review]

Assisted reproductive technologies for male subfertility

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ABSTRACT

Background

Intra-uterine insemination (IUI), in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are frequently used fertility treatments for couples with male subfertility. The use of these treatments has been subject of discussion. Knowledge on the effectiveness of fertility treatments for male subfertility with different grades of severity is limited. Possibly, couples are exposed to unnecessary or ineffective treatments on a large scale.

Objectives

To evaluate the effectiveness and safety of different fertility treatments (expectant management, timed intercourse (TI), IUI, IVF and ICSI) for couples whose subfertility appears to be due to abnormal sperm parameters.

Search methods

We searched for all publications that described randomised controlled trials (RCTs) of the treatment for male subfertility. We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, PsycINFO and the National Research Register from inception to 14 April 2015, and web-based trial registers from January 1985 to April 2015. We applied no language restrictions. We checked all references in the identified trials and background papers and contacted authors to identify relevant published and unpublished data.

Selection criteria

We included RCTs comparing different treatment options for male subfertility. These were expectant management, TI (with or without ovarian hyperstimulation (OH)), IUI (with or without OH), IVF and ICSI. We included only couples with abnormal sperm parameters.

Data collection and analysis

Two review authors independently selected the studies, extracted data and assessed risk of bias. They resolved disagreements by discussion with the rest of the review authors. We performed statistical analyses in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration. The quality of the evidence was rated using the GRADE methods. Primary outcomes were live birth and ovarian hyperstimulation syndrome (OHSS) per couple randomised.

Main results

The review included 10 RCTs (757 couples). The quality of the evidence was low or very low for all comparisons. The main limitations in the evidence were failure to describe study methods, serious imprecision and inconsistency.

IUI versus TI (five RCTs)

Two RCTs compared IUI with TI in natural cycles. There were no data on live birth or OHSS. We found no evidence of a difference in pregnancy rates (2 RCTs, 62 couples: odds ratio (OR) 4.57, 95% confidence interval (CI) 0.21 to 102, very low quality evidence; there were no events in one of the studies).

Three RCTs compared IUI with TI both in cycles with OH. We found no evidence of a difference in live birth rates (1 RCT, 81 couples: OR 0.89, 95% CI 0.30 to 2.59; low quality evidence) or pregnancy rates (3 RCTs, 202 couples: OR 1.51, 95% CI 0.74 to 3.07; I^2 = 11%, very low quality evidence). One RCT reported data on OHSS. None of the 62 women had OHSS.

One RCT compared IUI in cycles with OH with TI in natural cycles. We found no evidence of a difference in live birth rates (1 RCT, 44 couples: OR 3.14, 95% CI 0.12 to 81.35; very low quality evidence). Data on OHSS were not available.

IUI in cycles with OH versus IUI in natural cycles (five RCTs)

We found no evidence of a difference in live birth rates (3 RCTs, 346 couples: OR 1.34, 95% CI 0.77 to 2.33; I^2 = 0%, very low quality evidence) and pregnancy rates (4 RCTs, 399 couples: OR 1.68, 95% CI 1.00 to 2.82; I^2 = 0%, very low quality evidence). There were no data on OHSS.

IVF versus IUI in natural cycles or cycles with OH (two RCTs)

We found no evidence of a difference in live birth rates between IVF versus IUI in natural cycles (1 RCT, 53 couples: OR 0.77, 95% CI 0.25 to 2.35; low quality evidence) or IVF versus IUI in cycles with OH (2 RCTs, 86 couples: OR 1.03, 95% CI 0.43 to 2.45; I^2 = 0%, very low quality evidence). One RCT reported data on OHSS. None of the women had OHSS.

Overall, we found no evidence of a difference between any of the groups in rates of live birth, pregnancy or adverse events (multiple pregnancy, miscarriage). However, most of the evidence was very low quality.

There were no studies on IUI in natural cycles versus TI in stimulated cycles, IVF versus TI, ICSI versus TI, ICSI versus IUI (with OH) or ICSI versus IVF.

Authors' conclusions

We found insufficient evidence to determine whether there was any difference in safety and effectiveness between different treatments for male subfertility. More research is needed.

PLAIN LANGUAGE SUMMARY

Treatments for male subfertility

Review question

Cochrane authors reviewed the evidence about the effectiveness of different treatments for couples with male subfertility.

Background

Intra-uterine insemination (IUI), in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are frequently-used fertility treatments for couples with low male fertility (subfertility). In IUI, the man's sperm is prepared and placed in the womb (uterus). Thus, the sperm is close to the place where the embryo is made (conception site). IUI can be performed with or without ovarian hyperstimulation (OH). In an OH cycle, women receive drugs to stimulate the ovaries (the organs that produce the eggs (called oocytes)) to increase the number of available oocytes. The main side effects of these drugs are multiple pregnancy (production of two or more embryos (early stage in the development of a baby)) and ovarian hyperstimulation syndrome (OHSS; the ovaries produce too many eggs). In IVF and ICSI, the fertilisation (where the egg and sperm are together and produce an embryo) is outside the body. The oocytes are retrieved from the woman using an ultrasound-guided needle, piercing the vaginal wall to reach the ovaries. Through this needle, follicular fluid, which contains the oocyte, can be aspirated. It is common to remove between 10 and 15 oocytes. In IVF, the eggs are mixed with the sperm in a culture dish. In ICSI, sperm are injected directly into the oocytes to cause fertilisation. The fertilised oocytes are treated for two to six days in a medium that contains nutrients and are then placed in the uterus.

Study characteristics

We searched medical databases for randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) investigating male subfertility. We found 10 randomised controlled trials, all comparing different treatments for couples with male subfertility, with a total of 757 couples. The studies evaluated the following treatment options: timed intercourse (TI; where sex occurred at a recommended time in the menstrual cycle) (with or without OH), IUI (with or without OH), IVF and ICSI. The evidence was current to April 2015. We were mainly interested in how many women had live births and OHSS.

Key results

We found no evidence of a difference in live birth or pregnancy rates between treatments. We also found no evidence of a difference between any of the groups in rates of adverse effects (multiple pregnancy, miscarriage). Available data on OHSS was too limited for us to draw any conclusions.

Quality of the evidence

Most of the evidence was of low or very low quality. The main limitations were failure to describe study methods, small sample sizes and inconsistency in how trials were conducted. Evidence was available for only six of the 14 comparisons that we evaluated. More research is needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. IUI in natural cycles compared to TI in natural cycles for male subfertility

IUI in natural cycles compared to TI in natural cycles for male subfertility

Patient or population: couples with male subfertility
Settings: single centre (Australia, Italy)
Intervention: IUI in natural cycles
Comparison: TI in natural cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of couples (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI in natural cycles	IUI in natural cycles				
Live birth rate	Not reported in any included studies				-	-
OHSS	Not reported in any included studies				-	-
Pregnancy rate per couple (all cycles) Follow-up: 9-12 months	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 4.57** (0.21 to 101.61)	62 (2 studies)	⊕⊖⊖⊖ **very low** [1,2]	-

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IUI:** intra-uterine insemination; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio; **TI:** timed intercourse.

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

[1] Risk of bias was very serious: 1. Francavilla 2009, allocation concealment: high risk (on chronological basis), 2. Francavilla 2009, other bias: high risk (no stratification by diagnosis category of subfertility).
[2] There was very serious imprecision, with small sample sizes and very few events.

Summary of findings 2. IUI in stimulated cycles compared to TI in stimulated cycles for male subfertility

IUI in stimulated cycles compared to TI in stimulated cycles for male subfertility

Patient or population: couples with male subfertility
Settings: single centre (Greece, Italy, The Netherlands)
Intervention: IUI in stimulated cycles
Comparison: TI in stimulated cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of couples (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI in stimulated cycles	IUI in stimulated cycles				
Live birth rate per couple (all cycles) Follow-up: 3 months	**220 per 1000**	**200 per 1000** (78 to 421)	**OR 0.89** (0.30 to 2.59)	81 (1 study)	⊕⊕⊖⊖ **low** [1]	-
OHSS per couple Follow-up: 6 months	See comment	See comment	Not estimable	59 (1 study)	⊕⊕⊖⊖ **low** [1]	-
Pregnancy rate per couple (all cycles) Follow-up: 3-6 months	**175 per 1000**	**243 per 1000** (136 to 395)	**OR 1.51** (0.74 to 3.07)	202 (3 studies)	⊕⊖⊖⊖ **very low** [1,2]	-
Multiple pregnancy rate per couple Follow-up: 3 months	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 3.15** (0.12 to 79.69)	81 (1 study)	⊕⊕⊖⊖ **low** [3]	-
Miscarriage rate per couple Follow-up: 3 months	**73 per 1000**	**75 per 1000** (15 to 300)	**OR 1.03** (0.19 to 5.42)	81 (1 study)	⊕⊕⊖⊖ **low** [3]	-

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IUI:** intra-uterine insemination; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio; **TI:** timed intercourse.

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

[1] There was very serious imprecision, with small sample size.
[2] Inconsistency was serious between Melis 1995 (favoured TI + OH) and Gregoriou 1996 and Nan 1994 (favoured IUI + OH).
[3] There was very serious imprecision, with small sample sizes and findings were compatible with substantial benefit in either group.

Summary of findings 3. IUI in stimulated cycles compared to TI in natural cycles for male subfertility

IUI in stimulated cycles compared to TI in natural cycles for male subfertility

Patient or population: couples with male subfertility
Settings: single centre (Italy)
Intervention: IUI in stimulated cycles
Comparison: TI in natural cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of couples (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI in natural cycles	IUI in stimulated cycles				
Live birth rate per couple (all cycles) Follow-up: 9 months	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 3.14** (0.12 to 81.35)	44 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	-
OHSS	Not reported in any included studies					-
Pregnancy rate per couple (all cycles) Follow-up: 9 months	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 3.14** (0.12 to 81.35)	44 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	-

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IUI:** intra-uterine insemination; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio; **TI:** timed intercourse.

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

[1] Risk of bias was very serious: 1. Allocation concealment: high risk (on chronological basis), 2. Other bias: high risk (no stratification by diagnosis category of subfertility).
[2] There was very serious imprecision, with small sample sizes and very few events.

Summary of findings 4. IUI in stimulated cycles compared to IUI in natural cycles for male subfertility

IUI in stimulated cycles compared to IUI in natural cycles for male subfertility

Patient or population: couples with male subfertility
Settings: single and multicentre (Italy, the Netherlands, USA)
Intervention: IUI in stimulated cycles
Comparison: IUI in natural cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of couples (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IUI in natural cycles	IUI in stimulated cycles				
Live birth rate per couple (all cycles) Follow-up: 6-9 months	**172 per 1000**	**218 per 1000** (138 to 326)	**OR 1.34** (0.77 to 2.33)	346 (3 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	-
OHSS	Not reported in any included studies				-	-
Pregnancy rate per couple (all cycles) Follow-up: 4-9 months	**148 per 1000**	**226 per 1000** (148 to 329)	**OR 1.68** (1.00 to 2.82)	399 (4 studies)	⊕⊖⊖⊖ **very low** [1,3,4]	-
Miscarriage rate per couple Follow-up: 6-9 months	**53 per 1000**	**56 per 1000** (11 to 238)	**OR 1.06** (0.20 to 5.63)	115 (2 studies)	⊕⊖⊖⊖ **very low** [5,6]	-

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IUI:** intra-uterine insemination; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio.

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

[1] Risk of bias was very serious: 1. Francavilla 2009, allocation concealment: high risk (on chronological basis), 2. Arici 1994, Francavilla 2009, and Guzick 1999, other bias: high risk (no stratification by diagnosis category of subfertility.
[2] Inconsistency was serious between Cohlen 1998a and Goverde 2000 (favoured IUI in natural cycles) and Arici 1994, Francavilla 2009, and Guzick 1999 (favoured IUI in stimulated cycles).
[3] There was serious imprecision, with small sample sizes.
[4] Inconsistency was serious between Cohlen 1998a (favoured IUI in natural cycles) and Arici 1994, Francavilla 2009, and Guzick 1999 (favoured IUI in stimulated cycles).
[5] Risk of bias was very serious: Francavilla 2009, allocation concealment: high risk (on chronological basis) and other bias: high risk (no stratification by diagnosis category of subfertility).
[6] There was serious imprecision, findings were compatible with no benefit in either group.

Summary of findings 5. IVF compared to IUI in natural cycles for male subfertility

IVF compared to IUI in natural cycles for male subfertility

Patient or population: couples with male subfertility
Settings: single centre (the Netherlands)
Intervention: IVF
Comparison: IUI in natural cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of couples (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IUI in natural cycles	IVF				
Live birth rate per couple (all cycles) Follow-up: 6 months	**407 per 1000**	**346 per 1000** (147 to 618)	**OR 0.77** (0.25 to 2.35)	53 (1 study)	⊕⊕⊖⊖ **low** [1]	-
OHSS	Not reported in any included studies				-	-

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IUI:** intra-uterine insemination; **IVF:** in vitro fertilisation; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio.

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

[1] There was very serious imprecision, with small sample sizes.

Summary of findings 6. IVF compared to IUI in stimulated cycles for male subfertility

IVF compared to IUI in stimulated cycles for male subfertility

Patient or population: couples with male subfertility
Settings: single and multicentre (the Netherlands)
Intervention: IVF

Comparison: IUI in stimulated cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of couples (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IUI in stimulated cycles	IVF				
Live birth rate per couple (all cycles) Follow-up: 6-12 months	**452 per 1000**	**460 per 1000** (262 to 669)	**OR 1.03** (0.43 to 2.45)	86 (2 studies)	⊕⊖⊖⊖ **very low** [1,2]	-
OHSS per couple Follow-up: 6 months	See comment	See comment	Not estimable	36 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	No OHSS occurred
Pregnancy rate per couple (all cycles) Follow-up: 6 months	**611 per 1000**	**666 per 1000** (341 to 886)	**OR 1.27** (0.33 to 4.97)	36 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	-

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IUI:** intra-uterine insemination; **IVF:** in vitro fertilisation; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio.

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

[1] Risk of bias was serious: Bensdorp 2015, other bias: high risk (no stratification by diagnosis category of subfertility).
[2] There was very serious imprecision, with small sample sizes.

BACKGROUND

Description of the condition

Male subfertility is a common condition among subfertile couples. It has been estimated to be directly responsible for approximately 30% of problems with conception and to be a contributory factor in 50% (Crosignani 1994; Hull 1985). Over time, different definitions of male subfertility have been used. A normal quality semen sample was described as having a sperm concentration of 20 million/mL or greater, total motility 50% or greater, normal morphology in 50% or greater and no sperm antibodies (WHO 1987). In 1992, The World Health Organization (WHO) changed its criteria for normal sperm morphology from 50% to 30% (WHO 1992). When strict criteria for morphology were used, greater than 14% was considered normal (Kruger 1993). Since 2010, the reference values for a normal quality semen sample have been revised and the most important changes to the reference limits were semen volume of 1.5 mL or greater, a sperm concentration of 15 million/mL or greater, total motility 40% or greater and normal morphology in 4% or greater (Cooper 2010; WHO 2010). Despite the worldwide use of the WHO criteria, these are unable to distinguish men who are likely to father a child from men who are not. However, the correlation that has been established is a continuous one between total motile sperm count (TMSC) and the probability of natural conception (van der Steeg 2011). In couples undergoing intra-uterine insemination (IUI), the TMSC also appears to have a consistent, direct relationship with the pregnancy rate, but there is no definite predictive threshold for success (Tijani 2010). The post-wash TMSC probably has the most predictive value because it reflects both sperm concentration and motility as well as the effects of sperm processing (van Weert 2004). Because of the different definitions for male subfertility worldwide it is difficult to estimate what proportion of fertility treatments are associated with this indication, or how it affects the overall success rate.

Description of the intervention

IUI is a frequently used fertility treatment for couples with male subfertility (Cohlen 2005; Goverde 2000). In IUI, a small volume of prepared semen is injected trans-cervically into the uterine cavity around the expected time of ovulation. The rationale behind this procedure is to bypass the cervix and to bring the semen closer to the released oocyte. In addition, washing of semen and the selection of motile sperm (by semen preparation) might further increase the chances of fertilisation (Duran 2002a). It has been argued that the method of sperm preparation might influence the probability of conception (Duran 2002b), but there is insufficient evidence to recommend any specific preparation technique (Boomsma 2007). IUI can be used with or without ovarian hyperstimulation (OH), which increases the number of available oocytes at the site of conception. It has also been suggested that it would overcome subtle ovulation disorders that cannot be detected by routine investigations (Zikopoulos 2005). OH is achieved by administering drugs such as anti-oestrogens (e.g. clomiphene citrate) or gonadotrophins, sometimes combined with gonadotrophin-releasing hormone (GnRH) agonists or, more recently, antagonists (Cantineau 2007).

In natural cycles, the pre-ovulatory luteinising hormone (LH) surge is the best indicator of the initiation of ovulation (WHO 1980). Ovulation occurs 35 to 38 hours after the onset of the LH rise in blood (Hoff 1983; Testart 1982). In stimulated cycles, the chances of adequate timing are increased by the administration of an ovulatory triggering injection of human chorionic gonadotrophin (hCG). In order to time the hCG injection, the diameter of the largest follicle (mostly 16 to 18 mm) is determined with sonographic measurements. It has been determined that the largest follicle is the most probable to rupture and will do so approximately 38 hours after the hCG injection (Andersen 1995; Martinez 1991). Therefore, it is most favourable to inseminate around 35 to 45 hours after hCG administration.

Other, more invasive and expensive, fertility treatments for couples with male subfertility are in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). Both methods use controlled ovarian hyperstimulation (COH), which pursues three main objectives: hypophyseal activity suppression, multiple follicle growth stimulation and ovulation induction. Hypophyseal activity suppression, by a GnRH agonist or antagonist, prevents premature ovulation and allows for the timed collection of mature oocytes. Follicle-stimulating hormone (FSH), sometimes combined with LH, is used to stimulate the growth of multiple follicles. Ovulation is induced by hCG or a GnRH agonist and is indicated when multiple follicles of 16 mm or greater are present with sonographic measurements. The optimal timing for ovulation induction remains uncertain, and more studies are necessary to explore the optimal timing (Mochtar 2011; Tarlatzis 2006). Oocyte harvesting is performed approximately 36 hours after hCG or GnRH agonist administration. In IVF, the retrieved oocytes and spermatozoa are put together in a culture dish to achieve fertilisation; for ICSI, a single selected sperm is injected directly into the cytoplasm of the oocyte. The purpose of ICSI is to overcome a potential failure of the sperm to activate the oocyte to initiate fertilisation. After fertilisation, the fertilised oocytes are cultured in a growth medium for two to six days and monitored for embryonic development. Based on morphological criteria for quality, one or two embryos are transferred into the uterine cavity and supernumerary good-quality embryos are cryopreserved. Luteal phase supplementation with progesterone or hCG is necessary to sustain endometrial stimulation.

How the intervention might work

IUI, IVF and ICSI are used to improve the live birth rates in couples experiencing male subfertility.

Why it is important to do this review

The use of fertility treatments in male subfertility has been under debate. Some authors consider that IUI should be offered as first-line therapy before IVF and ICSI are offered (Bhattachary 2000; Cohlen 2005; Goverde 2000; Gregoriou 1996; Nan 1994). Other authors have questioned its effectiveness in male subfertility (Guzick 1998). It has also been suggested that IUI in male subfertility would be advantageous only when a certain threshold value of motile sperm count can be achieved (van Voorhis 2001; van Weert 2004). When OH is used to enhance the effectiveness of IUI, the prevalence of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy rates increases. The most recent National Institute for Health and Care Excellence (NICE) guideline states that for mild male subfertility, routine use of IUI, either with or without OH is not appropriate. Instead, expectant management for two years is recommended, before considering IVF (NICE 2013). Other authors recommend expectant management (for at least six months) over IUI (or another fertility treatment) in couples with

unexplained subfertility or moderate male factor (TMSC greater than three million) and a good or intermediate prognosis for natural conception (Hunault 2004; Steures 2006). IVF, introduced in the late 1970s as a treatment for tubal infertility, was also proposed as a therapeutic option for male subfertility (Cohen 1984). Direct and randomised comparisons between IVF and IUI are scarce and in favour of the latter in terms of cost-effectiveness (Bensdorp 2015; Goverde 2000; Tjon-Kon-Fat 2015). However, there is no clear cutoff value for semen quality to support the choice for IVF or IUI. ICSI provided the possibility of genetic offspring even to people with severely compromised semen parameters (Palermo 1992). More recently, the use of ICSI has increased, also for men with borderline or even normal semen characteristics, without clear evidence of its benefits (Bhattachary 2001; Kim 2007) or even its possible harm (Boulet 2015). The cutoff values for semen parameters used to decide between conventional IVF and ICSI are generally experience-based (Tournaye 2012), and vary per country/centre/laboratory. Performing a split IVF-ICSI cycle in which sibling oocytes are either inseminated conventionally or micro-injected, may prevent complete fertilisation failure in one out of four IVF cycles for moderate male factor subfertility (Kihaile 2003; van der Westenlaken 2005).

This review investigated the benefits and disadvantages of expectant management or timed intercourse (TI), IUI with or without OH, IVF and ICSI in couples with male subfertility.

OBJECTIVES

To evaluate the effectiveness and safety of different fertility treatments (expectant management, timed intercourse (TI), IUI, IVF and ICSI) for couples whose subfertility appears to be due to abnormal sperm parameters.

METHODS

Criteria for considering studies for this review

Types of studies

We included both published and unpublished randomised controlled trials (RCTs). We assessed the method of randomisation to determine whether the studies were truly randomised. In the case of cross-over trials, we only included them if pre-cross-over data were available. We incorporated trials that included a subset of participants with male subfertility if data were available for that subset.

Types of participants

Couples with male subfertility who had been trying to conceive for at least one year were eligible for inclusion. We included all couples with male factor subfertility, including oligo-, terato-, asthenospermia, or a combination of these, preferably measured by two separate semen samples.
Routine fertility evaluation should have consisted of confirmed ovulatory status (basal body temperature (BBT) chart, mid-luteal progesterone or sonographic evidence of ovulation) and low risk for tubal pathology according to the medical history (Coppus 2007).

Types of interventions

We included RCTs with at least one of the following comparisons:

1. IUI versus TI or expectant management both in natural cycles;
2. IUI versus TI both in cycles with OH;
3. IUI in natural cycles versus TI in cycles with OH;
4. IUI in cycles with OH versus TI or expectant management in natural cycles;
5. IUI in natural cycles versus IUI in cycles with OH;
6. IVF versus TI or expectant management in natural cycles;
7. IVF versus TI in cycles with OH;
8. IVF versus IUI in natural cycles;
9. IVF versus IUI in cycles with OH;
10. ICSI versus TI or expectant management in natural cycles;
11. ICSI versus TI in cycles with OH;
12. ICSI versus IUI in natural cycles;
13. ICSI versus IUI in cycles with OH;
14. ICSI versus IVF.

We excluded trials comparing methods using insemination other than IUI, such as intracervical insemination (ICI), gamete intrafallopian transfer (GIFT) and fallopian tube sperm perfusion. In addition, we excluded trials comparing different types of ovarian stimulation protocol, as this is the subject of a different review (Cantineau 2007).

Types of outcome measures

Primary outcomes

1. Live birth rate, defined as delivery of a live foetus after 20 completed weeks of gestational age, per couple.
2. Incidence of OHSS per couple.

Secondary outcomes

1. (Clinical) pregnancy rates, defined as evidence of a gestational sac, confirmed by ultrasound, per couple.
2. Multiple pregnancy rates.
3. Miscarriage rates.
4. Total fertilisation failure rates per couple during IVF.

Search methods for identification of studies

Electronic searches

We searched for all published and unpublished RCTs that described (or might have described) treatments for male subfertility with no language restrictions. Marian Showell, Trials Search Co-ordinator of the Cochrane Gynaecology and Fertility Group, performed a search of the following:

1. the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of controlled trials (inception to April 2015) (Appendix 1);
2. the Cochrane Central Register of Controlled Trials (CENTRAL; inception to April 2015) (Appendix 2);
3. MEDLINE (inception to April 2015) (Appendix 3);
4. EMBASE (inception to April 2015) (Appendix 4);
5. PsycINFO (inception to April 2015) (Appendix 5);
6. CINAHL (inception to April 2015) (Appendix 6).

We placed no language restrictions.

We combined the MEDLINE search with the Cochrane highly sensitive search strategy for identifying RCTs, which appears in

the *Cochrane Handbook of Systematic Reviews of Interventions* (Section 6.4.11) (Higgins 2011). We combined the EMBASE, PsycINFO and CINAHL searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials included the following:

1. trial registers for ongoing and registered trials:
   a. ClinicalTrials.gov, a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home), and the WHO International Clinical Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx);
2. conference abstracts in the Web of Knowledge (wokinfo.com/);
3. OpenSIGLE database for grey literature from Europe (opensigle.inist.fr/);
4. LILACS database, as a source of trials from the Portuguese and Spanish speaking world (regional.bvsalud.org/php/index.php?lang=en) (choose 'LILACS' in 'all sources' drop-down box);
5. PubMed (www.ncbi.nlm.nih.gov/pubmed/).

We searched the databases using the medical subject headings (MeSH terms) and keywords in Appendix 7.

Searching other resources

We checked the reference lists of all identified studies for relevant articles. We performed a handsearch of abstracts of the American Society for Reproductive Medicine (1999 to April 2015) and the European Society for Human Reproduction and Embryology (1997 to April 2015) meetings.

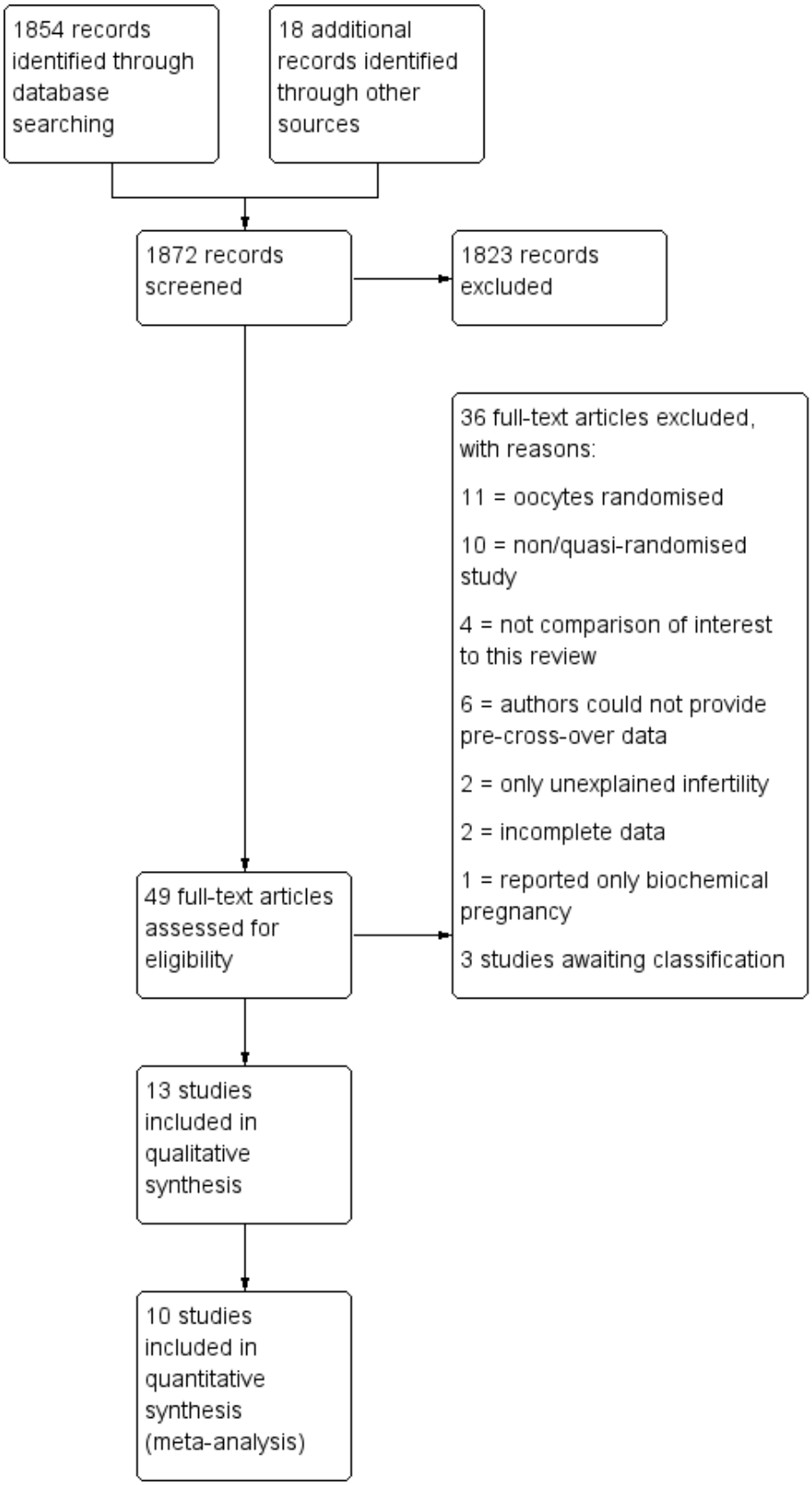
When important information was lacking from the original publications, we tried to contact the authors. We incorporated additional information in the review.

Data collection and analysis

Selection of studies

After screening the titles and abstracts retrieved by the search, we obtained full texts of all potentially eligible studies. Two review authors (MC and MvW) independently selected the trials to be included according to the above-mentioned criteria. We resolved disagreements by consensus or through arbitration by a third review author (AB). We documented the selection process with a PRISMA flow chart (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

The same two review authors independently used a data extraction form to extract data from published reports. We resolved disagreements by consensus or through arbitration by a third review author (AB). This data extraction form included information on the type of study, quality of the selected studies, types of participants, types of interventions and the types of outcome measures (Appendix 8). An analysis of agreement between the two review authors on assessment of the method of randomisation and study design resulted in 100% agreement.

Assessment of risk of bias in included studies

As part of the data collection process, two review authors (MC and MvW) independently extracted data for trial characteristics that have been recognised as potential sources of bias, such as the method used in generating the allocation sequence, how allocation was concealed and differences in drop-out rates between study arms. We used the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Higgins 2011). Where there was uncertainty, we contacted the authors to clarify aspects of study design. We resolved disagreements by consensus or through arbitration by a third review author (AB).

Two review authors independently assessed the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 using the following domains (Higgins 2011):

1. selection bias (random sequence generation and allocation concealment);
2. performance bias (blinding of participants and personnel);
3. detection bias (blinding of outcome assessors);
4. attrition bias (incomplete outcome data);
5. reporting bias (selective reporting);
6. other bias.

These domains were assessed to have:

1. high risk of bias;
2. unclear risk of bias;
3. low risk of bias.

We resolved disagreements by discussion or by consulting a third review author. We described all judgements fully and presented the conclusions in the 'Risk of bias' table, which was incorporated into the interpretation of review findings by means of sensitivity analyses.

We judged that blinding of the researcher, the personnel or the participants could not influence any of the outcomes. Therefore, we assessed all included trials at low risk of bias for blinding.

Measures of treatment effect

We performed statistical analyses in accordance with the guidelines for statistical analysis developed by Cochrane, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Higgins 2011).
All outcomes were binary. We expressed results for each included study as Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CI).

Unit of analysis issues

The primary analysis was per couple randomised. If an included study only reported per cycle data, we contacted the author for additional information. We planned to include studies that could not provide us with per couple data in the review but not in the meta-analysis, and describe them separately. We included both parallel group and cross-over trials in the analysis. For cross-over trials, we used only pre-cross-over data. Furthermore, we counted multiple live births (e.g. twins or triplets) as one live birth event.

Dealing with missing data

For missing data, we attempted to contact the authors. When we could not obtain the missing data from the authors, we explained the assumptions we made in the extraction and analysis of the data. We analysed only the available data.

Assessment of heterogeneity

We noted statistical heterogeneity between the results of different studies by visually inspecting the scatter in the data points on the graphs and the overlap in their CIs and using the I^2 statistics. Following the *Cochrane Handbook for Systematic Reviews of Interventions*, we judged an I^2 value greater than 50% to indicate substantial heterogeneity. We used a random-effects model for sensitivity analysis and explored the original trials for clinical and methodological heterogeneity.

Assessment of reporting biases

Publication bias might influence the interpretation of the pooled results. To detect publication bias, we used a funnel plot, plotting sample size versus effect size, if there were sufficient studies. This plot is only relevant when five or more studies per comparison are included. The graph is symmetrical when bias is absent.

Data synthesis

If appropriate, we combined the data in a meta-analysis using Review Manager 5 (RevMan 2014), using a fixed-effect model and presenting OR with 95% CI. For reporting purposes, we translated primary outcomes to absolute risks.
We considered live birth rate and pregnancy outcomes as a positive consequence of treatment. For adverse outcomes such as OHSS, multiple pregnancy rate, miscarriage rate and total fertilisation failure, which are negative consequences, higher numbers were considered to be detrimental (increased odds signify relative harm). This needs to be take into consideration when interpreting the analyses.

Subgroup analysis and investigation of heterogeneity

A priori, we planned to perform separate subgroup analyses if there were more than two studies in each subgroup, for trials with different ovarian stimulation protocols (oral ovulation induction agents (anti-oestrogens) versus gonadotrophins (FSH, human menopausal gonadotropin (hMG)).

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes, to examine stability regarding the pooled outcomes.

1. Restriction to studies without high risk of bias.
2. Use of a random-effects model.

3. Use of risk ratio (RR) rather than OR.

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

We prepared a 'Summary of findings' table using GRADEpro software. This table evaluated the overall quality of the body of evidence for the review outcomes using GRADE criteria (study limitations, i.e. risk of bias, consistency of effect, imprecision, indirectness and publication bias). We justified, documented and incorporated judgements about evidence quality (high, moderate or low) into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The search strategy identified 2778 studies; after removing duplicates, 1854 studies remained. Handsearching identified another 18 studies. One review author (MC) screened the titles and abstracts and selected 49 studies for further evaluation. We excluded 36 studies with reasons and three studies were awaiting classification. Finally, the review included 10 studies (see Figure 1).

Included studies

Study design

Four of the 10 studies used a parallel design (Bensdorp 2015; Goverde 2000; Guzick 1999; Melis 1995). Bensdorp 2015 and Guzick 1999 published no separate data for male subfertility, but after correspondence with the first author and the author of another review (Veltman-Verhulst 2012), we could extract relevant data. Six studies used a cross-over design (Arici 1994; Cohlen 1998a; Francavilla 2009; Gregoriou 1996; Kerin 1984; Nan 1994). We only pooled pre-cross-over data in the meta-analysis. Three studies were three-arm trials (Bensdorp 2015; Francavilla 2009; Goverde 2000).

Elementary details concerning the studies are displayed in the Characteristics of included studies table.

Participants

The number of participants (couples) reported in the 10 included studies was 757. The sample size ranged from 21 to 254 couples.

Interventions

1. IUI versus TI or expectant management both in natural cycles

We extracted suitable data from one trial comparing IUI versus TI (Kerin 1984). The authors of Francavilla 2009 supplied unpublished pre-cross-over data. In Kerin 1984, one of the treatment arms instructed the participants to have "a single act of vaginal intercourse on the day the couple thought they were most fertile as detected by symptom thermal methods of ovulation detection", which can be considered to be expected management. No specifications regarding the number of outcomes were reported for this treatment arm.

2. IUI versus TI both in cycles with OH

One parallel trial addressed IUI versus TI both in cycles with OH (Melis 1995), and another two trials provided data after the first treatment period after one (Gregoriou 1996) and three (Nan 1994) cycles.

3. IUI in natural cycles versus TI in cycles with OH

We found no trials comparing IUI in natural cycles versus TI in cycles with OH.

4. IUI in cycles with OH versus TI or expectant management in natural cycles

The authors of Francavilla 2009 supplied unpublished pre-cross-over data.

5. IUI in cycles with OH versus IUI in natural cycles

Two parallel trials (Goverde 2000; Guzick 1999), and three cross-over trials reported and provided data comparing IUI in natural cycles versus IUI in cycles with OH (Arici 1994; Cohlen 1998a; Francavilla 2009). Arici 1994 and Francavilla 2009 submitted unpublished data to another review from which we could extract separate data. Cohlen 1998a provided pre-cross-over per couple data.

6. IVF versus TI or expectant management in natural cycles

We found no trials comparing IVF versus TI or expectant management in natural cycles.

7. IVF versus TI in cycles with OH

We found no trials comparing IVF versus TI in cycles with OH.

8. IVF versus IUI in natural cycles

One parallel trial compared IVF versus IUI in natural cycles (Goverde 2000).

9. IVF versus IUI in cycles with OH

Two parallel trials compared IVF versus IUI in cycles with OH (Bensdorp 2015; Goverde 2000).

10. ICSI versus TI or expectant management in natural cycles

We found no trials comparing ICSI versus TI or expectant management in natural cycles.

11. ICSI versus TI in cycles with OH

We found no trials comparing ICSI versus TI in cycles with OH.

12. ICSI versus IUI in natural cycles

We found no trials comparing ICSI versus IUI in natural cycles.

13. ICSI versus IUI in cycles with OH

We found no trials comparing ICSI versus IUI in cycles with OH.

14. ICSI versus IVF

We found no trials comparing ICSI versus IVF.

Outcomes

Five studies provided our main outcome of interest; live birth rate per couple (Bensdorp 2015; Francavilla 2009; Goverde 2000; Guzick 1999; Melis 1995).The other five studies could provide data on pregnancy per couple (Arici 1994; Cohlen 1998a; Gregoriou 1996; Kerin 1984; Nan 1994). As most trials did not mention the

results after each cycle separately, it was not possible to calculate cumulative pregnancy rates.

Two studies supplied information about OHSS in the mild male subfertility population (Bensdorp 2015; Nan 1994). For four studies, the OHSS data was not provided separately for the population with mild male subfertility (Francavilla 2009; Goverde 2000; Guzick 1999; Melis 1995). One study only provided the post-cross-over OHSS data (Cohlen 1998a).

Seven studies reported adverse outcomes (Bensdorp 2015; Cohlen 1998a; Goverde 2000; Guzick 1999; Kerin 1984; Melis 1995; Nan 1994). Six studies reported miscarriage or abortion (Bensdorp 2015; Cohlen 1998a; Francavilla 2009; Goverde 2000; Guzick 1999; Melis 1995). Eight studies reported multiple pregnancies (Bensdorp 2015; Cohlen 1998a; Francavilla 2009; Goverde 2000; Guzick 1999; Melis 1995; Kerin 1984; Nan 1994), and four studies reported ectopic pregnancies (Goverde 2000; Guzick 1999; Kerin 1984; Melis 1995). Two studies did not state any adverse outcomes (Arici 1994; Gregoriou 1996).
Often the details on adverse effects were not provided for male subfertility separately, or at the end of the trial of post-cross-over. Therefore, we could not use these data in the review.

Excluded studies

We excluded 36 studies for the following reasons: 10 studies were not RCTs (retrospective or commentary design, not randomised or quasi randomised) (Elizur 2004; Galle 1990; Goverde 2001; Hewitt 1985; Moolenaar 2015; Nulsen 1993; Plachot 2002; Prentice 1995; Xie 2015; Zayed 1997). Eleven studies randomised oocytes instead of couples (Aboulghar 1995; Aboulghar 1996; Fan 2012; Fishel 2000; Kastrop 1999; Kihaile 2003; Li 2004; Pisarska 1999; Tournaye 2002; van der Westerlaken 2006; Verheyen 1999). In four studies, none of the comparisons of interest was included (Cruz 1986; Friedman 1989; Karlström 2000; Melis 1987). Two studies did not include male subfertility participants (Agarwal 2004; Elzeiny 2014). Two studies published incomplete data (Buvat 1990; Soliman 1993) and one study reported on biochemical pregnancies only (Evans 1991). To this date, we have received no response from the authors for additional information. Six studies with a cross-over design could not supply their pre-cross-over data (Crosignani 1994; Ho 1989; Ho 1992; Kirby 1991; Martinez 1991; te Velde 1989). It is advocated that a particular concern with the cross-over design is the risk of a carry-over effect (Elbourne 2002; Khan 1996; McDonnell 2004). It may have been a source of bias and, therefore, we excluded these studies from the review. See the Characteristics of excluded studies table.

Studies awaiting classification

Three studies used a cross-over design where no pre-cross-over data were published (Aribarg 1995; Jaroudi 1998; Kerin 1987). We attempted to contact authors to get these pre-cross-over data, but to this date, we have received no response.

Risk of bias in included studies

Figure 2 presents our judgements about each methodological quality item, presented as percentages across all included studies, and Figure 3 summarises our judgements about each methodological quality item for each included study.

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

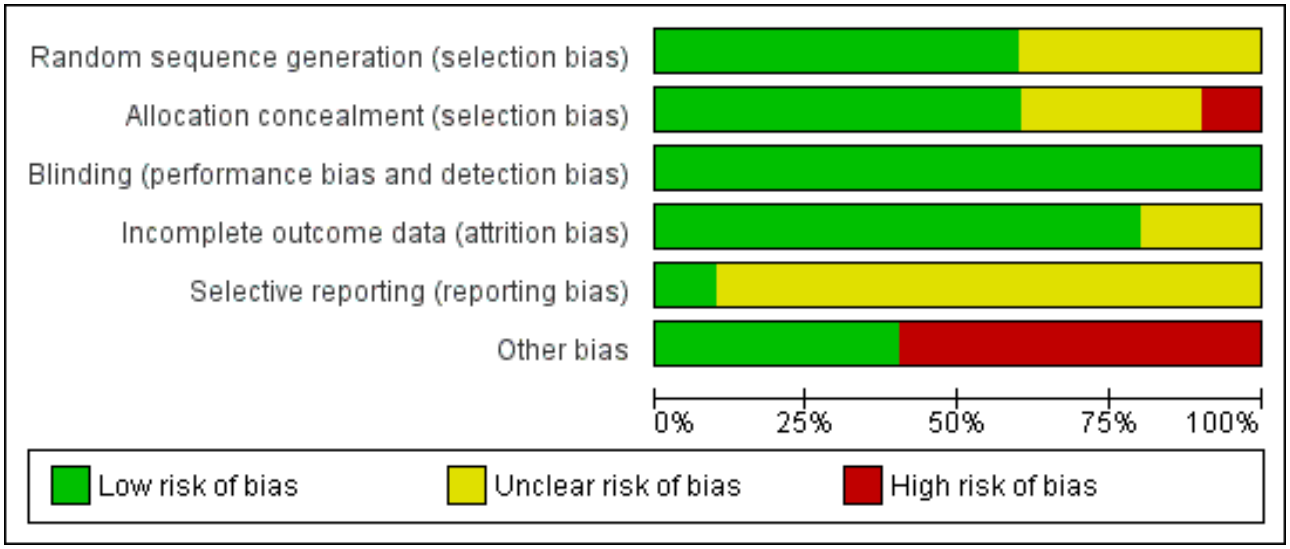
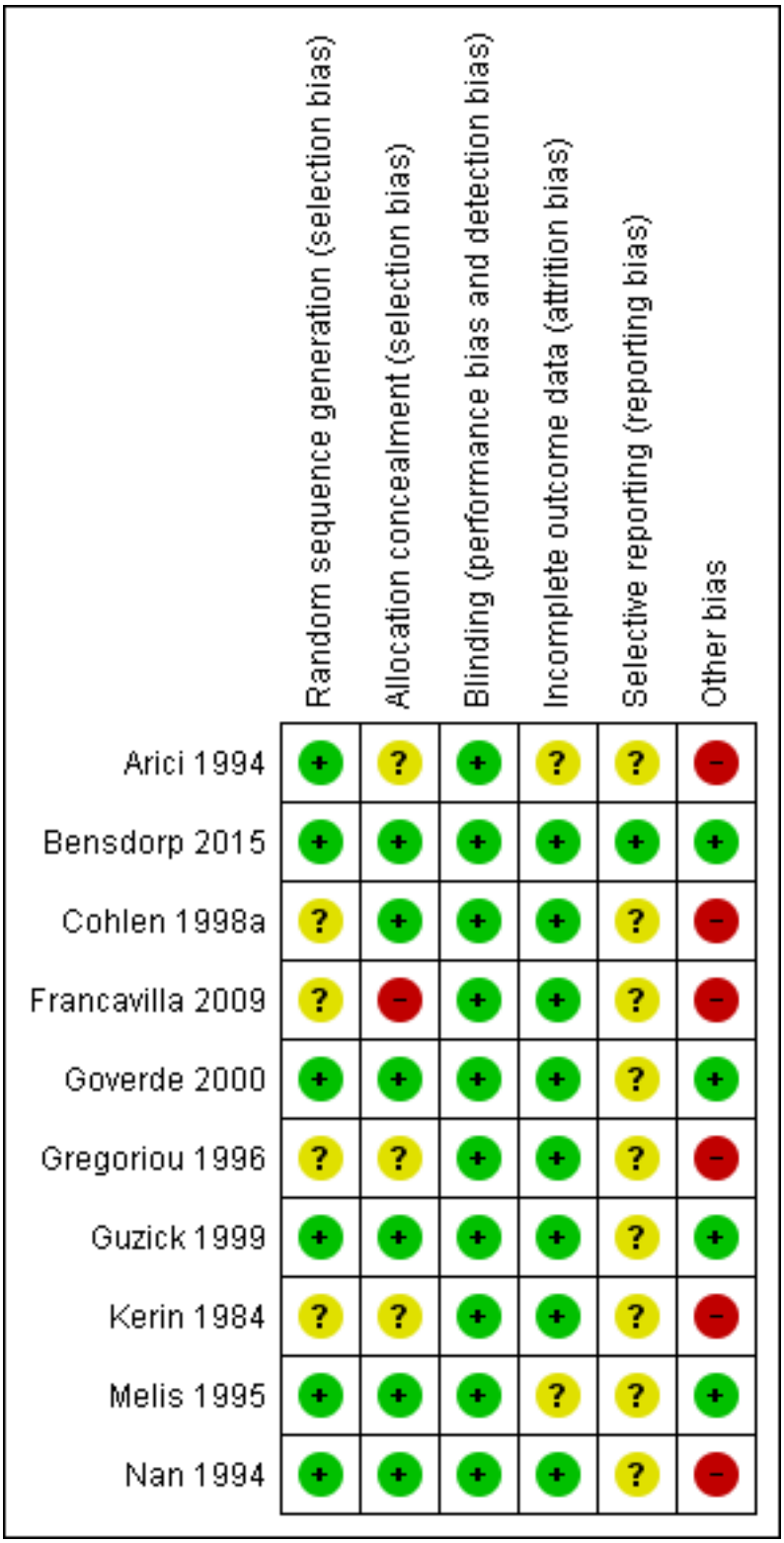


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Study design

Of the 10 studies, four had a parallel design (Bensdorp 2015; Goverde 2000; Guzick 1999; Melis 1995). Six studies were of cross-over alternating design, thus couples were initially randomised to one of the interventions and then alternated between treatment arms on each cycle. In Gregoriou 1996, the cross-over took place after three cycles.

Allocation

The methods of randomisation or allocation concealment were generally poor in the published information, which might increase the risk for selection bias. However, we received additional information about allocation methods for some studies.

Random sequence generation

Five studies mentioned the use of a computer-generated program for randomisation (Arici 1994; Bensdorp 2015; Goverde 2000; Guzick 1999; Melis 1995). One study used a random number table, not further specified (Nan 1994). The random sequence generation remained unclear for the other studies (Cohlen 1998a; Francavilla 2009; Gregoriou 1996; Kerin 1984). Sixty percent of the studies were at low risk of bias and 40% of the studies were at unclear risk of bias.

Allocation concealment

Four studies explicitly stated concealment of allocation (Bensdorp 2015; Cohlen 1998a; Goverde 2000; Melis 1995). After we had received additional information about allocation, we deemed two other trials at low risk of bias in this domain (Guzick 1999; Nan 1994). Concealment of allocation was done by the use of sealed opaque envelopes, locked computer files or white and black discs from a blinded bag. We deemed one study at high risk allocation concealment (Francavilla 2009). Concealment of allocation was done on chronological basis. The concealment of allocation was unclear for the other studies (Arici 1994; Gregoriou 1996; Kerin 1984). Sixty percent of the studies were at low risk of bias, 10% of the studies were at high risk of bias and 30% of the studies were at unclear risk of bias.

Blinding

None of the studies reported blinding. In trials comparing TI versus IUI or IUI versus IVF it is of course impossible to blind the participants. In trials of IUI with and without OH, blinding could technically be performed. However, often stimulation is administered intramuscularly, so blinding might be considered unethical. All studies were at low risk of bias with respect to blinding as we determined that it was unlikely to influence our review outcomes.

Incomplete outcome data

Nine studies reported information on drop-outs, cancelled cycles, or both (Arici 1994; Bensdorp 2015; Cohlen 1998a; Francavilla 2009; Goverde 2000; Guzick 1999; Kerin 1984 ; Melis 1995; Nan 1994). The number of drop-outs varied from 0% to 25%, the number of cancelled cycles varied from 4% to 19%. One study reported the drop-out of 17 couples before the start of the first treatment cycle (failed to return, refused randomisation, other subfertility factors) and included 75% (56/75) of the couples in their analysis (Arici 1994). One study reported the drop-out of 11 couples and included 88% (81/92) of the couples in their analysis (Melis 1995). Six studies reported on their drop-outs and analysed 100% of the couples included in their study (Bensdorp 2015; Cohlen 1998a; Goverde 2000; Gregoriou 1996; Kerin 1984; Nan 1994). The proportion of analysed couples remained unclear in two studies (Francavilla 2009; Guzick 1999).

Four studies stated that the most important reasons for cancelling a cycle were a premature or missed LH surge and OHSS (Cohlen 1998a; Goverde 2000; Gregoriou 1996; Nan 1994). Furthermore, Goverde 2000 reported that in 37 cycles there was no fertilisation after insemination of the aspirated oocytes during IVF. Melis 1995 stated that the most important reasons for cancelling a cycle were a poor response to ovulation induction and exaggerated response to ovulation induction.

Eighty percent of the studies were at low risk of bias and 20% of the studies were at unclear risk of bias.

Selective reporting

A total of 50% of the included studies reported live birth rates. The remaining studies defined (clinical) pregnancy rates (see Characteristics of included studies table). Ten percent of the studies were at low risk of bias and 90% of the studies were at unclear risk of bias.

Other potential sources of bias

Six studies used a cross-over design and there might be selectivity in availability of the data (Arici 1994; Cohlen 1998a; Francavilla 2009; Gregoriou 1996; Kerin 1984; Nan 1994). Forty percent of the studies were at low risk of bias and 60% of the studies were at high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** IUI in natural cycles compared to TI in natural cycles for male subfertility; **Summary of findings 2** IUI in stimulated cycles compared to TI in stimulated cycles for male subfertility; **Summary of findings 3** IUI in stimulated cycles compared to TI in natural cycles for male subfertility; **Summary of findings 4** IUI in stimulated cycles compared to IUI in natural cycles for male subfertility; **Summary of findings 5** IVF compared to IUI in natural cycles for male subfertility; **Summary of findings 6** IVF compared to IUI in stimulated cycles for male subfertility

See: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

Overall the meta-analyses included 10 studies with 757 couples. Three studies were three-arm trials, in which each full group has been used twice in a pair-wise comparison between arms.

1. IUI versus TI or expectant management both in natural cycles

Two studies compared IUI with TI both in natural cycles (Kerin 1984; Francavilla 2009).

Live birth rate per couple

Neither of the studies reported on live births.

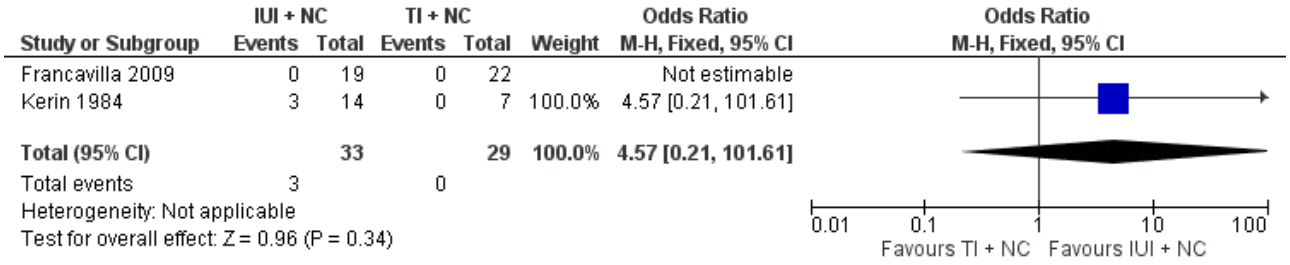
OHSS

Neither of the studies reported on OHSS.

Pregnancy rate per couple

Both studies reported clinical pregnancy rate. There was no evidence of a difference in pregnancy rate per couple for IUI versus TI in natural cycles (2 trials, 62 couples: OR 4.57, 95% CI 0.21 to 101.61; very low quality evidence). There were no events in one of the studies (Figure 4; Analysis 1.1).

Figure 4. Forest plot of comparison: 1 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in natural cycles (NC), outcome: 1.1 Pregnancy rate per couple (all cycles).



Multiple pregnancy

Neither of the studies reported on multiple pregnancy.

Miscarriage

Neither of the studies reported on miscarriage.

2. IUI versus TI both in cycles with OH

Three studies compared IUI with TI both in cycles with OH (Gregoriou 1996; Melis 1995; Nan 1994).

Live birth rate per couple

One study reported on live birth rate. There was no evidence of a difference in live birth rate per couple for IUI versus TI in stimulated cycles (1 trial, 81 couples: OR 0.89, 95% CI 0.30 to 2.59; low quality evidence) (Analysis 2.1). In absolute terms, this result implied that a 22% success rate using TI with OH would become between 2% and 38% using IUI with OH.

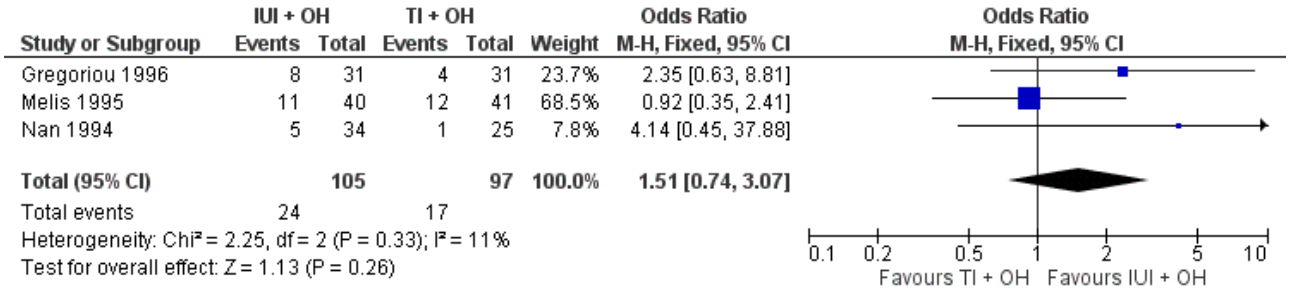
OHSS

OHSS occurred in none of the cycles (Nan 1994) (Analysis 2.2).

Pregnancy rate per couple

There was no evidence of a difference in pregnancy rate per couple for IUI versus TI in stimulated cycles (3 trials, 202 couples: OR 1.51, 95% CI 0.74 to 3.07; I^2 = 11%, very low quality evidence) (Figure 5; Analysis 2.3).

Figure 5. Forest plot of comparison: 2 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH), outcome: 2.3 Pregnancy rate per couple (all cycles).



Multiple pregnancy

There was no evidence of a difference in multiple pregnancy rate between IUI and TI in stimulated cycles (1 trial, 81 couples: OR 3.15, 95% CI 0.12 to 79.69; low quality evidence) (Analysis 2.4).

Miscarriage

There was no evidence of a difference in miscarriage rate per couple for IUI versus TI in stimulated cycles (1 trial, 81 couples: OR 1.03, 95% CI 0.19 to 5.42; low quality evidence) (Analysis 2.5).

3. IUI in natural cycles versus TI in cycles with OH

We found no trials comparing IUI in natural cycles versus TI in cycles with OH.

4. IUI in cycles with OH versus TI or expectant management in natural cycles

One study compared IUI with OH versus TI with natural cycles (Francavilla 2009).

Live birth rate per couple

One study reported on live birth rate. There was no evidence of a difference in live birth rate per couple for IUI with OH versus TI in natural cycles (1 trial, 44 couples: OR 3.14, 95% CI 0.12 to 81.35; very low quality evidence) (Analysis 4.1). In the TI group, there were no live births (0 of 29 couples), in the IUI group, 9% of couples had a live birth (3/33 couples).

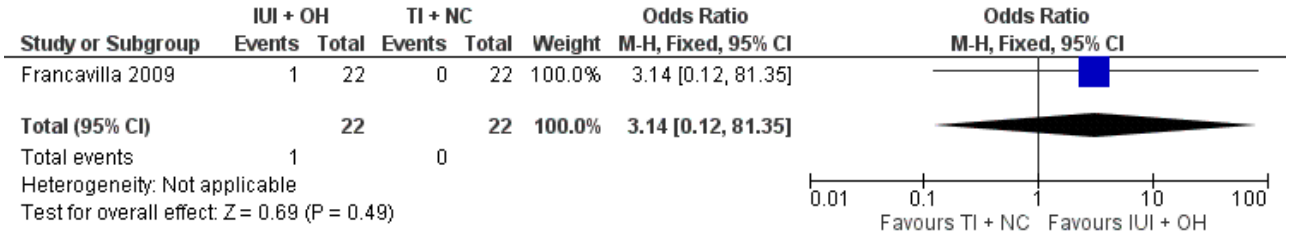
OHSS

There were no (pre-cross-over) data available.

Pregnancy rate per couple

There was no evidence of a difference in pregnancy rate per couple for IUI with OH versus TI in natural cycles (1 trial, 44 couples: OR 3.14, 95% CI 0.12 to 81.35; very low quality evidence) (Figure 6; Analysis 4.2).

Figure 6. Forest plot of comparison: 4 Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus timed intercourse (TI) in natural cycles (NC), outcome: 4.2 Pregnancy rate per couple (all cycles).



Multiple pregnancy

There were no (pre-cross-over) data available.

Miscarriage

There were no miscarriages reported.

5 IUI in cycles with OH versus IUI in natural cycles

Five studies compared IUI in cycles with OH with IUI in natural cycles (Arici 1994; Cohlen 1998a; Francavilla 2009; Goverde 2000; Guzick 1999).

Live birth rate per couple

One study reported on live births per treatment arm (Goverde 2000). Francavilla 2009 and Guzick 1999 provided data on live birth rate for the male subfertility group after we contacted them. There was no evidence of a difference in live birth rate per couple for IUI with OH versus IUI in natural cycles (3 trials, 346 couples: OR 1.34, 95% CI 0.77 to 2.33; I^2 = 0%, very low quality evidence) (Analysis 5.1). In absolute terms, this result implied that a 17% success rate using IUI in natural cycles would become between 13% and 30% using IUI with OH.

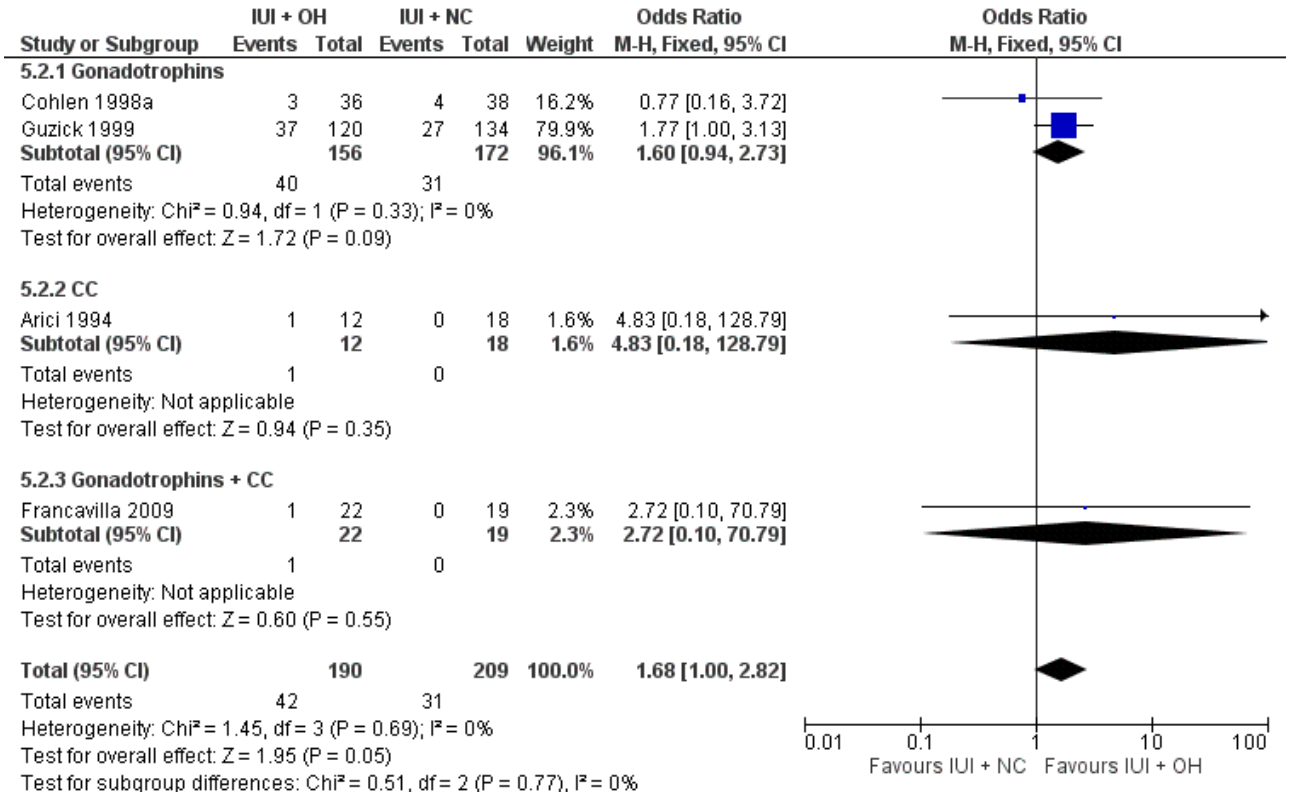
OHSS

None of the studies reported on OHSS.

Pregnancy rate per couple

Four studies reported on pregnancy rate per couple, after one cycle (Arici 1994; Cohlen 1998a; Francavilla 2009) or several cycles (Guzick 1999). There was no evidence of a difference in pregnancy rate per couple for IUI with OH versus IUI in natural cycles (4 trials, 399 couples: OR 1.68, 95% CI 1.00 to 2.82; I^2 = 0%, very low quality evidence) (Figure 7; Analysis 5.2).

Figure 7. Forest plot of comparison: 5 Intra-uterine insemination (IUI) in natural cycles (NC) versus IUI in cycles with ovarian hyperstimulation (OH) versus IUI in natural cycles (NC), outcome: 5.2 Pregnancy rate per couple (all cycles).



Multiple pregnancy

None of the studies reported on multiple pregnancy.

Miscarriage

Two studies reported on miscarriage rate (Cohlen 1998a; Guzick 1999). There was no evidence of a difference in miscarriage rate per couple for IUI with OH versus IUI in natural cycles (2 trials, 115 couples: OR 1.06, 95% CI 0.20 to 5.63; very low quality evidence). There were no events in one of the studies (Analysis 5.3).

6. IVF versus TI or expectant management in natural cycles

We found no trials comparing IVF versus TI or expectant management in natural cycles.

7. IVF versus TI in cycles with OH

We found no trials comparing IVF versus TI in cycles with OH.

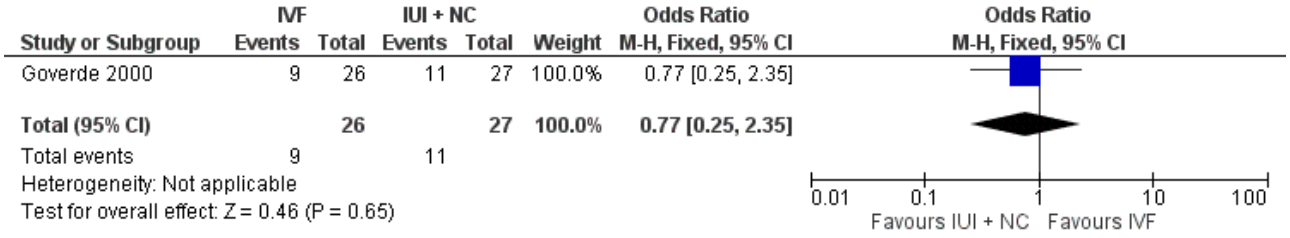
8. IVF versus IUI in natural cycles

One study compared IVF with IUI in natural cycles (Goverde 2000).

Live birth rate per couple

There was no evidence of a difference in live birth rate per couple for IVF versus IUI in natural cycles (1 trial, 53 couples: OR 0.77, 95% CI 0.25 to 2.35; low quality evidence) (Figure 8; Analysis 8.1). In absolute terms, this result implied that a 41% success rate using IUI in natural cycles would become between 9% and 61% using IVF.

Figure 8. Forest plot of comparison: 8 In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in natural cycles (NC), outcome: 8.1 Live birth rate per couple (all cycles).



OHSS

Severe OHSS occurred in three women of the IVF group for the whole study arm of whom the majority had unexplained subfertility. It was unclear whether any of the couples with mild male subfertility developed OHSS.

Pregnancy rate per couple

None of the studies reported on pregnancy rate.

Multiple pregnancy

None of the studies reported on multiple pregnancy.

Miscarriage

None of the studies reported on miscarriage.

Total fertilisation failure

Total fertilisation failure occurred in 37 IVF cycles (male and unexplained subfertility).

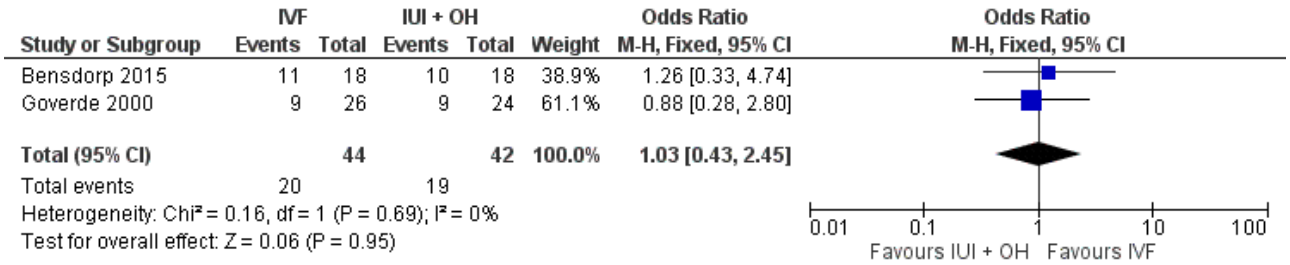
9. IVF versus IUI in cycles with OH

Two studies compared IVF with IUI with OH cycles (Bensdorp 2015; Goverde 2000).

Live birth rate per couple

There was no evidence of a difference in live birth rate per couple for IVF versus IUI cycles with OH (2 trials, 86 couples: OR 1.03, 95% CI 0.43 to 2.45; $I^2 = 0\%$, very low quality evidence) (Figure 9; Analysis 9.1). In absolute terms, this result implied that a 45% success rate using IUI cycles with OH would become between 25% and 66% using IVF.

Figure 9. Forest plot of comparison: 9 In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH), outcome: 9.1 Live birth rate per couple (all cycles).



OHSS

OHSS occurred in none of the IVF or IUI with OH cycles (Bensdorp 2015) (Analysis 9.2).

Pregnancy rate per couple

There was no evidence of a difference in pregnancy rate per couple for IVF versus IUI cycles with OH (1 trial, 36 couples: OR 1.27, 95% CI 0.33 to 4.97; low quality evidence) (Analysis 9.3).

Multiple pregnancy

Bensdorp 2015 reported two twins, one in the IUI with OH group, one in the IVF with single embryo transfer group.

Miscarriage

Bensdorp 2015 reported two miscarriages, one in the IUI with OH group, one in the IVF with single embryo transfer group.

Total fertilisation failure

Goverde 2000 reported total fertilisation failure in 37 IVF cycles (male and unexplained subfertility).

10. ICSI versus TI or expectant management in natural cycles

We found no trials comparing ICSI versus TI or expectant management in natural cycles.

11. ICSI versus TI in cycles with OH

We found no trials comparing ICSI versus TI in cycles with OH.

12. ICSI versus IUI in natural cycles

We found no trials comparing ICSI versus IUI in natural cycles.

13. ICSI versus IUI in cycles with OH

We found no trials comparing ICSI versus IUI in cycles with OH.

14. ICSI versus IVF

We found no trials comparing ICSI versus IVF.

Sensitivity analyses

The use of RRs and use of a random-effects model did not substantially alter the findings for any of the comparisons and outcomes.

DISCUSSION

Summary of main results

The aim of this review was to investigate the effectiveness and safety of treatments for couples with male subfertility with regard to live birth rates. Because RCTs are considered to provide the best assessment of the effectiveness of treatments (Johnson 2003), we included only RCTs in this review. The meta-analyses could include 10 studies, see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; and Summary of findings 6. These studies reported data on six of the proposed comparisons and included 757 couples with male subfertility who underwent 4400 cycles. The trials in this review revealed that there is no evidence that one of the treatment options is superior to another.

However, the available evidence is limited due to small sample size and lack of high quality trials.

Overall completeness and applicability of evidence

The primary outcome for this review was live birth rate per couple. Not all of the trials reported this outcome. Furthermore, evidence was available for only six of the 14 comparisons that we evaluated. We found RCTs to compare expectant management or TI with IUI, IUI with and without OH and IUI with IVF. Unfortunately, we found no RCTs comparing IVF and ICSI. Although these treatments are used on a large scale for male subfertility globally, we only found studies comparing IVF and ICSI in couples with male subfertility with random allocation of oocytes to fertilisation by insemination or injection only (Aboulghar 1995; Aboulghar 1996; Fan 2012; Fishel 2000; Kastrop 1999; Kihaile 2003; Li 2004; Pisarska 1999; Tournaye 2002; van der Westerlaken 2006; Verheyen 1999). Embryos, irrespective of mode of fertilisation, were transferred according to quality. Therefore, we could draw no conclusions on the effect of IVF or ICSI on pregnancy rate in these studies.

Only a few studies reported on adverse effects. Globally, OHSS and multiple pregnancy rates are considered to be an adverse outcome in subfertility practice (Dias 2006; Healy 2004). The risk of perinatal mortality and maternal morbidity associated with multiple pregnancy has become increasingly unacceptable. Therefore, the aim in fertility treatment is shifting from focusing on pregnancy rates alone to the birth of healthy term singletons (Fauser 2005). The use of OH, as part of the IUI treatment, increases the number of available oocytes at the site of conception and thereby might increase the prevalence of OHSS and multiple pregnancy rates. We could not establish on what scale IUI with OH influence OHSS and multiple pregnancy rates in this review. In the literature, only a few studies reported on the differences in multiple pregnancy rates between fertility treatments (Bensdorp 2015; Mansour 2014; Practice Committee of the ASRM 2012; Sullivan 2013). Bensdorp 2015 found no difference in OHSS or multiple pregnancy rate between IUI with OH and IVF with single embryo transfer in couples experiencing male and unexplained subfertility. Unfortunately, other studies did not report on OHSS rates for couples with male subfertility separately and, therefore, we could draw no firm conclusion from this study for couples experiencing male subfertility, due to the lack of power.

WHO criteria are often applied when defining normal semen quality, but they have little prognostic value. Pregnancy has been achieved with IUI with semen that was below these thresholds (Dickey 1999), and also men whose sperm met these standards have been found infertile (Hamilton 2015). In addition, the distinction between male subfertility (semen parameters below the levels of normality defined by WHO) and unexplained subfertility (semen parameters above the levels of normality defined by WHO) is indefinite. Many trials have been performed to analyse the relationship between semen quality and parameters or the TMSC and natural fertility. For clinical practice, it would be useful to have a test that could distinguish subfertile men with good chances of conception from those with poor odds, rather than discriminating between fertile and subfertile men (Verhoeve 2006). There is evidence for a continuous correlation between TMSC and the probability of natural conception (van der Steeg 2011). The predictive capacity of threshold values for (post-wash) TMSC, progressive motility as well as the role of sperm morphology are yet to be established (Matorras 1995; Ombelet 1997). It appears that semen quality contributes to the effectiveness of IUI (Duran 2002a; Ombelet 2003; Steures 2004; Tijani 2010; Wainer 2004), and that there is a threshold below which IUI is no longer effective (Dickey 1999; van Weert 2004). Furthermore, semen quality seems to play a role in predicting total fertilisation failure in IVF cycles (Repping 2002; Rhemrev 2001).

Other screening tests have been proposed in male subfertility, such as sperm deoxyribonucleic acid (DNA) integrity tests. There are several techniques to measure gross sperm DNA fragmentation (e.g. the sperm chromatin structure assay (SCSA), the sperm chromatin dispersion test (SCD), the TUNEL (terminal deoxyribonucleotide transferase-mediated dUTP-X Nick end-labelling) assay and the Comet assay). An association between the presence of DNA abnormalities in sperm and pregnancy outcome has been established (Avendano 2010; Bakos 2008; Duran 2002a; Simon 2014). In view of the debatable accuracy of these tests to predict pregnancy rates, they do not seem to be of use in practice (Practice Committee of the ASRM 2013).

Quality of the evidence

See Figure 2 and Figure 3.

The quality of the evidence for most comparisons was low or very low. The method of randomisation and allocation concealment were unclear in some trials. Blinding could not be performed due to the nature of the interventions, but this was unlikely to affect the outcomes in this review. The trials included in the meta-analysis had several limitations, which were most prominent in the oldest studies. These studies had small sample sizes, used a cross-over design, had a limited duration of follow-up that was unequal between the studies and the definition of male subfertility and the clinical protocols used varied among the studies. Methodological quality within studies with a cross-over design in fertility trials have been under debate. A cross-over design could result in an overestimation of the treatment effect (Khan 1996; Norman 2000). Whether this overestimation could be statistically corrected for or whether it is clinically relevant remains unclear (Cohlen 1998b; McDonnell 2004; Vail 2003), therefore, we only used the pre-cross-over data. Furthermore, most studies have determined pregnancy rates as the endpoint, while live birth rate was our primary outcome. The latest updated Cochrane guidelines for analysing and presenting results emphasise the use of pregnancy and live birth per woman or couple in the meta-analysis. However, in practice such data are not always available.

Potential biases in the review process

Our searches aimed to identify all potentially eligible studies. Besides the potential biases discussed above, there might be some bias due to differential definitions of male subfertility. The trials used different definitions with respect to the numbers of semen samples required, how many and which parameters were assessed, and the thresholds that were subsequently applied for inclusion. Most of the trials used the WHO criteria, in accordance with the year of the study performed.

Agreements and disagreements with other studies or reviews

Conclusion of the previous version of this review and another review were in line with our findings (Bensdorp 2007a; Tournaye 2012). The Cochrane review on the use of IUI in couples

experiencing unexplained subfertility found evidence of a higher pregnancy rate in IUI versus TI, both in stimulated cycles (Veltman-Verhulst 2012). This review also found a higher live birth rate in IUI with OH cycles versus IUI in natural cycles. There was no evidence of a difference in multiple pregnancy rates. In the Cochrane review on the use of IVF versus expectant management or IUI with OH in couples experiencing unexplained subfertility the evidence of a difference was inconclusive (Pandian 2012).

AUTHORS' CONCLUSIONS

Implications for practice

The data outlined in this review demonstrated that for the treatment of couples with male subfertility, the evidence from randomised controlled trials is insufficient. No firm conclusions can be drawn about the relative effectiveness of expectant management, intra-uterine insemination (IUI), with or without ovarian hyperstimulation (OH), in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). More research is needed.

Implications for research

There is need for large prospective multicentre trials with adequate concealment of allocation and comparing the effectiveness of different treatments for couples with male subfertility. In our opinion, priority should be to assess relative merits of ICSI versus IVF.

Data should be reported as the live birth rate per couple or at least as the ongoing pregnancy rate per couple. Adverse events should also be reported. Cut-off values of sperm characteristics such as total motile sperm count before and after preparation could be explored in future trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arici 1994

Methods	Design: cross-over alternating Pre-cross-over data: available Power calculation: not stated ITT: no ITT Number of couples randomised: 75 Number of couples analysed: 56 Number of couples included in this review: 30 Number of started cycles: not stated Number of completed cycles: 95 Number of drop-outs: 17 before starting first treatment cycles (failed to return (n = 9), refused randomisation (n = 5), other subfertility factors (n = 3)) and 27 during the study (moved out of the geographical area (n = 3), failed to return (n = 6), cross-over (n = 18)). 2 couples became pregnant before the initiation of the first treatment cycle Number of cancelled cycles: not stated Centre: single-centre, private infertility practice of the University of Texas, Southwestern Medical Center at Dallas, TX, USA
Participants	Couples: male (n = 26) and unexplained (n = 30) subfertility Definition male subfertility: sperm concentration < 20 million/mL, total motility < 50%, normal morphology < 50%, or a combination of these (WHO 1987) Number of semen samples: 2 Age of women (whole group): mean 33 years (range 24-41) Duration of subfertility: mean 3.5 years (range 2.4-5.5) Primary/secondary subfertility: not stated

Arici 1994 *(Continued)*

	Ovulatory status: BBT, luteal progesterone > 10 ng/mL or in-phase late luteal endometrial biopsy
	Tubal patency: DLS, HSG, or both
	PCT: not stated
	Previous treatment: endocrinologically/surgically correctable factors were treated, no previous ART
	Exclusion criteria: sperm antibodies
Interventions	Comparison: IUI with OH cycles vs. IUI in natural cycles
	Treatment duration: maximum of 4 cycles
	Method OH: CC 50 mg days 5-9
	Timing ovulation for IUI in natural cycles: LH surge urine
	Timing ovulation for IUI + OH cycles: measurement follicles > 18 mm
	Ovulation induction (IUI + OH cycles): hCG 10,000 IM when ≥ 1 follicles 18 mm
	Number of IUI per cycle: 1 or 2
	Timing IUI in natural cycles: first on day of LH peak, a second next day when possible
	Timing IUI + OH cycles: single IUI 32 hours after injection
	Sperm preparation: wash (human tubal fluid) and centrifugation
	Number of inseminated spermatozoa: not stated
	Cancellation criteria: women exhibiting an anovulatory cycle at any time during the study
Outcomes	PR per couple for the first cycle, PR per completed cycle
	OHSS: not stated
	Miscarriage rate: not stated
	Multiple PR: not stated
	Ectopic PR: not stated
	Definition/diagnosis pregnancy: gestational sac confirmed by USS
Notes	Large number of drop-outs. Authors supplied unpublished pre-cross-over data. No stratification by diagnosis category of subfertility, unequal division of couples between treatment options

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced

Arici 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Less than 95% of the couples included in analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available, adverse effects not stated
Other bias	High risk	Cross-over design

Bensdorp 2015

Methods	Design: parallel study
	Power calculation (for whole group): stated
	ITT: done
	Number of couples randomised: 602 (male subfertility, n = 57)
	Number of couples analysed: 602 (male subfertility, n = 57)
	Number of couples included in this review: 36
	Number of started cycles: 104
	Number of completed cycles: 97
	Number of drop-outs: 4 (personal reasons (n = 2), medical reasons (n = 2))
	Number of cancelled cycles: 7 (no embryo transfer (n = 4), no IUI (n = 3))
	Centre: multicentre, 17 centres, the Netherlands
Participants	Couples: unexplained (n = 545) and mild male (n = 57) subfertility
	Definition male subfertility: pre-wash TMSC 3-10 million
	Number of semen samples: not stated
	Mean age of women (whole group): IUI + OH 34 years (SD ± 3.67), IVF-SET 33 years (SD ± 3.39), IVF-MNC 33 years (SD ± 3.50)
	Duration of subfertility (mean (IQR) for whole group): IUI + OH 2.30 years (1.82-3.13), IVF-SET 2.13 years (1.73-3.01), IVF-MNC 2.14 years (1.77-2.81)
	Primary/secondary subfertility: mixed
	Ovulatory status: done
	Tubal patency: chlamydia antibody test, HSG or DLS
	PCT: not stated
	Previous treatment: none
	Exclusion criteria: anovulation, double-sided tubal disease, severe endometriosis, premature ovarian failure and endocrine disorders
Interventions	Comparison: IVF-SET (n = 18) vs. IVF-MNC (n = 21) vs. IUI in cycles with OH (n = 18)
	Treatment duration: maximum 12 months (3 cycles of IVF-SET plus subsequent cryo cycles, 6 cycles of IVF-MNC or 6 cycles of IUI with COH)

Bensdorp 2015 *(Continued)*

	Method OH for IVF-SET: long or short agonist or antagonist protocol (adhere to local stimulation protocols), COH using FSH 150 IU Method OH for IVF-MNC: daily injections of GnRH antagonist 0.25 mg and FSH 150 IU when the leading follicle had a diameter of ≥ 14 mm Method OH for IUI: CC 100 mg (cycle day 3-7) or FSH 75 IU (daily) Timing ovulation for IVF-SET: measurement of ≥ 2 follicles of ≥ 18 mm Timing ovulation for IVF-MNC: measurement of a follicle of 17-18 mm Timing ovulation for IUI + OH cycles: measurement of at least 1 follicle of 17-18 mm Ovulation induction for IVF: hCG 10,000 IU Ovulation induction for IUI + OH cycles: hCG 5000 IU Number of IUI per cycle: 1 Timing IUI + OH cycles: 36 hours after hCG Semen preparation: not stated Number of inseminated spermatozoa: not stated Embryo transfer: 2-4 days after oocyte retrieval 1 good-quality embryo or 2 embryos if no good embryos were available After results of pilot study only SET Luteal phase support (IVF): hCG 1500 IU on day 5, 8 and 11 after oocyte retrieval Cancellation criteria IUI: OHSS (> 3 follicles ≥ 16 mm or > 5 follicles > 12 mm) Cancellation criteria IVF: not stated
Outcomes	Live birth and PR per couple OHSS: stated Miscarriage rate: stated Multiple PR: stated Ectopic PR: not stated Definition/diagnosis pregnancy: confirmed by USS
Notes	Power calculation: 200 couples were needed per treatment group to obtain an 80% power to detect a difference of 12.5% between IUI with COH and IVF-SET Inclusion criteria: women aged 18-38 years, an unfavourable prognosis for natural conception (Hunault < 30%) and diagnosis of unexplained or mild male subfertility. Author supplied separate data for male subfertility. No stratification by diagnosis category of subfertility

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A web-based generated program

Bensdorp 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Unique numbers with allocation code
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data
Selective reporting (reporting bias)	Low risk	Protocol available (Bensdorp 2009)
Other bias	Low risk	No other bias

Cohlen 1998a

Methods	Design: cross-over alternating
	Pre-cross-over data: available
	Power Calculation: stated
	ITT: done
	Number of couples randomised: 74
	Number of couples analysed: 74
	Number of couples included in this review: 74
	Number of started cycles: 320
	Number of completed cycles: 308
	Number of drop-outs: 6 (personal reasons)
	Number of cancelled cycles: 12 (premature or missed LH surge (n = 7), OHSS (n = 5))
	Centre: single centre, Utrecht, the Netherlands
Participants	Couples: male subfertility
	Definition male subfertility: concentration < 20 million/mL, motility < 40%, normal morphology < 40%, or a combination of these
	Number of semen samples: ≥ 2
	Age of women: 30.7 years (range 24-39)
	Duration of subfertility: 3.1 years (range 2-9)
	Primary/secondary subfertility: mixed
	Ovulatory status: BBT and luteal progesterone > 9.7 ng/mL
	Tubal patency: HSG, DLS, or both
	PCT: done

Cohlen 1998a *(Continued)*

	Previous treatment: not stated
	Exclusion criteria: sperm antibodies, cervical factor
Interventions	Comparison: IUI with OH cycles vs. IUI in natural cycles
	Treatment duration: maximum 6 cycles
	Method OH: HMG 75 IU/day up to HMG 150 IU/day starting on cycle day 3
	Timing ovulation for IUI in natural cycles: LH surge blood
	Timing ovulation for IUI + OH cycles: measurement follicles ≥ 18 mm or LH surge blood
	Ovulation induction (IUI + OH cycles): hCG 5000 IU
	Number of IUI per cycle: 1
	Timing IUI in natural cycles: 26 hours after LH surge
	Timing IUI + OH cycles: 38-40 hours after hCG
	Sperm preparation: wash (Ham's F10) and Percoll
	Number of inseminated spermatozoa: no conception observed below threshold of < 1 million motile spermatozoa
	Cancellation criteria: ≥ 4 follicles ≥ 18 mm or oestradiol > 1635 pg/mL, premature LH surge, no LH surge detected
Outcomes	PR and live birth rate per started and completed cycle
	OHSS rate: stated
	Miscarriage rate: stated
	Multiple PR: stated
	Ectopic PR: not stated
	Definition/diagnosis pregnancy: hCG in urine + USS at 6-7 weeks
Notes	Power calculation: 150 cycles per treatment would be needed to detect an 8% difference (numbers based on previous studies) between natural cycles vs. stimulated cycles

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data, adequate description of drop-outs

Cohlen 1998a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Cross-over design

Francavilla 2009

Methods	Design: cross-over alternating Pre-cross-over data: not stated Power calculation: stated ITT: not stated Number of couples randomised: not stated Number of couples analysed: 73 Number of couples included in this review: 63 Number of started cycles: 384 Number of completed cycles: 384 Number of drop-outs: not stated Number of cancelled cycles: none Centre: single centre, L'Aquila, Italy
Participants	Couples: male subfertility (OAT) (n = 63), immunological subfertility (n = 10) Definition male subfertility: motile sperm count < 10 million/mL (due to oligozoospermia (< 20 million/mL), asthenozoospermia (< 50% progressive motility)), teratozoospermia (normal sperm morphology < 15%), immunological subfertility, or a combination of these Number of semen samples: ≥ 2 Age of women: ≤ 40 years Duration of subfertility: ≥ 2 years Primary/secondary subfertility: primary Ovulatory status: mid-luteal phase progesterone ≥ 10 ng/mL, day 3 FSH < 10 IU/mL Tubal patency: HSG, DLS, or both PCT: done Previous treatment: not stated Exclusion criteria: < 1 million motile spermatozoa after semen preparation
Interventions	Comparison: TI in natural cycles vs. IUI with OH cycles vs. IUI in natural cycles Treatment duration: maximum 9 cycles (6 IUI cycles) Method OH: CC 50 mg/day (cycle day 3-7) and hMG 75 IU/day (cycle day 8 and 9)

Francavilla 2009 *(Continued)*

	Timing of ovulation: LH surge urine or measurement of at least 1 follicle ≥ 20 mm when no LH surge was detected Ovulation induction (when no LH surge was detected): hCG 10,000 IU Number of IUI per cycle: 1 or 2 Timing IUI: the day after LH surge and in 2 consecutive days if the LH surge was detected in the evening or 39-41 hours after hCG Timing intercourse: the day after LH surge Sperm preparation: swim up procedure Number of inseminated spermatozoa: not stated Cancellation criteria: not stated
Outcomes	PR per completed cycle, authors supplied live birth rates per completed cycle OHSS: stated Miscarriage rate: stated Multiple PR: stated Ectopic PR: not stated Definition/diagnosis pregnancy: intrauterine gestational sac detected by USS
Notes	Authors supplied unpublished pre-cross-over data. No stratification by diagnosis category of subfertility (male subfertility and immunological subfertility)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	High risk	On chronological basis
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors supplied unpublished pre-cross-over data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Cross-over design

Goverde 2000

Methods	Design: parallel study

Goverde 2000 *(Continued)*

	Power calculation (for whole group): stated ITT: done Number of couples randomised: 258 Number of couples analysed: 258 Number of couples included in this review: 77 Number of started cycles: 963 (male subfertility = 293) Number of completed cycles: 184 Number of drop-outs (whole group): > 10% Number of cancelled cycles (whole group): > 10% Centre: single centre, Vrije Universitieit Medical Centre, Amsterdam, the Netherlands
Participants	Couples: male (n = 77) and unexplained (n = 179) subfertility Definition male subfertility: TMSC of < 20 million progressively motile sperm Number of semen samples: 3 out of 5 Mean age of women (only male subfertility): IUI + OH 31.7 years (SD ± 3.92), IUI in natural cycle 31.6 years (SD ± 3.73), IVF 32.1 years (SD ± 4.20) Duration of subfertility (only male subfertility): IUI + OH 4.2 years (SD ± 1.9), IUI in natural cycle 3.9 years (SD ± 1.7), IVF 4.5 years (SD ± 2.8) Primary/secondary subfertility: mixed Ovulatory status: BBT, endometrial biopsy Tubal patency: DLS + HSG PCT: done Previous treatment: not stated Exclusion criteria: cycle disorders, untreated endometriosis, bilateral occluded tubes or semen sample yielded < 1 million progressively motile spermatozoa after processing, > 20% carried antibodies or > 50% had no acrosome
Interventions	Comparison: IUI with OH cycles vs. IUI in natural cycles vs. IVF Treatment duration: maximum 6 cycles Method OH for IUI: FSH 75 IU (starting dose) Method OH for IVF: women < 38 years: 'long' protocol: GnRH agonist and FSH or hMG 150-225 IU; women > 38 years: 'short' protocol Timing ovulation for IUI in natural cycles: LH surge urine Timing ovulation for IUI + OH cycles: measurement 1-3 follicles > 18 mm or LH surge urine Timing ovulation for IVF: measurement at least 1 follicle > 18 mm and 3 follicles > 16 mm Ovulation induction (IUI + OH cycles and IVF): hCG 10,000 IU Number of IUI per cycle: 1 Timing IUI in natural cycles: 20-30 hours after LH surge

Goverde 2000 *(Continued)*

	Timing IUI + OH cycles: 20-30 hours after LH surge, 40-42 hours after hCG when no LH surge was detected Semen preparation: Percoll gradient technique Number of inseminated spermatozoa: not stated Embryo transfer: 48-72 hours after oocyte retrieval: women ≤ 35 years: maximum 2 embryos; women > 35 years: maximum 3 embryos Luteal phase support (IVF): 3 doses of progesterone 200 mg/day intravaginally, in case of breakthrough bleeding hCG 1500 IU every 48 hour Cancellation criteria IUI: > 3 follicles of ≥ 18 mm or > 6 follicles of ≥ 14 mm Cancellation criteria IVF: serum oestradiol > 20,000 nmol/L
Outcomes	Live birth rate per couple (PR include only pregnancies that resulted in at least 1 live birth) OHSS: stated Miscarriage rate: not stated Multiple PR: stated Ectopic PR: not stated Definition/diagnosis pregnancy: LH urine and USS confirmation
Notes	Power calculation: 80 couples were needed per treatment group to obtain a 90% power to detect a difference of 9% between IUI and IVF. Stratification for woman's age, duration of subfertility, diagnosis, category of subfertility, presence of either 1 or 2 ovaries

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbered masked and sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data, adequate description of drop-outs/cancellations
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Gregoriou 1996

Methods	Design: cross-over after 3 cycles

Gregoriou 1996 *(Continued)*

	Pre-cross-over data: available Power calculation: not stated ITT: not stated Number of couples randomised: 62 Number of couples analysed: 62 Number of couples included in this review: 62 Number of started cycles: 314, before cross-over 172 Number of completed cycles: 258, before cross-over 143 Number of drop-outs: not stated Number of cancelled cycles: 56 Centre: single centre, Athens, Greece
Participants	Couples: male subfertility Definition male subfertility: sperm concentration < 20 million/mL, progressive motility < 30%, normal morphology < 40%, or a combination of these Number of semen samples: 3 Age of women: mean 30.5 years (SD ± 2.6) Duration of subfertility: mean 5.8 years (SD ± 3.9) Primary/secondary subfertility: mixed Ovulatory status: BBT, luteal progesterone ≥ 32 nmol/L and in-phase endometrial biopsy Tubal patency: HSG and DLS PCT: not stated Previous treatment: not stated Exclusion criteria: abnormal serum levels of testosterone, dehydroepiandrosterone-sulphate, prolactin or thyroid-stimulating hormone in women
Interventions	Comparison: IUI with OH cycles vs. TI with OH Treatment duration: maximum 6 cycles Method OH: day 3-9 hMG 75 IU/day, if no increase in serum oestradiol was observed, dose increased to hMG 150 IU/day for next 5 days Timing ovulation: measurement of follicle > 16 mm and oestradiol ≤ 5500 pmol/L, 24 hours after last hMG Ovulation induction: hCG 10,000 IU Number of IUI per cycle: 1 Timing IUI: 36-40 hours after hCG administration Timing intercourse: 36-40 hours after hCG administration Sperm preparation: wash (Ham's 10) 2-layer Percoll gradient (40% and 90%) Number of inseminated spermatozoa: not stated

Gregoriou 1996 *(Continued)*

	Cancellation criteria: OH
Outcomes	PR per completed and per started cycle OHSS: not stated Miscarriage: not stated Multiple PR: not stated Ectopic PR: not stated Definition/diagnosis pregnancy: hCG serum and gestational sac on USS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data (pre- and after cross-over)
Selective reporting (reporting bias)	Unclear risk	No protocol available, adverse effects not stated
Other bias	High risk	Cross-over design

Guzick 1999

Methods	Design: parallel Power calculation: not stated ITT: unclear Number of couples randomised: 932 Number of couples analysed: not stated Number of couples included in this review: 254 Number of started cycles: 4676 Number of completed cycles: 2678 Number of drop-outs: 167 Number of cancelled cycles: 292

Guzick 1999 *(Continued)*

	Centre: multicentre, 10 clinical sites, USA
Participants	Couples: male and unexplained subfertility
	Definition male subfertility: sperm concentration < 20 million/mL, motility < 50%
	Number of semen samples: not stated
	Age of women (whole group): 32 years (SD ± 4)
	Duration of subfertility: IUI in natural cycle 34 months (SD ± 4), IUI with OH cycle 35 (SD ± 5)
	Primary/secondary subfertility: mixed
	Ovulatory status: in phase endometrial biopsy
	Tubal patency: DLS + HSG
	PCT: not stated
	Previous treatment: none
	Exclusion criteria: antisperm antibodies
Interventions	Comparison: IUI with OH cycles vs. IUI in natural cycles (ICI in natural cycles vs. ICI with OH cycles)
	Treatment duration: maximum 6 cycles
	Method OH: FSH 150 IU days 3-7, from day 8 onwards dose adjusted
	Timing ovulation for IUI in natural cycles: LH surge urine
	Timing ovulation for IUI + OH cycles: measurement of 2 follicles ≥ 18 mm, serum oestradiol concentration 500-3000 pg/mL
	Ovulation induction (IUI + OH cycles): hCG 10,000 IU
	Number of IUI per cycle: 1
	Timing IUI in natural cycles: day after LH surge
	Timing IUI + OH cycles: 36-40 hours after hCG
	Sperm preparation: Ham's F-10
	Number of inseminated spermatozoa: not stated
	Cancellation criteria: if no surge in urinary excretion LH for IUI in natural cycle or for IUI + OH if serum oestradiol after 3 days > 3000 pg/mL
Outcomes	Live birth per couple or cycle, PR per couple or cycle
	OHSS rate: stated
	Miscarriage rate: stated
	Multiple PR: stated
	Ectopic PR: stated
	Definition/diagnosis pregnancy: hCG measured on day 15 and 17
Notes	Author provided separate data for male subfertility, but states that randomisation might not hold
Risk of bias	

Guzick 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block procedure
Allocation concealment (selection bias)	Low risk	Locked computer files
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Author supplied separate data for male subfertility
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Kerin 1984

Methods	Design: cross-over alternating
	Pre-cross-over data: partly extractable
	Power calculation: not stated
	ITT: not stated
	Number of couples randomised: 35
	Number of couples analysed: 35
	Number of couples included in this review: 21
	Number of started cycles: not stated
	Number of completed cycles: 39
	Number of drop-outs: not stated
	Number of cancelled cycles: not stated
	Centre: single centre, Adelaide, Australia
Participants	Couples: male subfertility
	Definition male subfertility: ≥ 2 of the following criteria: sperm density < 40 million/mL, motility < 45%, normal morphology < 40%, < 60 million motile spermatozoa
	Number of semen samples: ≥ 3
	Age of women: not stated
	Duration of subfertility: > 3 years, not further specified
	Primary/secondary subfertility: not stated

Kerin 1984 *(Continued)*

	Ovulatory status: luteal progesterone > 20 nmol/L Tubal patency: laparoscopic tubal dye insufflation test PCT: done Previous treatment: not stated Exclusion criteria: positive PCT
Interventions	Comparison: IUI in natural cycles vs. TI in natural cycles vs. natural cycles Treatment duration: maximum 12 cycles Timing ovulation natural cycles: symptothermal methods Timing ovulation TI in natural cycles and IUI in natural cycles: LH surge Ovulation induction: none Timing IUI: day of LH surge Timing intercourse: day after LH surge Number of inseminations: 1 Sperm preparation: Wittingham's T6 medium wash with swim-up Number of inseminated spermatozoa: stated Cancellation criteria: not stated
Outcomes	PR per completed cycle OHSS: not stated Miscarriage rate: not stated Multiple PR: not stated Ectopic PR: not stated Definition/diagnosis pregnancy: not further defined
Notes	Pre-cross-over data only partly available. No reply from author, received letter back as wrongly addressed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pre-cross-over data partly available

Kerin 1984 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available, adverse effects not stated
Other bias	High risk	Cross-over design

Melis 1995

Methods	Design: parallel Power calculation: not stated ITT: no Number of couples randomised: 200 Number of couples analysed: 184 Number of couples included in this review: 81 Number of started cycles: not stated Number of completed cycles: 462, 213 for male subfertility Number of drop-outs/cancelled cycles: 16; 11 for male subfertility (family problems (n = 5), poor response to ovulation induction (n = 3), exaggerated response to ovulation induction (n = 8) Centre: single centre, Cagliari, Italy
Participants	Couples: male (n = 92) and unexplained (n = 108) subfertility Definition male subfertility: sperm concentration 10-20 million/mL, progressive motility 15-25%, total motility 30-50%, normal morphology 30-50% Number of semen samples: ≥ 2 Age of women: 34.2 years (SD ± 4.8, range 27-36) Duration of subfertility: 51.2 months (SD ± 14.3) Primary/secondary subfertility: not stated Ovulatory status: in-phase endometrial biopsy, USS evidence ovulation, female endocrine profile Tubal patency: DLS, HSG PCT: done Previous treatments: all couples had received 3 cycles CC-induced TI and 3 cycles CC-induced IUI Exclusion criteria: severe male subfertility, female factor subfertility
Interventions	Comparison: IUI with OH cycles vs. TI with OH cycles Treatment duration: maximum 3 cycles Method OH: 3 ampoules FSH starting from cycle day 3, personally adjusted to endocrine monitoring and USS Timing of ovulation induction: measurement of at least 2 follicle ≥ 16 mm and oestradiol 800-1500 pg/mL Ovulation induction: 10.000 hCG 36 hours after last injection FSH

Melis 1995 *(Continued)*

	Number of IUI per cycle: 1
	Timing of IUI: 30-36 hours after hCG
	Timing intercourse: 12 hours after hCG
	Sperm preparation: wash (Menezo B2) and swim unconventional layering technique
	Number of inseminated spermatozoa: not stated
	Cancellation criteria: oestradiol > 1500 pg/mL or poor response to OH
Outcomes	PR per couple PR per completed cycle
	OHSS: stated
	Miscarriage rate: stated
	Multiple PR: stated
	Ectopic PR: stated
	Definition/diagnosis pregnancy: hCG (> 25 IU/L) in serum always confirmed by USS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Less than 95% of the couples included in analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Nan 1994

Methods	Design: cross-over alternating
	Pre-cross-over data: available
	Power calculation: not stated
	ITT: not stated
	Number of couples randomised: 76

Nan 1994 *(Continued)*

	Number of couples analysed: 76
	Number of couples included in this review: 59
	Number of started cycles: 249
	Number of completed cycles: 202
	Number of drop-outs: not stated
	Number of cancelled cycles: 47
	Centre: single centre, University Hospital Utrecht, the Netherlands
Participants	Couples: male subfertility
	Definition male subfertility: sperm concentration < 20 million/mL, total motility < 40%, normal morphology < 40%, or a combination of these
	Number of semen samples: 4
	Age of women: 32 years (range 24-39)
	Duration of subfertility: 4.5 years (range 2-10)
	Primary/secondary subfertility: mixed
	Ovulatory status: BBT, luteal progesterone ≥ 31 nmol/L
	Tubal patency: DLS, HSG
	PCT: done
	Previous fertility treatment: not stated
	Exclusion criteria: sperm antibodies
Interventions	Comparison: IUI with OH cycles vs. TI with OH cycles
	Treatment duration: maximum 6 cycles
	Method OH: 150 IU HMG/day starting from cycle day 3
	Timing ovulation: measurement of leading follicle ≥ 18 mm and LH surge
	Ovulation induction: hCG 10,000 IU
	Number of IUI per cycle: 1
	Timing IUI: 38-40 hours after hCG injections or following morning in case LH surged
	Timing intercourse: evening next day, or same evening in case LH surged
	Method of semen preparation; Wash (Ham's F10) and Percoll gradient technique
	Number of inseminated spermatozoa: not stated
	Cancellation criteria: ≥ 4 follicles ≥ 18 mm or oestradiol > 6000 pmol/L
Outcomes	Live birth per cycle, PR per completed cycle, PR per started cycle
	OHSS: stated
	Miscarriage rate: stated
	Multiple PR: stated

Nan 1994 *(Continued)*

	Ectopic PR: not stated Abruptio placenta: stated Definition/diagnosis pregnancy: HCG urine and USS confirmation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Numbered sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding stated, but outcome was not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Cross-over design

ART: assisted reproductive technique; BBT: basal body temperature; CC: clomiphene citrate; COH: controlled ovarian hyperstimulation; DLS: diagnostic laparoscopic surgery; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotrophin; hMG: human menopausal gonadotrophin; HSG: hysterosalpingography; ICI: intra-cervical insemination; IQR: interquartile range; IM: intramuscular; ITT: intention to treat; IU: international unit; IUI: intra-uterine insemination; IVF: in vitro fertilisation; LH: luteinising hormone; MNC: modified natural cycle; n: number of couples; OAT: oligoasthenoteratozoospermia; OH: ovarian hyperstimulation; OHSS: ovarian hyperstimulation syndrome; PCT: post coital test; PR: pregnancy rate; SD: standard deviation; SET: single embryo transfer; TI: timed intercourse; TMSC: total motile sperm count; USS: ultrasound scan.

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

Study	Reason for exclusion
Aboulghar 1995	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Aboulghar 1996	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Agarwal 2004	Unexplained subfertility couples
Buvat 1990	Number of couples receiving IUI and TI was not stated
Crosignani 1994	Authors could not provide pre-cross-over data
Cruz 1986	Different comparison: IUI vs. ICI
Elizur 2004	Not an RCT, but a retrospective study

Study	Reason for exclusion
Elzeiny 2014	Unexplained subfertility couples
Evans 1991	Biochemical pregnancies only, no response from the author
Fan 2012	Oocytes were randomised between IVF and ICSI, no outcome data available per couple
Fishel 2000	Oocytes were randomised between IVF and ICSI, no outcome data available per couple
Friedman 1989	Preliminary report, different comparison: IUI vs. ICI
Galle 1990	Not an RCT, but an observational study
Goverde 2001	Not an RCT, correspondence
Hewitt 1985	Not an RCT, an observational study
Ho 1989	Authors could not provide pre-cross-over data
Ho 1992	Authors could not provide pre-cross-over data
Karlström 2000	Compares IUI both with different forms of OH
Kastrop 1999	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Kihaile 2003	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Kirby 1991	Authors could not provide pre-cross-over data
Li 2004	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Martinez 1991	Authors could not provide pre-cross-over data
Melis 1987	Different comparison: ICI in natural cycle vs. ICI with OH
Moolenaar 2015	Not an RCT, but a retrospective study
Nulsen 1993	Not an RCT: quasi randomised, biochemical pregnancies only
Pisarska 1999	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Plachot 2002	Not an RCT: oocytes were quasi randomised between IVF and ICSI
Prentice 1995	Not an RCT: quasi randomised, based on hospital case record number
Soliman 1993	Incomplete data on treatment of control group
te Velde 1989	Authors could not provide pre-cross-over data
Tournaye 2002	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
van der Westerlaken 2006	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Verheyen 1999	Oocytes were randomly divided between IVF and ICSI, no outcome data available per couple
Xie 2015	Not an RCT

Study	Reason for exclusion
Zayed 1997	Not an RCT: quasi randomised, patient preference

ICI: intra-cervical insemination; ICSI: intracytoplasmic sperm injection; IUI: intra-uterine insemination; IVF: in vitro fertilisation; OH: ovarian hyperstimulation; RCT: randomised controlled trial; TI: timed intercourse.

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

Aribarg 1995

Methods	Design: cross-over alternating
	Pre-cross-over data: not stated
	Power calculation: not stated
	ITT: not done, could not be extracted
	Number of couples randomised: not stated
	Number of couples analysed: 50
	Number of started cycles: not stated
	Number of completed cycles: 495
	Number of drop-outs: not stated
	Number of cancelled cycles: not stated
	Centre: single centre, Chulalongkorn University, Bangkok, Thailand
Participants	Couples: male subfertility
	Definition male subfertility: sperm concentration 1-20 million/mL, motility < 50%, normal morphology < 30%, or a combination of these (WHO 1992)
	Number of semen samples: 2
	Age of women: mean 25.5 years (range 23-37)
	Duration of subfertility: mean 3.7 years (range 2-15)
	Primary/secondary subfertility: not stated
	Ovulatory status: BBT
	Tubal patency: DLS and HSG
	PCT: not stated
	Previous treatments: not stated
	Exclusion criteria: severe oligospermia < 1 million/mL, semen with evidence of bacterial infection, women with endometriosis, hormonal, tubal or ovulatory disturbance diagnosed
Interventions	Comparison: IUI with OH cycles vs. TI in natural cycles
	Treatment duration: maximum 4-6 cycles
	Method of OH: CC 100 mg/day (cycle day 3-7)
	Ovulation induction: none

Aribarg 1995 *(Continued)*

	Number of IUI per cycle: 1, sometimes 2
	Timing of IUI: timed by USS, BBT and LH surge urine
	Timing of intercourse: evening of the day of the LH surge and on the following day
	Sperm preparation: wash and swim up, Ham's F-10 medium
	Number of inseminated spermatozoa: no conception observed below threshold of < 5 million motile spermatozoa
	Cancellation criteria: not stated
Outcomes	PR per completed cycle
	OHSS: not stated
	Miscarriage rate: stated
	Multiple PR: stated
	Ectopic PR: not stated
	Definition/diagnosis pregnancy: hCG in blood and confirmation by USS, clinical examination
Notes	Quality of spermatozoa in terms of their concentration and motility before and after sperm washing was compared
	No pre-cross-over data available, no reply from author

Jaroudi 1998

Methods	Design: cross-over alternating
	Pre-cross-data: not stated
	Power calculation: not stated
	ITT: not stated
	Number of couples randomised: 36
	Number of couples analysed: 36
	Number of started cycles: not stated
	Number of completed cycles: 110
	Number of drop-outs: not stated
	Number of cancelled cycles: not stated
	Centre: single centre, Riyadh, Saudi Arabia
Participants	Couples: male subfertility
	Definition male subfertility: sperm count 1-20 million/mL or motility 10-30% with > 1 million total spermatozoa
	Number of semen samples: 3
	Age of women: 27 years (SD ± 3.7)

Jaroudi 1998 *(Continued)*

	Duration of subfertility: 6.5 years (SD ± 3.0)
	Primary/secondary subfertility: not stated
	Ovulatory status: not stated
	Tubal patency: HSG
	PCT: not stated
	Previous treatment: not stated
	Exclusion criteria: not stated
Interventions	Comparison: IUI with OH cycles vs. TI with OH cycles
	Treatment duration: maximum 6 cycles
	Method OH: hMG 150 IU/day started from cycle day 3 (adjusting to woman's response), buserelin acetate spray 500 µg/day started from cycle day 2
	Timing of ovulation: measurement of 3-5 follicles > 15 mm and appropriate plasma oestradiol concentration (800 pmol/L per follicle)
	Ovulation induction: hCG 10,000 IU
	Number of IUI per cycle: 1
	Timing of IUI: 34 hours after hCG
	Timing of intercourse: 36 hours after hCG
	Luteal support: progesterone 200 mg/day
	Sperm preparation: Percoll gradient technique
	Number of inseminated spermatozoa: not stated
	Cancellation criteria: not stated
Outcomes	PR per completed cycle
	OHSS: not stated
	Miscarriage rate: not stated
	Multiple PR: not stated
	Ectopic PR: not stated
	Definition/diagnosis pregnancy: USS 6-7 weeks' gestational sac
Notes	No pre-cross-over data available, no reply from author

Kerin 1987

Methods	Design: cross-over alternating
	Pre-cross-over data: not stated
	Power calculation: not stated
	ITT: not stated

Kerin 1987 *(Continued)*

	Number of couples randomised: not stated Number of couples analysed: not stated Number of started cycles: not stated Number of completed cycles: 509 Number of drop-outs: not stated Number of cancelled cycles: not stated Centre: single centre, Los Angeles, USA
Participants	Couples: male subfertility Definition male subfertility: assessment of at least 2 abnormalities: • moderate: sperm concentration 10-40 million/mL, sperm motility 30-40%, sperm morphology 30-40%, or a combination of these • severe: sperm density < 10 million/mL, motility < 30%, morphology < 30%, or a combination of these Number of semen samples: 3 Age of women: < 41 years, not specified Duration of subfertility: ≥ 3 years, not specified Primary/secondary subfertility: primary Ovulatory status: normal endocrine profile (LH, FSH, prolactin) Tubal patency: tested, not further specified PCT: not stated Previous treatment: not stated Exclusion criteria: sperm antibodies, endometriosis, sperm count < 100,000 after preparation
Interventions	Comparison: IUI in natural cycles vs. TI in natural cycles Treatment duration: maximum 12 cycles Timing of ovulation: LH surge urine Ovulation induction: none Number of IUI per cycle: 1 Timing of IUI: first of second day after LH surge Timing of intercourse: day of LH surge Sperm preparation: swim up procedure Number of inseminated spermatozoa: stated Cancellation criteria: not stated
Outcomes	PR per completed cycle OHSS: not stated Miscarriage rate: stated

Kerin 1987 *(Continued)*

	Multiple PR: not stated Ectopic PR: stated Definition/diagnosis pregnancy: not stated
Notes	Stratified for moderate semen defect and severe semen defect Compared IUI within 24 hours and within 48 hours after LH surge No pre-cross-over data available, no reply from author

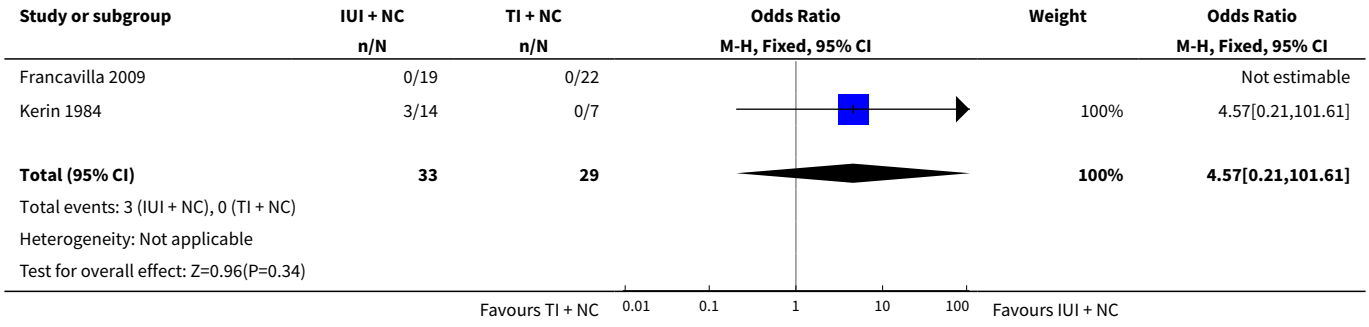
BBT: basal body temperature; CC: clomiphene citrate; DLS: diagnostic laparoscopic surgery; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotrophin, hMG: human menopausal gonadotrophin; HSG: hysterosalpingography; ITT: intention to treat; IUI: intra-uterine insemination; LH: luteinising hormone; OH: ovarian hyperstimulation; OHSS: ovarian hyperstimulation syndrome; PCT= post coital test, PR: pregnancy rate; SD: standard deviation; TI: timed intercourse; USS: ultrasound scan.

DATA AND ANALYSES

Comparison 1. Intra-uterine insemination (IUI) versus timed intercourse (TI) both in natural cycles (NC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy rate per couple (all cycles)	2	62	Odds Ratio (M-H, Fixed, 95% CI)	4.57 [0.21, 101.61]

Analysis 1.1. Comparison 1 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in natural cycles (NC), Outcome 1 Pregnancy rate per couple (all cycles).

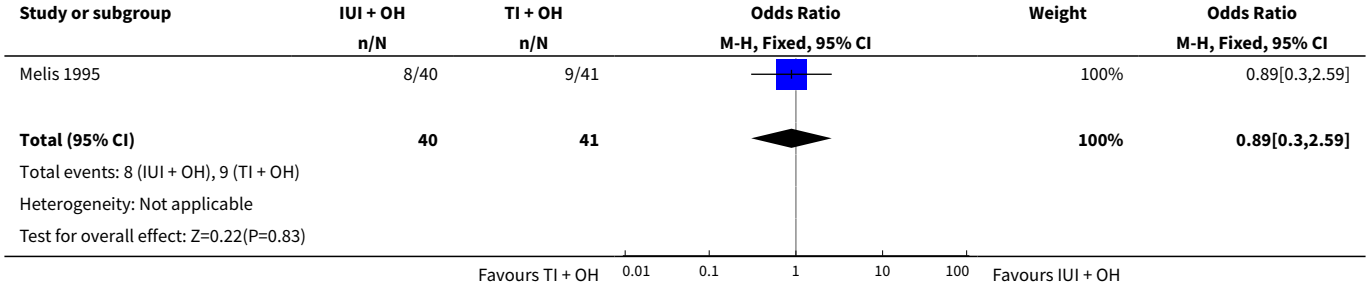


Comparison 2. Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH)

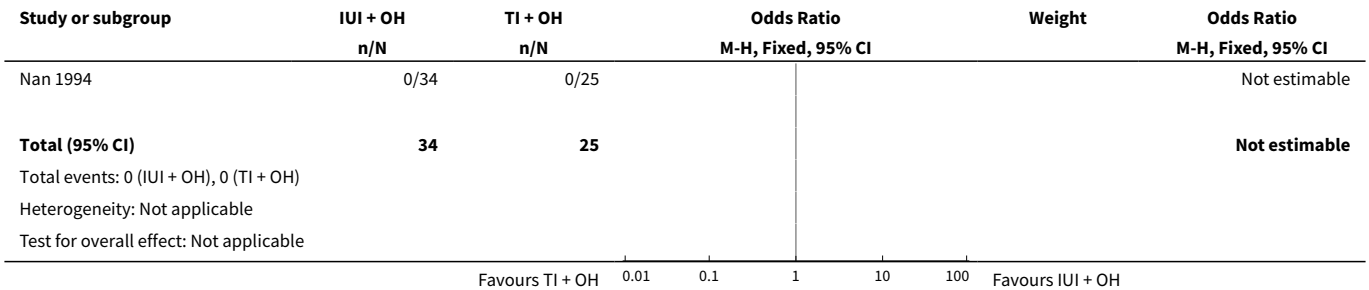
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.30, 2.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 OHSS per couple	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Pregnancy rate per couple (all cycles)	3	202	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.74, 3.07]
4 Multiple pregnancy rate per couple	1	81	Odds Ratio (M-H, Fixed, 95% CI)	3.15 [0.12, 79.69]
5 Miscarriage rate per couple	1	81	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.19, 5.42]

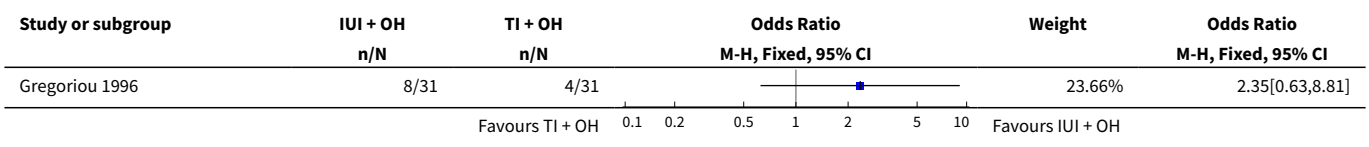
Analysis 2.1. Comparison 2 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH), Outcome 1 Live birth rate per couple (all cycles).

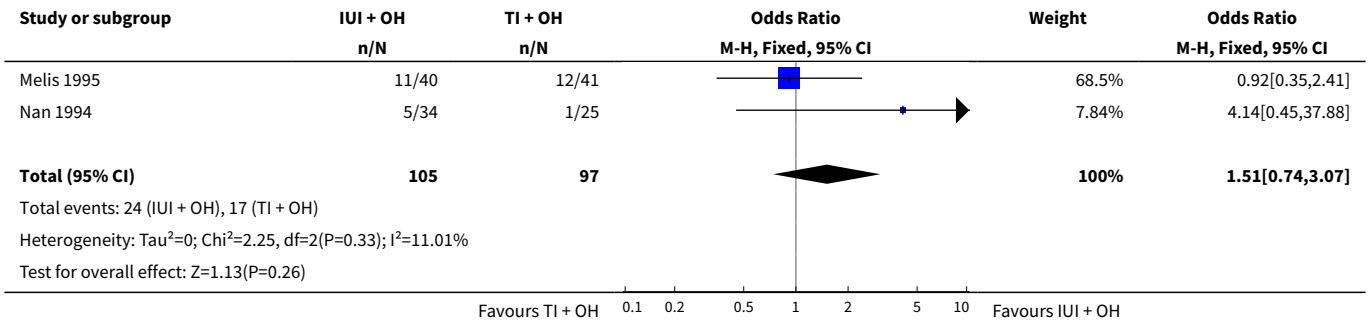


Analysis 2.2. Comparison 2 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH), Outcome 2 OHSS per couple.

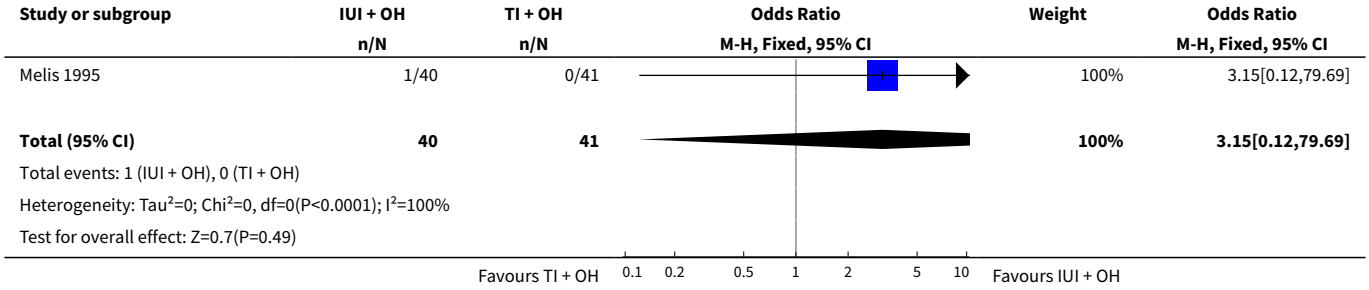


Analysis 2.3. Comparison 2 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH), Outcome 3 Pregnancy rate per couple (all cycles).

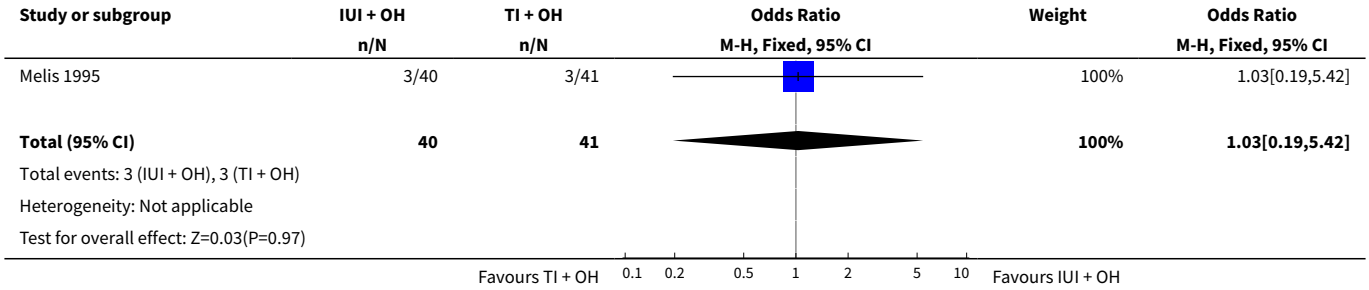




Analysis 2.4. Comparison 2 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH), Outcome 4 Multiple pregnancy rate per couple.



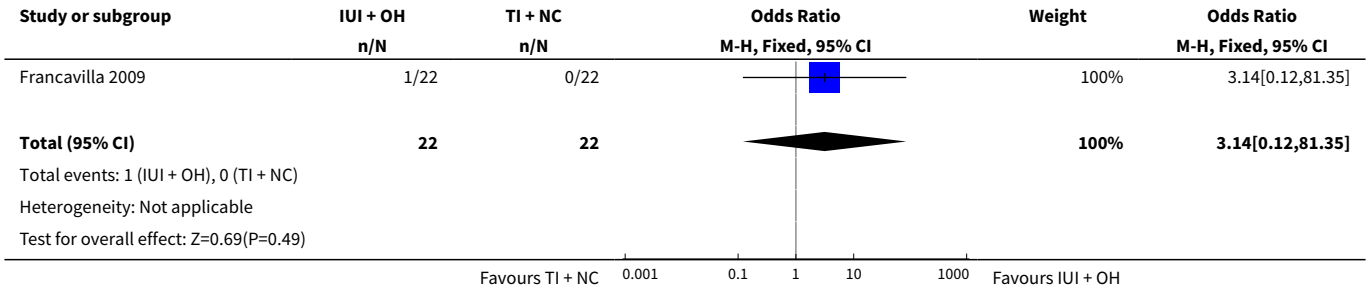
Analysis 2.5. Comparison 2 Intra-uterine insemination (IUI) versus timed intercourse (TI) both in cycles with ovarian hyperstimulation (OH), Outcome 5 Miscarriage rate per couple.



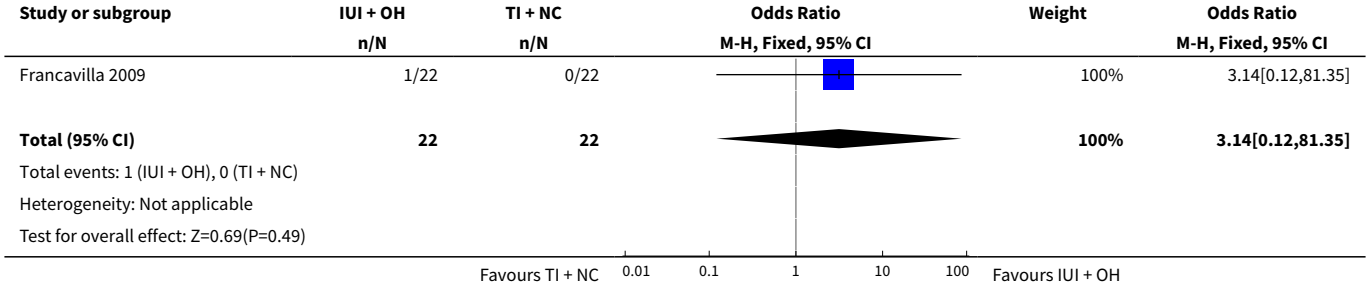
Comparison 4. Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus timed intercourse (TI) in natural cycles (NC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	1	44	Odds Ratio (M-H, Fixed, 95% CI)	3.14 [0.12, 81.35]
2 Pregnancy rate per couple (all cycles)	1	44	Odds Ratio (M-H, Fixed, 95% CI)	3.14 [0.12, 81.35]

Analysis 4.1. Comparison 4 Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus timed intercourse (TI) in natural cycles (NC), Outcome 1 Live birth rate per couple (all cycles).



Analysis 4.2. Comparison 4 Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus timed intercourse (TI) in natural cycles (NC), Outcome 2 Pregnancy rate per couple (all cycles).



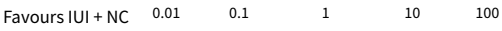
Comparison 5. Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus IUI in natural cycles (NC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	3	346	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.77, 2.33]
1.1 Gonadotrophins	2	305	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.75, 2.29]
1.2 Gonadotrophins + clomiphene citrate (CC)	1	41	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [0.10, 70.79]
2 Pregnancy rate per couple (all cycles)	4	399	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [1.00, 2.82]
2.1 Gonadotrophins	2	328	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.94, 2.73]
2.2 CC	1	30	Odds Ratio (M-H, Fixed, 95% CI)	4.83 [0.18, 128.79]
2.3 Gonadotrophins + CC	1	41	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [0.10, 70.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Miscarriage rate per couple	2	115	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.20, 5.63]

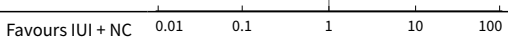
Analysis 5.1. Comparison 5 Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus IUI in natural cycles (NC), Outcome 1 Live birth rate per couple (all cycles).

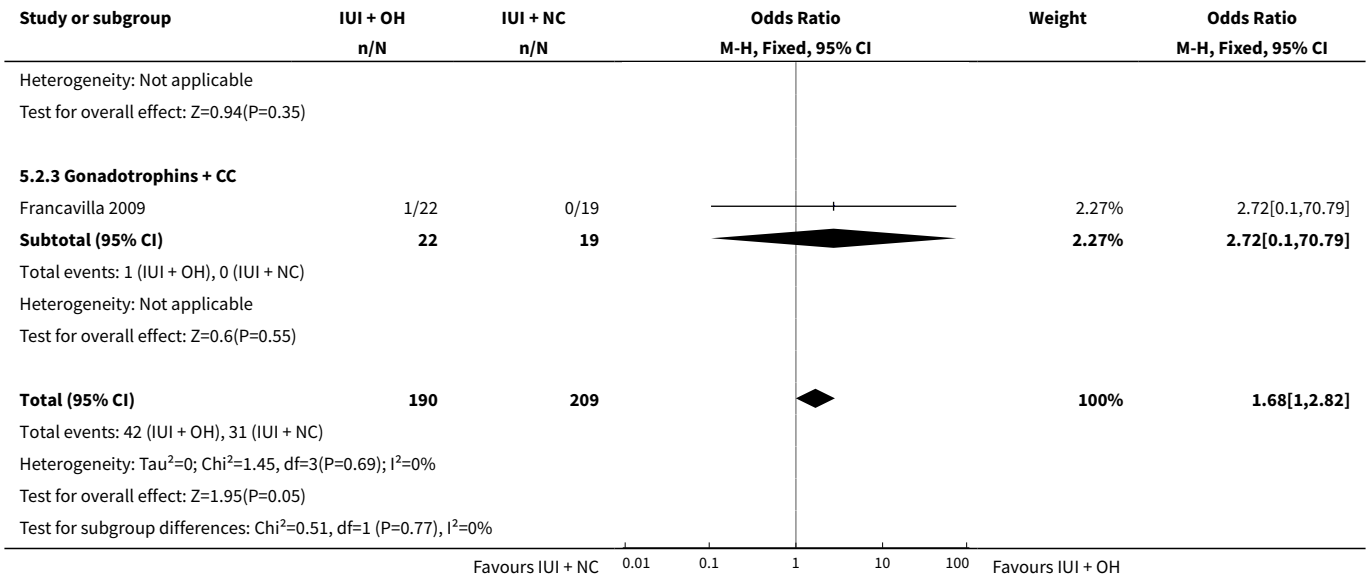
Study or subgroup	IUI + OH n/N	IUI + NC n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Gonadotrophins					
Goverde 2000	9/24	11/27		29.5%	0.87[0.28,2.7]
Guzick 1999	25/120	20/134		68.22%	1.5[0.78,2.87]
Subtotal (95% CI)	**144**	**161**		**97.72%**	**1.31[0.75,2.29]**
Total events: 34 (IUI + OH), 31 (IUI + NC)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
5.1.2 Gonadotrophins + clomiphene citrate (CC)					
Francavilla 2009	1/22	0/19		2.28%	2.72[0.1,70.79]
Subtotal (95% CI)	**22**	**19**		**2.28%**	**2.72[0.1,70.79]**
Total events: 1 (IUI + OH), 0 (IUI + NC)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
Total (95% CI)	**166**	**180**		**100%**	**1.34[0.77,2.33]**
Total events: 35 (IUI + OH), 31 (IUI + NC)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=1.05(P=0.29)					
Test for subgroup differences: Chi^2=0.19, df=1 (P=0.67), I^2=0%					



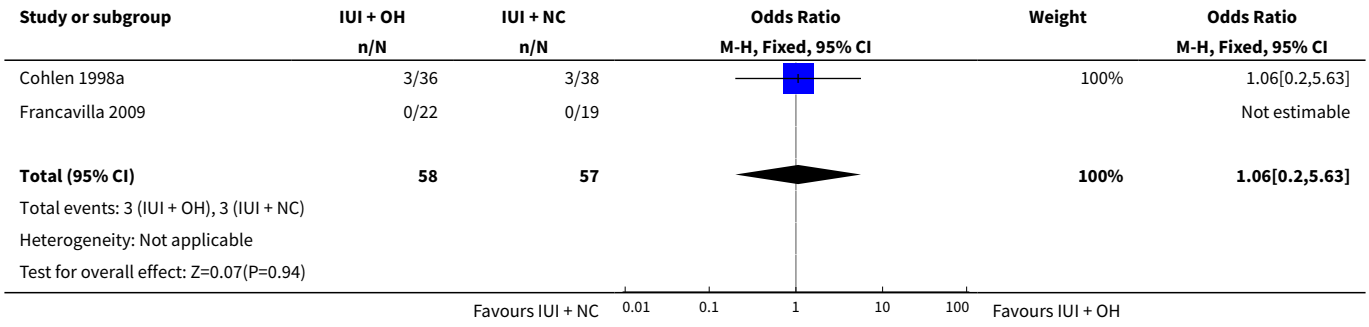
Analysis 5.2. Comparison 5 Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus IUI in natural cycles (NC), Outcome 2 Pregnancy rate per couple (all cycles).

Study or subgroup	IUI + OH n/N	IUI + NC n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.2.1 Gonadotrophins					
Cohlen 1998a	3/36	4/38		16.16%	0.77[0.16,3.72]
Guzick 1999	37/120	27/134		79.94%	1.77[1,3.13]
Subtotal (95% CI)	**156**	**172**		**96.11%**	**1.6[0.94,2.73]**
Total events: 40 (IUI + OH), 31 (IUI + NC)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=1.72(P=0.09)					
5.2.2 CC					
Arici 1994	1/12	0/18		1.63%	4.83[0.18,128.79]
Subtotal (95% CI)	**12**	**18**		**1.63%**	**4.83[0.18,128.79]**
Total events: 1 (IUI + OH), 0 (IUI + NC)					





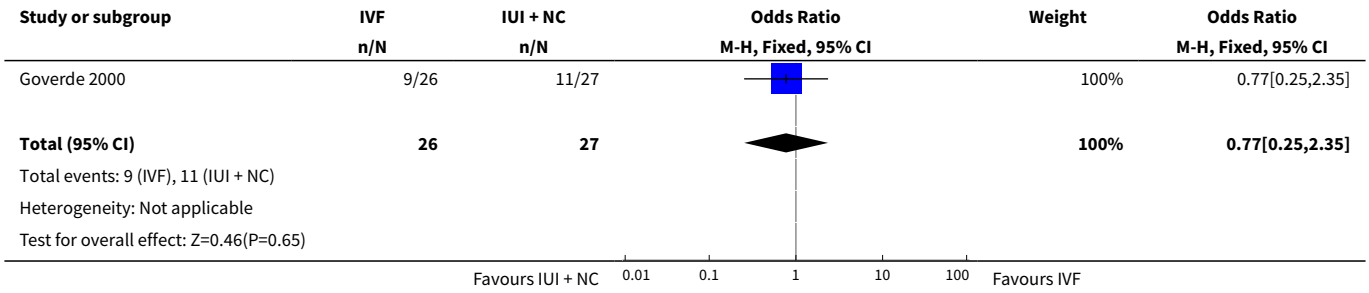
Analysis 5.3. Comparison 5 Intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH) versus IUI in natural cycles (NC), Outcome 3 Miscarriage rate per couple.



Comparison 8. In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in natural cycles (NC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.25, 2.35]

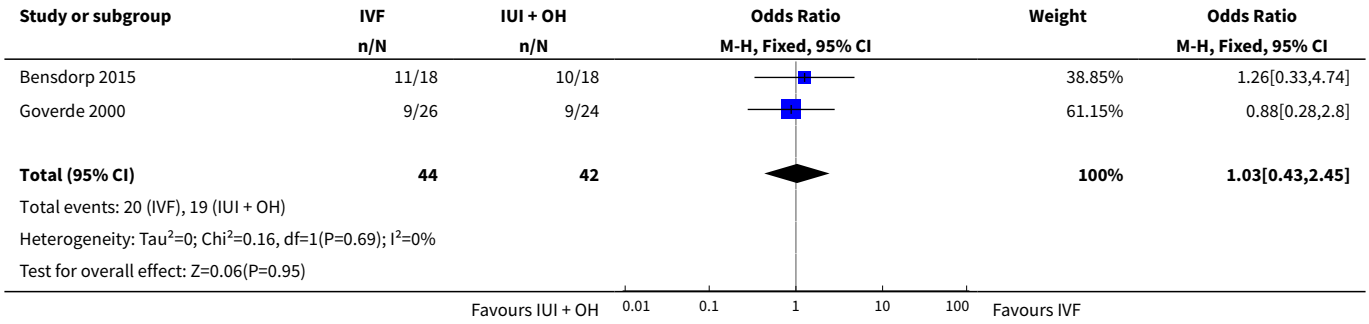
Analysis 8.1. Comparison 8 In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in natural cycles (NC), Outcome 1 Live birth rate per couple (all cycles).



Comparison 9. In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH)

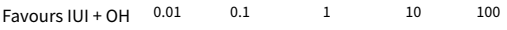
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	2	86	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.43, 2.45]
2 OHSS per couple	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Pregnancy rate per couple (all cycles)	1	36	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.33, 4.97]

Analysis 9.1. Comparison 9 In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH), Outcome 1 Live birth rate per couple (all cycles).



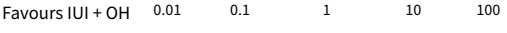
Analysis 9.2. Comparison 9 In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH), Outcome 2 OHSS per couple.

Study or subgroup	IVF n/N	IUI + OH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bensdorp 2015	0/18	0/18			Not estimable
Total (95% CI)	**18**	**18**			**Not estimable**
Total events: 0 (IVF), 0 (IUI + OH)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 9.3. Comparison 9 In vitro fertilisation (IVF) versus intra-uterine insemination (IUI) in cycles with ovarian hyperstimulation (OH), Outcome 3 Pregnancy rate per couple (all cycles).

Study or subgroup	IVF n/N	IUI + OH n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bensdorp 2015	12/18	11/18		100%	1.27[0.33,4.97]
Total (95% CI)	**18**	**18**		**100%**	**1.27[0.33,4.97]**
Total events: 12 (IVF), 11 (IUI + OH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.35(P=0.73)					



APPENDICES

Appendix 1. MDSG search strategy

From inception to 14 April 2015

Keywords CONTAINS "subfertility-male" or "idiopathic asthenospermia" or "idiopathic oligozoospermia" or "oligo-asthenozoospermia" or "Oligoasthenospermia" or "oligoasthenoteratozoospermia"or"oligospermia"or"oligozoospermia" or "asthenospermia" or "asthenozoospermia"or"azoospermia"or"varicocele"or"varicocele-embolization"or"varicocele ligation" or "varicocele-outcome" or "varicocelectomized " or "varicocelectomy" or "Male" or "male factor" or "male fertility" or "male infertility" or "male subfertility" or "unexplained infertility" or "unexplained subfertility" or "teratozoospermic" or "sperm damage" or "sperm disorders" or "sperm DNA damage" or "sperm DNA integrity" or "sperm extraction techniques" or "sperm motility"
AND
Keywords CONTAINS "IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection" or "superovulation" or "superovulation induction" or "IUI" or "insemination, intrauterine " or "Intrauterine Insemination" or "ART" or "artificial insemination" or "assisted reproduction techniques" or "controlled ovarian hyperstimulation" or "controlled ovarian stimulation" or "COH" or "COH IUI" or "ovulation induction" or "ovulation stimulation" or "timed intercourse" or "expectant management" or "Natural cycle" or "natural cycles" or "coitus" or "wait and see" or Title CONTAINS"IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection" or "superovulation" or "controlled ovarian hyperstimulation" (22 hits)

Appendix 2. CENTRAL search strategy

From inception to 14 April 2015

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (1753)
2 embryo transfer$.tw. (1135)

3 vitro fertili?ation.tw. (1571)
4 ivf.tw. (2386)
5 icsi.tw. (910)
6 intracytoplasmic sperm injection$.tw. (518)
7 (blastocyst adj2 transfer$).tw. (121)
8 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (2457)
9 assisted reproduct$.tw. (510)
10 artificial insemination.tw. (97)
11 iui.tw. (380)
12 intrauterine insemination$.tw. (489)
13 ovulation induc$.tw. (566)
14 (ovari$ adj2 stimulat$).tw. (966)
15 superovulat$.tw. (154)
16 ovarian hyperstimulation.tw. (668)
17 COH.tw. (162)
18 (ovari$ adj2 induction).tw. (32)
19 timed intercourse.tw. (38)
20 expectant management.tw. (318)
21 natural cycle$.tw. (106)
22 exp Coitus/ (270)
23 coitus.tw. (92)
24 intra-uterine insemination$.tw. (41)
25 watchful waiting.tw. (226)
26 or/1-25 (6305)
27 exp male infertility/ (506)
28 (asthenozoospermia or oligospermia or azoospermia).tw. (219)
29 Asthenospermia.tw. (33)
30 Teratospermia.tw. (2)
31 (male$ adj2 subfertil$).tw. (66)
32 (male$ adj2 infertil$).tw. (360)
33 (subfertil$ adj2 men).tw. (22)
34 (infertil$ adj2 men).tw. (142)
35 (male$ adj2 fertility).tw. (59)
36 oligoasthenoteratozoospermi$.tw. (17)
37 (idiopathic adj3 infertil$).tw. (80)
38 (idiopathic adj3 subfertil$).tw. (11)
39 Oligozoospermi$.tw. (99)
40 Aspermi$.tw. (2)
41 Teratospermia.tw. (2)
42 unexplained subfertility.tw. (15)
43 unexplained infertility.tw. (274)
44 or/27-43 (1183)
45 26 and 44 (553)

Appendix 3. MEDLINE search strategy

From inception to 14 April 2015

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (33481)
2 embryo transfer$.tw. (8656)
3 vitro fertili?ation.tw. (17653)
4 ivf.tw. (17313)
5 icsi.tw. (5854)
6 intracytoplasmic sperm injection$.tw. (5221)
7 (blastocyst adj2 transfer$).tw. (598)
8 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (54694)
9 assisted reproduct$.tw. (9783)
10 artificial insemination.tw. (5138)
11 iui.tw. (1280)
12 intrauterine insemination$.tw. (1897)
13 ovulation induc$.tw. (3509)
14 (ovari$ adj2 stimulat$).tw. (5151)

15 superovulat$.tw. (2972)
16 ovarian hyperstimulation.tw. (4003)
17 COH.tw. (1191)
18 (ovari$ adj2 induction).tw. (232)
19 timed intercourse.tw. (108)
20 expectant management.tw. (1780)
21 natural cycle$.tw. (929)
22 exp Coitus/ (6553)
23 coitus.tw. (2519)
24 intra-uterine insemination$.tw. (185)
25 watchful waiting.tw. (1698)
26 or/1-25 (83004)
27 exp male infertility/ (23103)
28 (asthenozoospermia or oligospermia or azoospermia).tw. (5858)
29 Asthenospermia.tw. (281)
30 Teratospermia.tw. (143)
31 (male$ adj2 subfertil$).tw. (625)
32 (male$ adj2 infertil$).tw. (8353)
33 (subfertil$ adj2 men).tw. (439)
34 (infertil$ adj2 men).tw. (3434)
35 (male$ adj2 fertility).tw. (4268)
36 oligoasthenoteratozoospermi$.tw. (301)
37 (idiopathic adj3 infertil$).tw. (940)
38 (idiopathic adj3 subfertil$).tw. (62)
39 Oligozoospermi$.tw. (1809)
40 Aspermi$.tw. (220)
41 Teratospermia.tw. (143)
42 unexplained subfertility.tw. (78)
43 unexplained infertility.tw. (1577)
44 or/27-43 (32348)
45 26 and 44 (7523)
46 randomized controlled trial.pt. (391583)
47 controlled clinical trial.pt. (89189)
48 randomized.ab. (316291)
49 randomised.ab. (62637)
50 placebo.tw. (165382)
51 clinical trials as topic.sh. (172188)
52 randomly.ab. (228234)
53 trial.ti. (136301)
54 (crossover or cross-over or cross over).tw. (63611)
55 or/46-54 (994662)
56 exp animals/ not humans.sh. (4023388)
57 55 not 56 (916956)
58 45 and 57 (667)

Appendix 4. EMBASE search strategy

From inception to 14 April 2015

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (55222)
2 embryo$ transfer$.tw. (13466)
3 in vitro fertili?ation.tw. (21550)
4 icsi.tw. (10216)
5 intracytoplasmic sperm injection$.tw. (6647)
6 (blastocyst adj2 transfer$).tw. (1178)
7 ivf.tw. (26204)
8 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (80903)
9 assisted reproduct$.tw. (14085)
10 artificial insemination.tw. (4861)
11 iui.tw. (2090)
12 intrauterine insemination$.tw. (2619)
13 ovulation induc$.tw. (4466)

14 (ovari$ adj2 stimulat$).tw. (7397)
15 superovulat$.tw. (3129)
16 ovarian hyperstimulation.tw. (5490)
17 COH.tw. (1597)
18 (ovar$ adj2 induction).tw. (305)
19 timed intercourse.tw. (166)
20 expectant management.tw. (2456)
21 natural cycle$.tw. (1323)
22 exp coitus/ (5440)
23 coitus.tw. (2448)
24 intra-uterine insemination$.tw. (303)
25 watchful waiting.tw. (2368)
26 or/1-25 (108525)
27 exp male infertility/ (32048)
28 (asthenozoospermia or oligospermia or azoospermia).tw. (6986)
29 Asthenospermia.tw. (340)
30 Teratospermia.tw. (177)
31 (male$ adj2 subfertil$).tw. (772)
32 (male$ adj2 infertil$).tw. (10861)
33 (subfertil$ adj2 men).tw. (496)
34 (infertil$ adj2 men).tw. (4297)
35 (male$ adj2 fertility).tw. (4919)
36 oligoasthenoteratozoospermi$.tw. (386)
37 (idiopathic adj3 infertil$).tw. (1242)
38 (idiopathic adj3 subfertil$).tw. (72)
39 Oligozoospermi$.tw. (2043)
40 Aspermi$.tw. (195)
41 Teratospermia.tw. (177)
42 unexplained subfertility.tw. (100)
43 unexplained infertility.tw. (2132)
44 or/27-43 (41854)
45 26 and 44 (11456)
46 Clinical Trial/ (842028)
47 Randomized Controlled Trial/ (366567)
48 exp randomization/ (65714)
49 Single Blind Procedure/ (19913)
50 Double Blind Procedure/ (119287)
51 Crossover Procedure/ (42210)
52 Placebo/ (253674)
53 Randomi?ed controlled trial$.tw. (113414)
54 Rct.tw. (16495)
55 random allocation.tw. (1392)
56 randomly allocated.tw. (21964)
57 allocated randomly.tw. (2006)
58 (allocated adj2 random).tw. (720)
59 Single blind$.tw. (15500)
60 Double blind$.tw. (148801)
61 ((treble or triple) adj blind$).tw. (434)
62 placebo$.tw. (211189)
63 prospective study/ (283895)
64 or/46-63 (1442620)
65 case study/ (31021)
66 case report.tw. (278028)
67 abstract report/ or letter/ (918503)
68 or/65-67 (1221392)
69 64 not 68 (1403772)
70 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5242944)
71 69 not 70 (1348753)
72 45 and 71 (1405)

Appendix 5. PsycINFO search strategy

From inception to 14 April 2015

1 exp reproductive technology/ (1385)
2 in vitro fertili?ation.tw. (568)
3 ivf-et.tw. (17)
4 (ivf or et).tw. (101465)
5 icsi.tw. (50)
6 intracytoplasmic sperm injection$.tw. (42)
7 (blastocyst adj2 transfer$).tw. (4)
8 assisted reproduct$.tw. (590)
9 artificial insemination.tw. (227)
10 iui.tw. (24)
11 intrauterine insemination$.tw. (19)
12 ovulation induc$.tw. (22)
13 (ovari$ adj2 stimulat$).tw. (49)
14 ovarian hyperstimulation.tw. (10)
15 COH.tw. (75)
16 superovulat$.tw. (5)
17 (ovari$ adj2 induction).tw. (5)
18 timed intercourse.tw. (5)
19 expectant management.tw. (20)
20 natural cycle$.tw. (41)
21 exp "Sexual Intercourse (Human)"/ (12585)
22 coitus.tw. (767)
23 intra-uterine insemination$.tw. (0)
24 watchful waiting.tw. (117)
25 or/1-24 (116058)
26 exp Infertility/ (1743)
27 (asthenozoospermia or oligospermia or azoospermia).tw. (38)
28 (male$ adj2 subfertil$).tw. (6)
29 (male$ adj2 infertil$).tw. (165)
30 (infertil$ adj2 men).tw. (73)
31 (male$ adj2 fertility).tw. (125)
32 oligoasthenoteratozoospermi$.tw. (1)
33 Asthenospermia.tw. (2)
34 (idiopathic adj3 infertil$).tw. (12)
35 Oligozoospermi$.tw. (4)
36 Aspermi$.tw. (5)
37 unexplained subfertility.tw. (1)
38 unexplained infertility.tw. (27)
39 or/26-38 (1930)
40 random.tw. (43215)
41 control.tw. (335612)
42 double-blind.tw. (18726)
43 clinical trials/ (8513)
44 placebo/ (4032)
45 exp Treatment/ (610630)
46 or/40-45 (936137)
47 25 and 39 and 46 (180)

Appendix 6. CINAHL search strategy

From inception to 14 April 2015

#	Query	Results
S60	S58 AND S59	31

(Continued)

S59	EM 2014* or EM 2015*	439,602
S58	S45 AND S57	264
S57	S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56	954,451
S56	TX allocat* random*	4,243
S55	(MH "Quantitative Studies")	13,282
S54	(MH "Placebos")	9,173
S53	TX placebo*	33,620
S52	TX random* allocat*	4,243
S51	(MH "Random Assignment")	38,985
S50	TX randomi* control* trial*	85,907
S49	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*))	763,614
S48	TX clinic* n1 trial*	170,899
S47	PT Clinical trial	77,668
S46	(MH "Clinical Trials+")	186,062
S45	S26 AND S44	930
S44	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	3,570
S43	TX unexplained infertility	102
S42	TX unexplained subfertility	20
S41	TX Oligozoospermi*	28
S40	TX (idiopathic adj3 subfertil*)	3
S39	TX (idiopathic adj3 subfertil*)	0
S38	TX(idiopathic N3 infertil*)	30
S37	TX oligoasthenoteratozoospermi*	9
S36	TX (male fertil*)	259
S35	TX (infertil* N2 men)	169
S34	TX (subfertil* N2 men)	18

(Continued)

S33	TX (male* N2 infertil*)	485
S32	TX (male* N2 subfertil*)	34
S31	TX Asthenospermia	3
S30	TX (asthenozoospermia or oligospermia or azoospermia)	141
S29	TX sperm*	3,014
S28	(MH "Sperm Motility") OR (MH "Spermatozoa") OR (MH "Sperm Count") OR "sperm"	2,161
S27	"male infertility"	327
S26	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	8,262
S25	TX intra-uterine insemination	9
S24	TX coitus	1,743
S23	(MM "Coitus")	762
S22	TX natural cycle*	118
S21	TX expectant management	398
S20	TX timed intercourse	19
S19	TX (ovari* N2 induction)	12
S18	TX COH	62
S17	TX ovarian hyperstimulation	333
S16	TX superovulat*	23
S15	TX ovulation induc*	574
S14	TX intrauterine insemination	149
S13	TX IUI	79
S12	TX artificial insemination	453
S11	TX assisted reproduct*	1,296
S10	(MM "Insemination, Artificial")	242
S9	(MM "Reproduction Techniques+")	3,949
S8	TX intracytoplasmic sperm injection*	234
S7	TX embryo* N3 transfer*	769

(Continued)

S6	TX ovar* N3 hyperstimulat*	336
S5	TX ovari* N3 stimulat*	246
S4	TX IVF or TX ICSI	1,248
S3	(MM "Fertilization in Vitro")	1,445
S2	TX vitro fertilization	2,849
S1	TX vitro fertilisation	266

Appendix 7. Other electronic sources search strategy (PubMed)

timed intercourse; expectant management; natural cycle; intrauterine; intra uterine; intra-uterine; insemination; inseminate; IUI; artificial insemination; AI; artificial insemination husband; AIH; ovarian hyperstimulation; in vitro fertilization; IVF; intracytoplasmic sperm injection; ICSI; male infertility; male subfertility; oligoasthenoteratozoospermia; oligospermia; asthenospermia; teratospermia; (randomised controlled trial [Publication Type], controlled clinical trials [Publication Type], randomised controlled trials, random allocation, double-blind method, single-blind method, clinical trial [Publication Type], clinical trials, (clinical AND trial*)).

Appendix 8. Data extraction table

Type of studies
Randomised controlled trials (RCTs) only.

Trial quality
1. Randomisation:

- truly randomised, e.g. blocked randomisation list, on-site computer system, centralised randomisation scheme, random number tables or drawing lots;
- stated without further description, or not stated.

2. Concealment of allocation:

- adequate (low risk of bias), e.g. sealed opaque envelopes or third party randomisation;
- inadequate (high risk of bias), e.g. open list of random numbers, open envelops, tables;
- stated without further description or not stated (unclear risk of bias)

3. Study design:

- parallel design, cross-over design or not clear (we included only parallel group studies or pre-cross-over data in the meta-analysis);
- single centre or multicentre.

4. Blinding:

- if appropriate, were the couple, the care provider and the outcome assessor blinded?

5. Analysis:

- by intention to treat (ITT);
- power calculation (prospective power calculation, no power calculation or not stated).

6. Drop-outs:

- number or percentage of drop-outs;
- reasons for and details on drop-outs (selective drop-out?).

7. Cancelled cycles:

- number or percentage of cancelled cycles;

- reasons for cancelled cycles.

Study participants

8. Prognostic factors:

- type of subfertility;
- woman's age;
- duration of subfertility;
- primary or secondary subfertility.

9. Male subfertility:

- definition;
- number of semen samples

10. Basic fertility work-up:

- regular menstrual cycles with basal body temperature (BBT) charts, normal mid-luteal progesterone or sonographic evidence of ovulation;
- patent tubes on hysterosalpingography or laparoscopy, or low risk for tubal pathology according to the medical history (Coppus 2007);
- postcoital test.

11. Previous fertility treatment

12. Exclusion criteria

Type of interventions

13. Comparison of treatment:

- timed intercourse or expectant management (with or without ovarian hyperstimulation (OH));
- intra-uterine insemination (IUI) (with or without OH);
- in vitro fertilisation (IVF);
- intracytoplasmic sperm injection (ICSI).

14. Stimulation protocols:

- type and dosage of drugs for mild OH;
- days of ovarian stimulation;
- use and timing of ovulation induction;
- cancellation criteria, risk of multiple pregnancies or ovarian hyperstimulation syndrome (OHSS);
- use of luteal support.

15. Semen sample preparation techniques:

- amount of semen injected, number of motile spermatozoa;
- method of sperm preparation (washing and centrifugation technique, swim up technique, other).

16. Insemination characteristics

- use of single or double insemination;
- number of treatment cycles;
- actual timing of IUI (time form luteinising hormone (LH) surge, time from human chorionic gonadotrophin (hCG) administration to IUI).

Type of outcome measures

17. Primary outcomes:

- live birth rate per couple;
- incidence OHSS.

18 Secondary outcomes:

- pregnancy rate per couple;
- incidence of multiple pregnancies;
- incidence of miscarriage;
- incidence of total fertilisation failure during IVF.

WHAT'S NEW

Date	Event	Description
21 January 2016	New citation required and conclusions have changed	The scope of the review was extended to more invasive treatments for male subfertility (IVF and ICSI)
21 January 2016	New search has been performed	More extended review plus updated up to 13 April 2015. Added studies: Bensdorp 2015; Francavilla 2009.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 4, 2007

Date	Event	Description
11 November 2008	Amended	Converted to new review format.
23 August 2007	New citation required and conclusions have changed	Substantive amendement

CONTRIBUTIONS OF AUTHORS

M Cissen: took the lead in rewriting the protocol. Performed the literature search, selected trials and performed data extraction and analysis. Wrote the review.

AJ Bensdorp: primary author of the previous publication of the review (Bensdorp 2007b). Assisted in rewriting the protocol.

BJ Cohlen: primary author of the first publication of the review (Cohlen 1998; Cohlen 2000). Substantial contribution writing update.

JP de Bruin: formulation of research question; substantial contribution writing update.

S Repping: formulation of research question; substantial contribution writing update.

M van Wely: helped in rewriting the protocol and writing the review. As the second review author, she selected trials and performed data extraction and analysis.

DECLARATIONS OF INTEREST

None known for any of the review authors.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Birth Rate; *Coitus; *Fertilization; *Infertility, Male; *Ovulation Induction; Insemination, Artificial [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male; Pregnancy