Cochrane Library

Cochrane Database of Systematic Reviews

Intra-uterine insemination for unexplained subfertility (Review)

Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ

Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ.
Intra-uterine insemination for unexplained subfertility.
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD001838.
DOI: 10.1002/14651858.CD001838.pub5.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Intra-uterine insemination for unexplained subfertility

Susanne M Veltman-Verhulst[1], Edward Hughes[2], Reuben Olugbenga Ayeleke[3], Ben J Cohlen[4]

[1]University Medical Center Utrecht, Department of Reproductive Medicine and Gynecology, Utrecht, Netherlands. [2]Department of Obstetrics and Gynaecology, McMaster University, REI Consultant, ONE Fertility, Hamilton, Canada. [3]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [4]Department of Obstetrics & Gynaecology, Isala Clinics, Location Sophia, Zwolle, Netherlands

Contact address: Susanne M Veltman-Verhulst, University Medical Center Utrecht, Department of Reproductive Medicine and Gynecology, Room F5.126, PO Box 85500„ Utrecht, 3508 GA, Netherlands. veltmanverhulst@gmail.com.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2016.
Review content assessed as up-to-date: 22 December 2015.

Citation: Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ. Intra-uterine insemination for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD001838. DOI: 10.1002/14651858.CD001838.pub5.

ABSTRACT

Background

Intra-uterine insemination (IUI) is a widely used fertility treatment for couples with unexplained subfertility. Although IUI is less invasive and less expensive thAppendixan in vitro fertilisation (IVF), the safety of IUI in combination with ovarian hyperstimulation (OH) is debated. The main concern about IUI treatment with OH is the increase in multiple pregnancy rate. This is an update of a Cochrane review (Veltman-Verhulst 2012) originally published in 2006 and updated in 2012.

Objectives

To determine whether, for couples with unexplained subfertility, IUI improves the live birth rate compared with timed intercourse (TI), or expectant management, both with and without ovarian hyperstimulation (OH).

Search methods

We searched the Cochrane Gynaecology and Fertility (formerly Cochrane Menstrual Disorders and Subfertility Group) Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, inception to Issue 11, 2015), Ovid MEDLINE, Ovid EMBASE, PsycINFO and trial registers, all from inception to December 2015 and reference lists of articles. Authors of identified studies were contacted for missing or unpublished data. The evidence is current to December 2015.

Selection criteria

Truly randomised controlled trial (RCT) comparisons of IUI versus TI, in natural or stimulated cycles. Only couples with unexplained subfertility were included.

Data collection and analysis

Two review authors independently performed study selection, quality assessment and data extraction. We extracted outcomes, and pooled data and, where possible, we carried out subgroup and sensitivity analyses.

Main results

We included 14 trials including 1867 women.

IUI versus TI or expectant management both in natural cycle

Live birth rate (all cycles)

There was no evidence of a difference in cumulative live births between the two groups (Odds Ratio (OR) 1.60, 95% confidence interval (CI) 0.92 to 2.78; 1 RCT; n = 334; moderate quality evidence). The evidence suggested that if the chance of a live birth in TI was assumed to be 16%, that of IUI would be between 15% and 34%.

Multiple pregnancy rate

There was no evidence of a difference in multiple pregnancy rate between the two treatment groups (OR 0.50, 95% CI 0.04 to 5.53; 1 RCT; n = 334; moderate quality evidence).

IUI versus TI or expectant management both in stimulated cycle

Live birth rate (all cycles)

There was no evidence of a difference between the two treatment groups (OR 1.59, 95% CI 0.88 to 2.88; 2 RCTs; n = 208; I^2 = 72%; moderate quality evidence). The evidence suggested that if the chance of achieving a live birth in TI was assumed to be 26%, the chance of a live birth with IUI would be between 23% and 50%.

Multiple pregnancy rate

There was no evidence of a difference in multiple pregnancy rates between the two treatment groups (OR 1.46, 95% CI 0.55 to 3.87; 4 RCTs, n = 316; I^2 = 0%; low quality evidence).

IUI in a natural cycle versus IUI in a stimulated cycle

Live birth rate (all cycles)

An increase in live birth rate was found for women who were treated with IUI in a stimulated cycle compared with those who underwent IUI in natural cycle (OR 0.48, 95% CI 0.29 to 0.82; 4 RCTs, n = 396; I^2 = 0%; moderate quality evidence). The evidence suggested that if the chance of a live birth in IUI in a stimulated cycle was assumed to be 25%, the chance of a live birth in IUI in a natural cycle would be between 9% and 21%.

Multiple pregnancy rate

There was no evidence of a difference in multiple pregnancy rate between the two treatment groups (OR 0.33, 95% CI 0.01 to 8.70; 2 RCTs; n = 65; low quality evidence).

IUI in a stimulated cycle versus TI or expectant management in a natural cycle

Live birth rate (all cycles)

There was no evidence of a difference in live birth rate between the two treatment groups (OR 0.82, 95% CI 0.45 to 1.49; 1 RCT; n = 253; moderate quality evidence). The evidence suggested that if the chance of a live birth in TI or expectant management in a natural cycle was assumed to be 24%, the chance of a live birth in IUI in a stimulated cycle would be between 12% and 32%.

Multiple pregnancy rate

There was no evidence of a difference in multiple pregnancy rate between the two treatment groups (OR 2.00, 95% CI 0.18 to 22.34; 2 RCTs; n = 304; moderate quality evidence).

IUI in natural cycle versus TI or expectant management in stimulated cycle

Live birth rate (all cycles)

There was evidence of an increase in live births for IUI (OR 1.95, 95% CI 1.10 to 3.44; 1 RCT, n = 342; moderate quality evidence). The evidence suggested that if the chance of a live birth in TI in a stimulated cycle was assumed to be 13%, the chance of a live birth in IUI in a natural cycle would be between 14% and 34%.

Multiple pregnancy rate

There was no evidence of a difference in multiple pregnancy rate between the groups (OR 1.05, 95% CI 0.07 to 16.90; 1 RCT; n = 342; moderate quality evidence).

The quality of the evidence was assessed using GRADE methods. Quality ranged from low to moderate, the main limitation being imprecision in the findings for both live birth and multiple pregnancy..

Authors' conclusions

This systematic review did not find conclusive evidence of a difference in live birth or multiple pregnancy in most of the comparisons for couples with unexplained subfertility treated with intra-uterine insemination (IUI) when compared with timed intercourse (TI), both with and without ovarian hyperstimulation (OH). There were insufficient studies to allow for pooling of data on the important outcome measures for each of the comparisons.

PLAIN LANGUAGE SUMMARY

Intra-uterine insemination for unexplained subfertility

Review question

Does intra-uterine insemination (IUI) treatment (with or without fertility drugs) lead to higher live birth rates in couples with unexplained subfertility as compared to timed intercourse or expectant management?

Background

IUI is a treatment often used for couples with unexplained subfertility. In an IUI cycle, the male partner's sperm is prepared and placed directly in the uterus at the time of ovulation. IUI cycles can be used in combination with fertility drugs to stimulate the ovaries and increase the number of available eggs. However, these drugs can have adverse effects and also increase the risk of multiple pregnancies. Expectant management and timed intercourse have also been shown to result in high pregnancy rates resulting in live birth. With this review we would like to enhance decision-making for starting treatment for couples with unexplained subfertility.

Study characteristics

Cochrane authors included 14 randomised controlled trials (1867 women) in this review, comparing women with unexplained subfertility undergoing fertility treatment with IUI with or without ovarian stimulation drugs. Women who underwent IUI treatment were compared to women who received ovarian stimulation drugs along with timed intercourse or couples who were randomised to expectant management. The main outcome of interest was live birth rate, but pregnancy rate, miscarriage rate and other adverse effects were also recorded. The evidence is current to December 2015.

Key results

There was no conclusive evidence of a difference between most treatment groups in cumulative live birth rates (i.e. rates at conclusion of a course of treatment), multiple pregnancy rates and other adverse effects for couples with unexplained subfertility undergoing intra-uterine insemination (IUI) when compared with timed intercourse (TI), both with and without ovarian hyperstimulation (OH).

Quality of the evidence

The evidence was of moderate quality for live birth and low to moderate quality for multiple pregnancy. The main limitation of the evidence was lack of precision in the findings for both live birth and multiple pregnancy.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

IUI compared to TI or expectant management both in natural cycle for unexplained subfertility

Patient or population: people with unexplained subfertility
Settings:
Intervention: IUI
Comparison: TI or expectant management both in natural cycle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI or expectant management both in natural cycle	IUI				
Live birth rate per couple (all cycles)	**156 per 1000**	**228 per 1000** (145 to 339)	**OR 1.60** (0.92 to 2.78)	334 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Multiple pregnancy rate per couple	**12 per 1000**	**6 per 1000** (0 to 63)	**OR 0.50** (0.04 to 5.53)	334 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Pregnancy rate per couple (all cycles)	**162 per 1000**	**228 per 1000** (145 to 338)	**OR 1.53** (0.88 to 2.64)	334 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Ovarian Hyperstimulation Syndrome rate per woman - not reported			Not estimable	-		
Miscarriage rate per couple	**54 per 1000**	**42 per 1000** (16 to 107)	**OR 0.77** (0.28 to 2.11)	334 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Ectopic pregnancy rate per couple	Not estimable		**OR 5.06** (0.24 to 106.2)	334 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	

*The basis for the **assumed risk** is 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; **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] Small sample size
[2] Effect estimate with wide confidence interval

BACKGROUND

Description of the condition

Of all couples presenting with fertility problems about 25% have no cause that can be identified (NICE 2013). Couples are classified as having unexplained subfertility when they have tried to conceive for at least one year and the fertility work-up showed patent fallopian tubes, an ovulatory menstrual cycle and a normal semen analysis.

Description of the intervention

Intra-uterine insemination (IUI) is a commonly-used treatment in couples with unexplained subfertility. IUI is a relatively simple procedure in which semen is 'washed' in the laboratory and inserted in the uterine cavity using a small catheter at the time of ovulation. IUI can be performed with or without drugs for ovarian hyperstimulation (OH). For correct timing of the insemination, cycle monitoring is performed. This is usually done by ultrasound assessment of follicle growth or by monitoring the preovulatory luteinizing hormone rise in blood or urine. In hyperstimulated cycles ovulation is often induced by an injection of human chorionic gonadotropin (hCG), which improves timing possibilities. In contrast to the IUI procedure, with expectant management, couples either receive cycle monitoring for correct timing of sexual intercourse, for example timed intercourse (TI), or no intervention at all.

How the intervention might work

The rationale for performing IUI is that the motile spermatozoa, which are morphologically normal, can be concentrated in a small volume and placed directly into the uterus close to the released oocyte. In this way the cervix, which also acts as a reservoir for sperm, is bypassed. Accurate timing of the insemination is therefore of great importance. IUI can be performed with or without ovarian hyperstimulation (OH). The two most commonly used drugs for ovarian hyperstimulation are clomiphene citrate (CC), which is an oral treatment, and gonadotropins administered by subcutaneous injection. The aim of OH is to increase the number of oocytes available for fertilisation and to enhance accurate timing.

The role of IUI in fertility treatment is often debated, in particular in terms of whether or not it is superior to TI and whether or not OH should be used at the same time (Cohlen 2005; Hughes 2003; Stewart 2003).

The use of OH in fertility treatment for unexplained subfertility has been both supported and criticised. When Hughes published a meta-analysis indicating that the average fecundability is approximately five-fold higher for treatment with IUI and OH (Hughes 1997), the Royal College of Obstetricians and Gynaecologists (RCOG 1998) concluded accordingly that "OH with IUI is an effective treatment for couples with unexplained infertility". However, major concerns about the incidence of multiple pregnancies were raised and OH became less popular. These concerns have resulted in an adjustment of the advice for treatment of couples with unexplained subfertility. The NICE fertility guideline states that "ovarian hyperstimulation should not be offered to women with unexplained subfertility" (NICE 2013).

It is usually difficult to target treatment especially when there is no known reason why women are not getting pregnant. The rationale for treatment with OH is to increase the number of mature follicles and trigger ovulation to facilitate optimum timing of IUI. It may also correct subtle abnormalities in follicular maturation and fertilisation and may improve the endometrial quality (Guzick 1998). However, Steures 2006a shows that for couples with unexplained subfertility and an intermediate prognosis there are no large beneficial effects of treatment with IUI and OH.

The increase of multiple pregnancies is a logical consequence of stimulated growth of multiple follicles. The incidence of multiple pregnancies after treatment with OH and IUI varies between 10% and 40%, and the overall contribution of this treatment to multiple births is estimated to be around 30% (Fauser 2005). The question is whether this multiple pregnancy rate is acceptable or whether it can be reduced to acceptable numbers. Recently, more and more evidence has been collected showing that mild ovarian hyperstimulation with strict cancellation criteria reduces the risk of achieving multiple pregnancies to approximately 10%, without compromising pregnancy rates (ESHRE 2006; Ragni 2006; Rumste 2006; Steures 2006b). Because maternal and neonatal morbidity and mortality rates are significantly increased in multiple pregnancies (Fauser 2005; Ombelet 2005), caregivers should take extra care to keep the multiple pregnancy rate to a minimum. Couples should be well informed by their physicians, especially as many couples desire to conceive twins (Ryan 2004) and prefer a higher pregnancy chance over safety.

Some authors state that treatment with OH results in an unacceptably high incidence of high-order multiple pregnancies (Gleicher 2000; Nan 1994) and treatment with IUI in natural cycles should be preferred (Fauser 2005; Goverde 2005). Others say that the risk of a multiple pregnancy could be reduced with strict monitoring of the people undergoing treatment (Dickey 2005; Tur 2005). Te Velde 1999 concluded that IUI with OH is an appropriate treatment option if done with a mild stimulation protocol, careful cycle monitoring and with strict cancellation criteria. It is, however, still not known to what extent multiple pregnancies can be avoided if these criteria are met. Besides, the use of strict cycle cancellation criteria might result in a reduced overall pregnancy rate. Several trials using mild stimulation protocols for IUI have been published, showing promising results of acceptable pregnancy rates with very low multiple pregnancy rates (Balasch 2004). As IVF allows better control over reducing the risk of a multiple pregnancy

(Gleicher 2000), and IVF with single embryo transfer is more and more accepted, it has been argued that IVF is a safer treatment option than IUI with OH. However a large RCT, Bensdorp 2015, showed low multiple pregnancy rates and comparable live birth rates in the IUI with OH group when compared to women undergoing IVF with single embryo transfer. Additionally, Goverde 2000 found IUI to be a more cost-effective treatment than IVF for couples with unexplained or male subfertility.

Why it is important to do this review

The first randomised controlled trial (RCT) of IUI for male factor infertility was published in 1984 and reported a favourable outcome for IUI compared with TI (Kerin 1984). Since then many trials have studied the efficacy of IUI for unexplained subfertility, with variable results. Subsequent RCTs have compared IUI with TI, with or without OH, and suggested a benefit of OH in combination with IUI (Hughes 1997). Goverde 2000 reported that mild ovarian hyperstimulation of IUI cycles did not yield higher pregnancy rates, though IUI is more cost-effective compared with in vitro fertilisation (IVF). Others stated that IUI alone is not efficacious, without some form of ovarian hyperstimulation (Bhattacharya 2008; Guzick 1998). Some studies suggested that both OH and IUI independently contributed to increased pregnancy rates (Aboulghar 2003; Hughes 1997). A meta-analysis of seven studies showed a significantly higher pregnancy rate for treatment with gonadotropins (28%) compared to treatment with CC (19%) when combined with IUI (Cantineau 2007).
Although ovarian hyperstimulation seems to result in higher pregnancy rates it also increases the incidence of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). These pose serious risks to the health of both mother and baby (Fauser 2005; Gleicher 2000; Nan 1994). The NICE fertility guidelines recommend IUI without OH for couples with unexplained subfertility because of the increased risk of multiple pregnancies and OHSS associated with OH (NICE 2013). This systematic review was therefore undertaken to assess the evidence on the benefits and side effects of IUI with or without OH, compared to timed intercourse, for couples with unexplained subfertility.

OBJECTIVES

To determine whether for couples with unexplained subfertility IUI improves the live birth rate compared with timed intercourse (TI) or expectant management, both with and without ovarian hyperstimulation (OH).

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias. We attempted to contact the author of the study if the randomisation or allocation method was unclear.
Trials that did not report separate data for women with unexplained subfertility and where such data were not obtainable from the authors were excluded. We assessed the trial design (crossover or parallel) and included crossover trials if pre-crossover data could be extracted.

Types of participants

1. Couples with unexplained subfertility, defined as follows.
   i) Normal ovulatory status (determined by either biphasic basal body temperature chart, normal luteal progesterone, in phase endometrial biopsy or ovulation detected with ultrasound).
   ii) Tubal patency (determined by hysterosalpingography or laparoscopy, or both).
   iii) A normal semen sample according to World Health Organization (WHO) criteria current at the time of trial.
   iv) Sperm concentration of at least 20 x 10^6 per ml:
      a) total motility of at least 50%,
      b) normal morphology of at least 30% (WHO 1987, at least 50%) or Kruger criteria,
      c) no anti-sperm antibodies.
2. Couples who had tried to conceive for at least one year.

Participants excluded were:
i) couples with a known cause of infertility including a moderate male factor, moderate to severe endometriosis (according to the American Society for Reproductive Medicine (ASRM) classification), tubal disease and a cervical factor.
We contacted study authors to obtain data of couples with unexplained infertility if groups of mixed infertility causes were studied. If relevant data could not be extracted separately for included participants, we excluded the study.
We excluded trials that included participants with mild to moderate endometriosis only.

Types of interventions

Trials with at least one of the following comparisons:
1. intra-uterine insemination (IUI) versus timed intercourse (TI), or expectant management both in a natural cycle;
2. IUI versus TI, or expectant management both in a stimulated cycle;
3. IUI in a natural cycle versus IUI in a stimulated cycle;

4. IUI in a stimulated cycle versus TI or expectant management in a natural cycle;

5. IUI in a natural cycle versus TI or expectant management in a stimulated cycle.

Ovarian hyperstimulation (OH) was achieved with either clomiphene citrate or gonadotropins.

We included expectant management as a variant of timed intercourse.

Interventions excluded:

1. intra-cervical insemination, because we consider this to be a different treatment modality (Ripps 1994) and it is the topic of another review (Besselink 2008);

2. donor insemination.

Types of outcome measures

Primary outcomes

1. Live birth rate per couple: (a) all cycles, (b) after one cycle treatment (subgroup). Live birth is defined as delivery of a live foetus after twenty completed weeks of gestational age

2. Multiple pregnancy rate per couple. Multiple pregnancies confirmed by ultrasound, with or without selective reduction, were recorded.

Secondary outcomes

3. Pregnancy rate per couple: (a) all cycles, (b) after one cycle treatment. Pregnancy includes clinical pregnancy, defined by the presence of an intra-uterine gestational sac or foetal heartbeat visualised by an ultrasound scan before 12 weeks, and/or ongoing pregnancy, defined as a pregnancy extending beyond 12 weeks of gestation, confirmed by ultrasound or delivery

Other adverse events:

4. Moderate or severe ovarian hyperstimulation syndrome (OHSS), rate per woman;

5. Miscarriage rate per couple;

6. Ectopic pregnancy rate per couple.

We excluded pregnancies confirmed only by detection of hCG in serum or urine (biochemical pregnancies). When pregnancy was not further defined, and remained unclear even after contacting the authors, we assumed the pregnancy to be clinical.

We used an intention-to-treat (ITT) analysis whenever possible. We assumed that women who dropped out or were excluded after randomisation were not pregnant. Women who were excluded because they conceived before receiving treatment were included as a success in the allocated group in the ITT analysis.

Search methods for identification of studies

We searched for all reports which describe (or might describe) randomised controlled trials of IUI with or without OH. The original search was performed in 2005 and the search was last updated in December 2015. We used the search strategy developed by Cochrane Gynaecology and Fertility (see Review Group details in *the Cochrane Library* for more information).

Electronic searches

We searched the:

1. Cochrane Gynaecology and Fertility (formerly the Cochrane Menstrual Disorders and Subfertility Group) Specialised Register (searched from inception to December 2015) (Appendix 1),

2. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* inception to 2015, Issue 11) (Appendix 2),

3. Ovid MEDLINE (1966 to December 2015) (Appendix 3),

4. Ovid EMBASE (1980 to December 2015) (Appendix 4),

5. PsycINFO (1806 to December 2015) (Appendix 5).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision; Lefebvre 2011). The EMBASE and PsycINFO searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/methodology/filters.html#random.

Other electronic sources of trials included:

1. trial registers for ongoing and registered trials (up to December 2015),

   i) http://www.clinicaltrials.gov (a service of the US National Institutes of Health),

   ii) http://www.who.int/trialsearch/Default.aspx (The World Health Organization International Trials Registry Platform search portal) Note: it is now mandatory for Cochrane reviews to include searches of trial registers;

2. DARE (Database of Abstracts of Reviews of Effects) in *The Cochrane Library* at http://onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html (for reference lists from relevant non-Cochrane reviews) (up to December 2015);

3. the Web of Knowledge http://wokinfo.com/ (another source of trials and conference abstracts) (up to December 2015);

4. OpenGrey - http://www.opengrey.eu/ for unpublished literature from Europe (up to December 2015);

5. LILACS database http://regional.bvsalud.org/php/index.php?lang=en (for trials from the Portuguese and Spanish speaking world) (up to December 2015);

6. PubMed and Google Scholar (for recent trials not yet indexed in MEDLINE) (up to December 2015).

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also handsearched relevant journals and conference abstracts that were

not covered in the Cochrane Gynaecology and Fertility register, in liaison with the Trials Search Co-ordinator.

Data collection and analysis

Selection of studies

After an initial screening of titles and abstracts retrieved by the search, we retrieved the full texts of all potentially eligible studies. Two review authors (SMV and ROA) independently examined these full-text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the 2015 update. We contacted study investigators as required, to clarify study eligibility. We resolved any disagreements as to study eligibility by discussion. We documented the selection process with a "PRISMA" flow chart (Liberati 2009).

Data extraction and management

Two review authors (SMV and ROA) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the review authors. We resolved any disagreements by discussion. Data extracted included study characteristics and outcome data. Where studies had multiple publications the authors collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review, and such studies had a single study ID with multiple references. We contacted study investigators for further data on methods or results, or both, as required.

Assessment of risk of bias in included studies

Two review authors (SMV and ROA) independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool (Higgins 2011) to assess: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias. We resolved disagreements by discussion or by involving a third review author. We described all judgements fully in the 'Risk of bias' table for each included study and incorporated our judgements into the interpretation of the review findings. These details were summarised and presented in Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

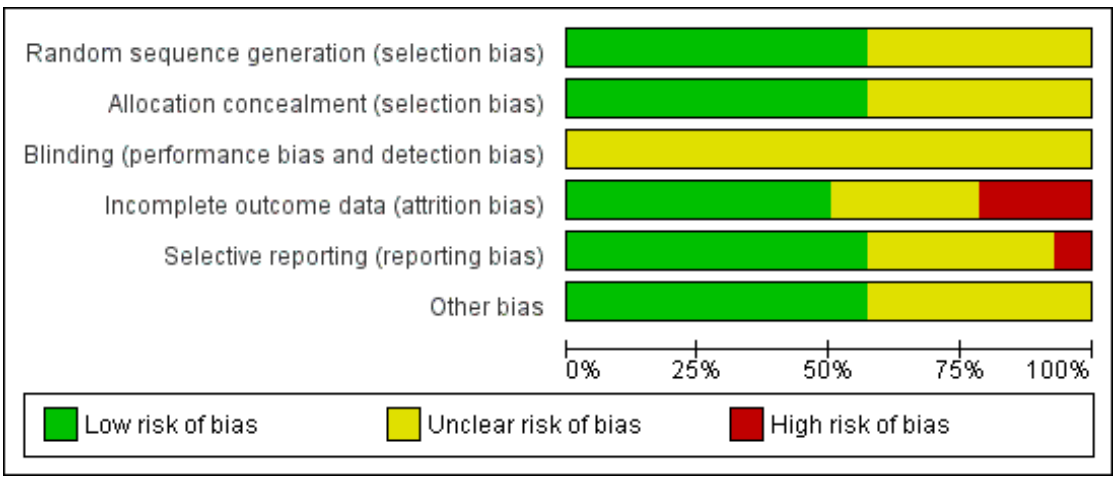
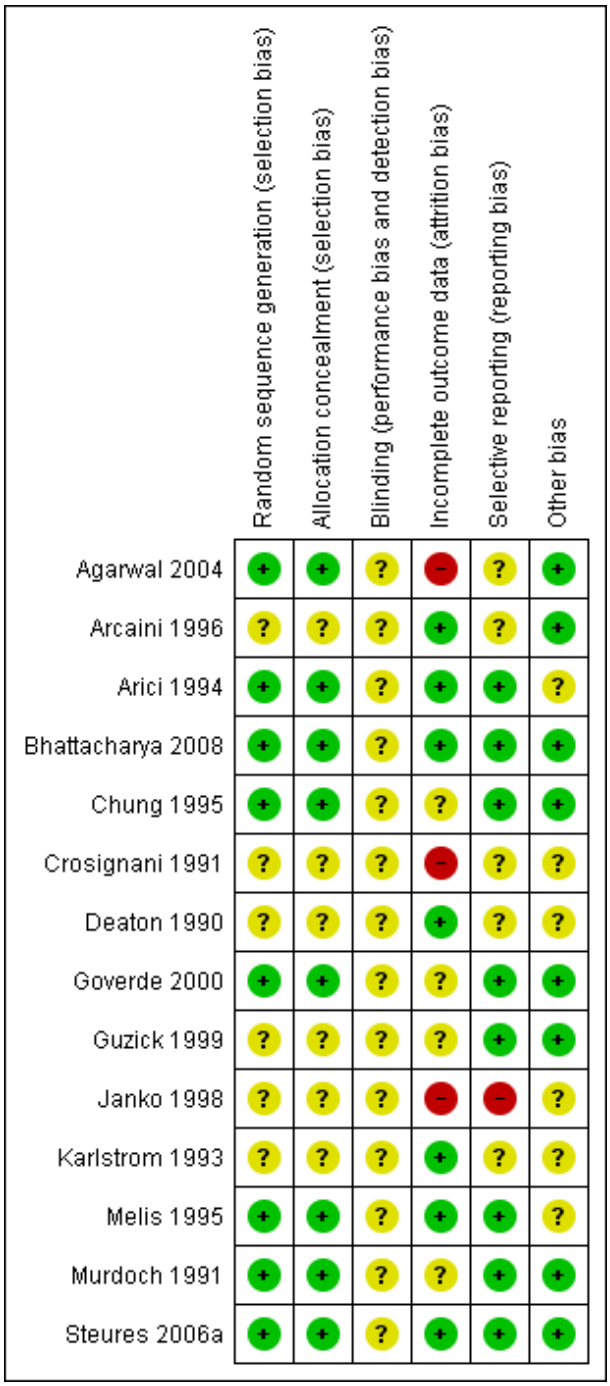


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

Only dichotomous data were reported in this review and we used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (OR). We reversed the direction of effect of individual studies, where required, to ensure consistency across trials. We presented 95% confidence intervals (CI) for all outcomes. We assessed whether the estimates calculated in the review for individual studies were compatible in each case with the estimates reported in the study publications.

Unit of analysis issues

We analysed data per randomised couple or woman, because per-treatment-cycle data may lead to biased results (Dias 2008). In the case of a crossover trial, we only analysed data prior to crossover. For studies where data did not allow analysis (e.g. per-cycle data) we contacted study authors for per-woman data. Where appropriate data were not obtained after contact with authors, we excluded such data (per-cycle) from meta-analyses. Multiple live births (e.g. twins or triplets) were counted as one live birth event.

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible. In the case of missing data we contacted authors of the published trials and included the newly obtained data in the analysis. However, where the study authors did not provide additional data, we assumed that no live births occurred in participants without a reported outcome. For other outcomes, we analysed only the available data.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity using the I^2 statistic (Higgins 2003). An I^2 statistic measurement greater than 50% was taken to indicate substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we minimised their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. Where there were multiple studies in an analysis, we used a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) (Sterne 2011).

Data synthesis

Where the studies were sufficiently similar, we combined the data using a fixed-effect model in the following comparisons:

1. intra-uterine insemination (IUI) versus timed intercourse (TI), both in a natural cycle;
2. IUI versus TI, both in a stimulated cycle;
3. IUI in a natural cycle versus IUI in a stimulated cycle;
4. IUI in a stimulated cycle versus TI in a natural cycle;
5. IUI in a natural cycle versus TI in a stimulated cycle.

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

When pre-crossover data were available, crossover trials were included in the analysis and pooled with parallel trials. Stratification for number of treatment cycles was done by analysing the first cycle, one to three cycles and more than three cycles separately, where possible.

Subgroup analysis and investigation of heterogeneity

Where data were available we planned to conduct a subgroup analysis to determine the separate evidence with regard to the number of treatment cycles for live birth and pregnancy, and methods of ovarian hyperstimulation but this could not be undertaken for most of the comparisons due to non-availability of data.
Where applicable we assessed heterogeneity using the I^2 statistic. We considered an I^2 value of greater than 50% as substantial heterogeneity (Deeks 2011). In the case of statistical heterogeneity the original trials were studied for clinical heterogeneity.

Sensitivity analysis

Specific items that we explored were as follows:

1. trials with adequate methodology versus those with poor methodology, where adequate methodology was defined as an adequate randomisation method, adequate allocation concealment, analysis by intention-to-treat and losses to follow up of less than 20%;
2. trials which might differ from others with respect to their participants, interventions or clinical criteria for defining outcomes.

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

We prepared 'Summary of findings' tables using GRADEpro software (GRADEpro GDT 2015). These tables evaluated the overall quality of the body of evidence for the review outcomes (live birth rate, multiple pregnancy rate, pregnancy rate, OHSS, miscarriage and ectopic pregnancy), using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias) (Schünemann 2011). Judgements about evidence quality (high, moderate or low) were justified, documented, and incorporated into reporting of results for each outcome.

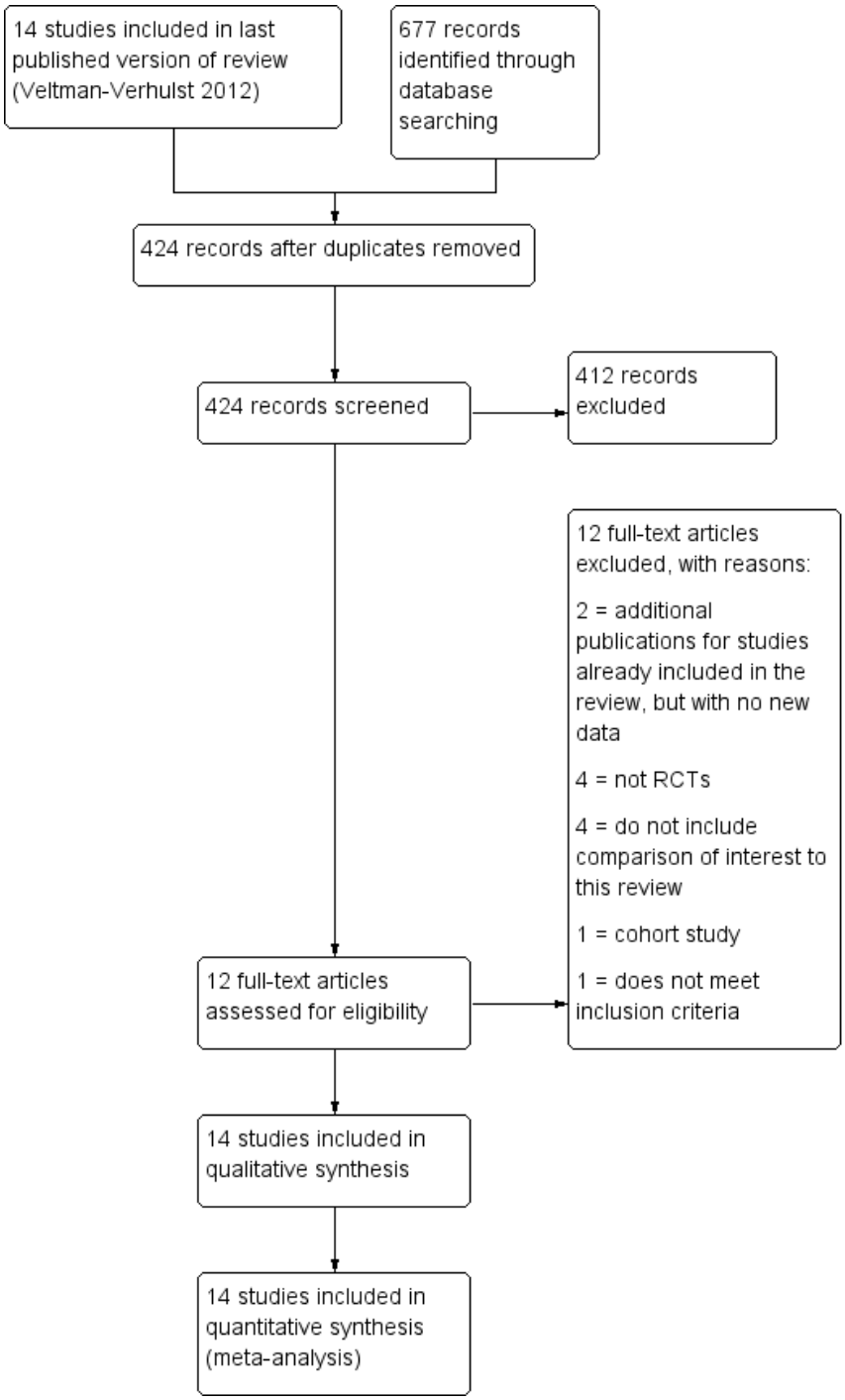
RESULTS

Description of studies

Results of the search

For the 2015 update:
The searches identified 424 records after removal of duplicates. We retrieved 12 potentially eligible full-text articles. All were found to be ineligible for inclusion. One study previously awaiting classification, Wordsworth 2011a, did not have relevant data for inclusion and has been listed as a secondary reference to Bhattacharya 2008. See Figure 3 for details of the screening and selection process.

Figure 3. Study flow diagram.



For previous versions of this review:
The initial database searches found over 700 articles. Of these, 198 were related to the subject. Their abstracts were searched by hand. This resulted in the selection of 25 trials reporting one or more of the comparisons of interest. A search performed in August 2010 retrieved two additional RCTs with a comparison of interest. The search was updated in July 2011 and one further article was retrieved (Wordsworth 2011a) which related to one of the included studies (Bhattacharya 2008) (see above). A total of 14 studies (19 articles were included in the review).
We attempted to contact all study authors to retrieve unpublished details and received 15 replies. Three replies resulted in the exclusion of the trials Nulsen 1993, Prentice 1995 and Serhal 1988. Seven study authors (Agarwal 2004; Arici 1994; Bhattacharya 2008; Guzick 1999; Melis 1995; Murdoch 1991; Steures 2006a) provided unpublished information or data, which were used in this analysis. Some authors could not provide us with the requested data. Others never returned the form.

Included studies

Design

A total of 14 RCTs were included. All trials were published in journals (Janko 1998 was published as an abstract only) and were available in English. The trials were carried out in different countries: USA (Arici 1994; Deaton 1990; Guzick 1999), Italy (Arcaini 1996; Melis 1995), UK (Bhattacharya 2008; Chung 1995; Murdoch 1991), India (Agarwal 2004), the Netherlands (Goverde 2000; Steures 2006a), Slovakia (Janko 1998), Sweden (Karlstrom 1993), and multiple European countries (Crosignani 1991).
Eleven were parallel group studies (Agarwal 2004; Arcaini 1996; Bhattacharya 2008; Chung 1995; Goverde 2000; Guzick 1999; Janko 1998; Karlstrom 1993; Melis 1995; Murdoch 1991; Steures 2006a), and three were crossover studies (Arici 1994; Crosignani 1991; Deaton 1990).

Power calculation

Bhattacharya 2008, Goverde 2000 and Steures 2006a were the only studies in which a power calculation was performed. All three studies reached the targeted inclusion number to obtain enough power (80% to 90% with 5% level of significance) to detect a clinically relevant improvement in live birth rate or pregnancy rate. Further details about the included trials are provided in the 'Characteristics of included studies' table.

Participants

The 14 trials comprised a total of 1866 women with unexplained subfertility.
The age of the women was mentioned in most trials, as either a mean ± standard deviation (SD) or a median and range. One trial (Janko 1998) did not report the women's age. The overall age reported in the studies was similar. The mean or median age was between 30 years to 33 years (with comparable SDs). The maximum age of the participants was stated in six studies, only one of whom was above the age of 40 years (Arici 1994).
The duration of subfertility was given in 10 trials and reported as a mean duration or range. Five studies only included couples with subfertility for more than at least three years. The overall subfertility duration ranged from one year to 15 years.

Types of subfertility

The definition of unexplained subfertility was similar between studies. Six trials enrolled participants with unexplained subfertility only. Five trials also included participants with male factor subfertility. In these studies the data for unexplained subfertility were either reported separately or obtained from the author. One study selected couples with unexplained subfertility and an intermediate prognosis (Steures 2006a). Four studies reported the inclusion of women with either surgically corrected endometriosis (Deaton 1990), mild or stage II treated endometriosis (Guzick 1999) or minimal/mild endometriosis(Bhattacharya 2008; Karlstrom 1993) which we considered to be unexplained subfertility. Melis 1995 specifically excluded participants if minor disorders such as minimal endometriosis were found in the investigation. Although our protocol stated to only include women with minimal and mild endometriosis we decided to include Deaton 1990 despite the inclusion of three participants (out of 51 participants in total) with moderate endometriosis.
All studies reported a thorough fertility investigation, including a laparoscopy. A semen analysis was performed at least once in all studies. In nine studies the semen quality was reported according to the WHO criteria. Twostudies (Arcaini 1996; Janko 1998) did not specify the criteria for a normal semen analysis. Chung 1995 used a sperm count per ejaculate instead of per ml. The data of Guzick 1999 were based only on a normal sperm count and a normal motility according to Kruger criteria.

Primary or secondary subfertility

Nine trials contained a mixed population of couples who had never achieved a pregnancy (primary subfertility) and those who had previously been pregnant (secondary subfertility). The remaining

trials did not give any description for inclusion of people with secondary subfertility.

Previous treatment

Couples who have previously had failed fertility treatment have a lower probability of conception in subsequent treatment attempts. It is, therefore, important in fertility trials to report if couples have undergone previous treatment. Of the 14 included studies only one trial included couples who had previously had unsuccessful fertility treatment (Melis 1995). Five trials did not include previously treated participants (Agarwal 2004; Arici 1994; Guzick 1999; Karlstrom 1993; Murdoch 1991) and the remaining trials did not provide information regarding previous treatment.

Interventions

Number of trials included per comparison

1. IUI versus TI both in a natural cycle: one trial (Bhattacharya 2008). We identified two other studies with this comparison (Kirby 1991; Martinez 1990). We excluded these studies from the analysis because they reported post-crossover per-cycle data only.
2. IUI versus TI both in a stimulated cycle: seven trials (Agarwal 2004; Arcaini 1996; Chung 1995; Crosignani 1991; Janko 1998; Karlstrom 1993; Melis 1995).
3. IUI in a natural cycle versus IUI in a stimulated cycle: four trials (Arici 1994; Goverde 2000; Guzick 1999; Murdoch 1991).
4. IUI in a stimulated cycle versus TI in a natural cycle: two trials (Deaton 1990; Steures 2006a).
5. IUI in a natural cycle versus TI in a stimulated cycle: one trial (Bhattacharya 2008).

Martinez 1990 studied all five comparisons, however there were no pre-crossover data available for couples with unexplained subfertility.

Agarwal 2004, although included in the review, was excluded from the primary analysis. This Indian study had a high dropout percentage (37%) in the treatment group which caused severely unbalanced groups. The main reason for dropout was financial constraints so this introduces a considerable bias. However, we performed a sensitivity analysis including this study.

In the most recent included studies, Bhattacharya 2008 and Steures 2006a, expectant management was performed instead of TI.

Treatment

The treatment methods varied substantially between studies. Seven studies used gonadotropins for ovarian hyperstimulation. Arcaini 1996 offered both gonadotropins and clomiphene citrate, which resulted in a high dose hyperstimulation. Five studies used clomiphene only, and Crosignani 1991 did not report the method of ovarian hyperstimulation. The different fertility centres in this multicentre trial used different treatments. More details on drug dose and method can be found in the prognostic factor table (Table 2) and 'Characteristics of included studies' table. Additional gonadotropin-releasing hormone agonist (GnRHa) was used by Chung 1995 and Murdoch 1991. All studies used human chorionic gonadotropin (hCG) (5000 to 10,000 IU) for triggering ovulation. Chung also provided hCG in the post-ovulatory phase.

The timing of IUI was similar among the studies. Follicle development was usually monitored by ultrasound scan (USS) and serum estradiol levels (serum-E_2). The hCG was given when the dominant follicles reached a mean diameter of 16 mm to 18 mm. Insemination was performed 30 hours to 48 hours after hCG administration. Arcaini 1996 performed a double insemination at 24 and 48 hours, and in the trial by Murdoch 1991 insemination took place on alternate days until ovulation was confirmed. Follicular development in natural cycles was monitored by ultrasound or luteinizing hormone (LH) urine tests, and intercourse was advised at 12 hours to 40 hours after the hCG or LH surge. Couples were mostly advised to have intercourse more than once.

In the studies with expectant management instead of TI (Bhattacharya 2008; Steures 2006a), couples were given general advice regarding the need for regular intercourse.

The number of cycles in included studies ranged from one to eight.

Cancellation criteria

The most serious adverse effects of ovarian hyperstimulation are multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). These risks can both be reduced by the cancellation of the treatment cycle if excessive follicle stimulation occurs. It is important that fertility trials report the cancellation criteria they applied. Firstly, to ensure that participants were not exposed to a higher risk of multiple pregnancy or OHSS to increase the pregnancy rate and secondly, to reduce the bias introduced by cancellation of treatment in initially randomised groups.

Ten studies described criteria for cancellation of the treatment cycle. Insemination or hCG administration did not take place if the cancellation criteria were met. Five studies used serum-E_2 levels to determine over- or under-stimulation as well as a maximum of dominant follicles (four follicles of a maximum 16 mm diameter). Arcaini 1996 accepted a maximum of six dominant follicles. Four studies did not describe any cancellation criteria.

Outcomes

Nine trials reported live birth, our primary outcome of interest. The other studies reported pregnancy as the main outcome. Pregnancy was confirmed by ultrasound in nine trials. In Guzick 1999 pregnancy was confirmed by two hCG measurements or live birth. Others did not report the method of pregnancy confirmation. The reported pregnancies were mostly clinical. The multiple pregnancy rate was mentioned in 12 trials, miscarriage in 10, ectopic preg-

nancy in 10, and OHSS in nine trials. These events were often reported as total numbers or as post-crossover data and therefore often could not be used in the meta-analysis.

Excluded studies

For the 2015 update 10 studies were excluded (Aanesen 2014; Check 2013; Barros Delgadillo 2008; Barros-Delgadillo 2010; Kabouk 2010; Leanza 2014a; Leanza 2014b; Peeraer 2013; Wadhwa 2013; Xu 2014). Two studies, Custers 2012 and Wordsworth 2011 were found to be further publications from the authors of Steures 2006a and Bhattacharya 2008 respectively, but had no new data relevant to this review. They have been listed as additional references for those included studies.

Four studies were not RCTs (Check 2013; Barros Delgadillo 2008; Leanza 2014a; Leanza 2014b), four did not include a comparison of interest to this review (Barros-Delgadillo 2010; Kabouk 2010; Peeraer 2013; Wadhwa 2013), one was a cohort study (Aanesen 2014) and one was ineligible as it investigated donor sperm (Xu 2014).

For the 2012 review 13 studies were excluded (see 'Characteristics of excluded studies' table).

Six studies clearly did not meet the inclusion criteria. Two studies were found not to be randomised studies (Aboulghar 1993; Serhal 1988). An inadequate method of randomisation was the reason for exclusion of another two trials (Nulsen 1993; Prentice 1995). One study (Tummon 1997) included women with endometriosis only and thus did not focus on unexplained subfertility. Martinez 1990 reported biochemically confirmed pregnancies only and was therefore excluded.

Another seven studies were excluded because the appropriate data needed for the meta-analysis were not obtainable. Ho 1998 did not report separate data for the couples with unexplained subfertility. Six studies (Doyle 1991; Evans 1991; Gregoriou 1995; Kirby 1991; Martinez 1991; Zikopoulos 1993) reported post-crossover per-cycle data only, instead of per randomised woman, and therefore could not be included. We contacted all authors to obtain pre-crossover data.

Studies awaiting classification

There are no studies awaiting classification. However if pre-crossover data of the excluded studies become available we will reconsider inclusion and report the studies in an update of this review.

Risk of bias in included studies

Allocation

In eight of the included studies (Agarwal 2004; Arici 1994; Bhattacharya 2008; Chung 1995; Goverde 2000; Melis 1995; Murdoch 1991; Steures 2006a), the methods used in sequence generation and allocation concealment were considered to be adequate and we, therefore, rated them as being at low risk of bias. In the remaining six trials (Arcaini 1996; Crosignani 1991; Deaton 1990; Guzick 1999; Janko 1998; Karlstrom 1993), the methods used in random sequence generation and allocation concealment were not sufficiently described to make a conclusive judgement, so we rated the risk of bias as unclear.

Blinding

None of the studies reported blinding. In trials comparing IUI with TI blinding is not possible. Trials comparing IUI with or without OH could be blinded. However, the use of subcutaneously administered ovarian hyperstimulation drugs complicates this. We rated all the included studies as unclear risk of bias in this domain as lack of blinding may not have any effect on the outcome measures.

Incomplete outcome data

We used an intention-to-treat (ITT) analysis when possible. In three trials an ITT analysis was not possible (Crosignani 1991; Deaton 1990; Karlstrom 1993) as the trials only reported the number of participants analysed.

In Murdoch 1991 one woman became pregnant spontaneously between treatment cycles. This pregnancy resulted in a live birth and was entered as such in the analysis. Goverde 2000 also reported spontaneous pregnancies that occurred between treatment cycles. Because it was unclear in which group these pregnancies occurred, they could not be used in the ITT analysis.

Six of the 14 included trials clearly mentioned the number of drop outs and the reasons for dropping out (Arici 1994; Deaton 1990; Goverde 2000; Guzick 1999; Melis 1995; Steures 2006a). Murdoch 1991 reported the number of drop outs but did not give any information on reasons for dropping out. Bhattacharya 2008 had a loss to follow-up of less than 1%. The studies with the highest losses to follow-up were Arcaini 1996 (dropout of 20.6%) and Agarwal 2004 (19%). In Agarwal the couples mainly left the study for financial reasons, which resulted in an unevenly distributed dropout rate of 37% in the treatment group as compared to 1% in the control group. The dropout rate usually increased in studies with a longer follow-up period. Because this review included trials with different durations, it was difficult to compare the dropout rates. We rated eight of the included studies as low risk of bias, three as unclear and another three as high risk of bias.

Selective reporting

There is a risk of selective reporting in this review. Live birth data were not reported in five studies (Arcaini 1996; Crosignani 1991; Deaton 1990; Janko 1998; Karlstrom 1993). Adverse events were often not reported per group but as a study total, which could not be included in the analysis. Multiple pregnancy rates were not

reported in two trials (Crosignani 1991; Janko 1998). We rated eight of the included studies as low risk of bias, five as unclear and one as high risk.

Other potential sources of bias

To reduce bias introduced by a crossover study design, we included pre-crossover data only. Three studies used a crossover design (Arici 1994; Crosignani 1991; Deaton 1990). In this design participants were initially randomised to the treatment or control group but then crossed-over to the other group after a certain number of treatment cycles. The duration of these studies varied from two to eight treatment cycles per couple. In two studies (Arici 1994; Crosignani 1991) the participants crossed over after one treatment cycle. In Deaton 1990 participants crossed over after four cycles. We rated eight of the included studies as low risk of bias because baseline demographic characteristics of participants between the two treatment groups were similar. The remaining six studies were assessed as unclear in this domain because there was insufficient information to make a conclusive judgement on the baseline demographic characteristics of participants.

Eleven studies used a parallel design, in which participants stayed in the group to which they were randomised. These trials offered a total of one to six treatment cycles per couple.

Effects of interventions

See: **Summary of findings for the main comparison** IUI compared to TI or expectant management both in natural cycle for unexplained subfertility; **Summary of findings 2** IUI compared to TI or expectant management both in stimulated cycle for unexplained subfertility; **Summary of findings 3** IUI in natural cycle compared to IUI in stimulated cycle for unexplained subfertility; **Summary of findings 4** IUI in stimulated cycle compared to TI or expectant management in natural cycle for unexplained subfertility; **Summary of findings 5** IUI in natural cycle compared to TI or expectant management in stimulated cycle for unexplained subfertility

This section describes the results of the meta-analyses and sensitivity analyses.

Comparison 1. IUI versus TI or expectant management both in a natural cycle

The results from this comparison were all obtained from Bhattacharya 2008. Data for the unexplained subfertility group only were provided by the trial author.

1.1 Live birth rate per couple (all cycles)

Analysis 1.1

One trial compared IUI in a natural cycle with expectant management and showed no evidence of a difference in cumulative live births between the two treatment groups (OR 1.60, 95% CI 0.92 to 2.78; 1 RCT, n = 334; moderate quality evidence). The evidence suggested that if the chance of a live birth using TI was assumed to be 16%, that of IUI would be between 15% and 34%.

1.2 Multiple pregnancy rate per couple

Analysis 1.2

There was no evidence of a difference in multiple pregnancy rate between the two treatment groups (OR 0.50, 95% CI 0.04 to 5.53; 1 RCT, n = 334; moderate quality evidence). The evidence suggested that if the risk of a multiple pregnancy using TI was assumed to be 1%, the risk using IUI would be between 0% and 6%.

1.3 Pregnancy rate per couple (all cycles)

Analysis 1.3

There was no evidence of a difference in pregnancy rates (all cycles) (OR 1.53, 95% CI 0.88 to 2.64; 1 RCT, n = 334; moderate quality evidence). Of the 167 women treated with IUI, 38 became pregnant compared to 27 of the 167 untreated women.

Other adverse events

1.4 Moderate or severe ovarian hyperstimulation syndrome rate per woman

Data on OHSS were not reported.

1.5 Miscarriage rate per couple

Analysis 1.4

There was no evidence of a difference in miscarriage rate between the two treatment groups. Sixteen miscarriages were reported in a total of 334 couples, seven in the IUI group and nine in the TI group (OR 0.77, 95% CI 0.28 to 2.11; 1 RCT, n = 334; moderate quality evidence).

1.6 Ectopic pregnancy rate per couple

Analysis 1.5

There was no evidence of a difference in ectopic pregnancy rate between the two treatment groups. Two ectopic pregnancies were reported in a total of 334 couples and they occurred in the IUI group (OR 5.06, 95% CI 0.24 to 106.21; 1 RCT, n = 334; moderate quality evidence).

Comparison 2. IUI versus TI or expectant management both in stimulated cycles

2.1 Live birth rate per couple (all cycles)

Analysis 2.1

Only two of the six trials included in the analysis reported live birth rates (Chung 1995; Melis 1995). There was no evidence of a difference in live birth in women who underwent IUI compared with the TI group (OR 1.59, 95% CI 0.88 to 2.88, I^2 = 72%; 2 RCTs, n = 208; moderate quality evidence). Statistical heterogeneity was detected (P = 0.06, I^2 = 71.7%) between the two studies. This may be explained by the fact that all participants in Melis 1995 had previously received fertility treatment.

2.2 Multiple pregnancy rate per couple

Analysis 2.2

Four studies reported their multiple pregnancies per treatment arm (Arcaini 1996, Chung 1995,Karlstrom 1993, Melis 1995, with a total of 17 multiple pregnancies in a total of 316 couples. Arcaini 1996, Chung 1995 and Karlstrom 1993 reported one high-order multiple pregnancy each. The studies reported 11 multiple pregnancies in the IUI group and six in the TI group (representing 13.5% of the total number of pregnancies in these studies). Pooling these studies resulted in no evidence of a difference (OR 1.46, 95% CI 0.55 to 3.87, I^2 = 0%; 4 RCTs, n = 316; low quality evidence).

2.3 Pregnancy rate per couple (all cycles)

Analysis 2.3

Six trials reported pregnancy rates per couple. There were 517 women included in this analysis and 149 cumulative pregnancies were reported. The pregnancy rate was higher in the IUI group (OR 1.69, 95% CI 1.14 to 2.53, I^2 = 8%; 7 RCTs, n = 517; low quality evidence) if all cycles were analysed. This suggested that if the chance of a pregnancy with timed intercourse was assumed to be 23%, the chance of a pregnancy in women using IUI would be between 26% and 43%. To check sensitivity to the model assumptions, the random-effects model was used and showed a similar result (OR 1.72, 95% CI 1.11 to 2.65).

If the study by Agarwal 2004 was included in the analysis the results change markedly. The OR becomes 1.25 (95% CI 0.88 to 1.78), crossing the line of no evidence of effect. Including this study also introduced a strong heterogeneity (P = 0.02, I^2 = 60%). This statistical heterogeneity caused by Agarwal 2004 supports our concerns about the validity of this trial, both from a statistical (high probability of bias) and from a clinical point of view. On the other hand, this sensitivity analysis showed the relative weakness of the significant difference we found. Therefore, our results should be interpreted with caution.

We performed a subgroup analysis for the number of treatment cycles. When we analysed the first treatment cycle only, no significant difference in pregnancy rate was seen (OR 1.54, 95% CI 0.82 to 2.88) and no heterogeneity detected (I^2 = 0%). As expected, cumulative pregnancy rates increased with a rising number of treatment cycles per couple. We were unable to determine the optimal number of treatment cycles that a couple should be offered. See Appendix 7 for details.

Other adverse events

2.4 Moderate to severe ovarian hyperstimulation syndrome rate per woman

Analysis 2.4

There was no evidence of a difference in OHSS rate between the two treatment groups (OR 2.75, 95% CI 0.11 to 69.83; 1 RCT, n = 68; low quality evidence).

2.5 Miscarriage rate per couple

Analysis 2.5

Twenty-seven miscarriages were reported in total. Fifteen were reported per treatment arm, nine in the IUI group and six in the TI group. There was no evidence of a difference in miscarriage rate between the two treatment groups (OR 1.66, 95% CI 0.56 to 4.88, I^2 = 0%; 2 RCTs, n = 208; moderate quality evidence).

2.6 Ectopic pregnancy rate per couple

Analysis 2.6

There were not enough data available to analyse the ectopic pregnancy rate. The occurrence of an ectopic pregnancy was reported by one study of 100 women. There was no evidence of a difference in ectopic pregnancy rate between the two treatment groups (OR 3.06, 95% CI 0.12 to 76.95; 1 RCT, n = 100; moderate quality evidence)

Comparison 3. IUI in a natural cycle versus IUI in a stimulated cycle

3.1 Live birth rate per couple (all cycles)

Analysis 3.1

Three trials reported the number of live births per treatment arm (Arici 1994; Goverde 2000; Murdoch 1991). We obtained the live birth data from Guzick 1999 after correspondence with the study authors. A substantial increase in live births was found for women treated with IUI and OH compared to women treated with IUI in natural cycle (OR 0.48, 95% CI 0.29 to 0.82; I^2 = 55%; 4 RCTs, n = 396, moderate quality evidence). The evidence suggested that if

the chance of a live birth in IUI in a stimulated cycle was assumed to be 25%, the chance of a live birth in IUI in a natural cycle would be between 9% and 21%. The random-effects model and analysis without ITT had similar results. See Appendix 8 for details.

3.2 Multiple pregnancy rate per couple

Analysis 3.2

There was no evidence of a difference in multiple pregnancy rate between the two treatment groups (OR 0.33, 95% CI 0.01 to 8.70; 2 RCTs, n = 65; low quality evidence). The evidence suggested that if the risk of multiple pregnancy in IUI in a stimulated cycle is assumed to be 2%, the risk of multiple pregnancy in IUI in a stimulated cycle would be between 0% and 23%.

3.3 Pregnancy rate per couple (all cycles)

Analysis 3.3

There was no evidence of a difference in pregnancy rate between the two treatment groups (OR 0.16, 95% CI 0.01 to 1.77 ;1 RCT, n = 26; moderate quality evidence).

Other adverse events

3.4 Moderate or severe ovarian hyperstimulation syndrome rate per woman

No estimable data were available for this outcome.

3.5 Miscarriage rate per couple

Analysis 3.5

One miscarriage in the OH group was reported by Arici 1994. Guzick 1999 reported a total miscarriage rate of approximately 24% in all couples undergoing IUI treatment. There was no evidence of a difference in miscarriage rate between the two treatment groups (OR 0.19, 95% CI 0.01 to 5.20; 1 RCT, n = 26; low quality evidence).

3.6 Ectopic pregnancy rate per couple

Analysis 3.6

There was no evidence of a difference in ectopic pregnancy rate between the two treatment groups (OR 0.15, 95% CI 0.01 to 3.02; 2 RCTs, n = 250; moderate quality evidence)

Comparison 4. IUI in a stimulated cycle versus TI or expectant management in a natural cycle

The results of this comparison were collected from Deaton 1990 and Steures 2006a. Because Steures 2006a selected couples with an intermediate chance of spontaneous pregnancy only, pooling of both studies was not considered appropriate.

4.1 Live birth rate per couple (all cycles)

Analysis 4.1

This was only reported by Steures 2006a and showed no evidence of a difference in live birth rate (OR 0.82, 95% CI 0.45 to 1.49; 1 RCT, n = 253; moderate quality evidence); The evidence suggested that if the chance of a live birth in TI or expectant management in a natural cycle was assumed to be 24%, the chance of a live birth in IUI in a stimulated cycle would be between 12% and 32%.

4.2 Multiple pregnancy rate per couple

Analysis 4.2

This outcome was investigated by two studies; there was no evidence of a difference in multiple pregnancy rate between the two treatment groups (OR 2.00, 95% CI 0.18 to 22.34; 2 RCTs, n = 304; moderate quality evidence). The evidence suggested that if the risk of a multiple pregnancy in TI or expectant management in natural cycle was assumed to be 1%, the risk of a multiple pregnancy in IUI in stimulated cycle would be between 0% and 13%.

4.3 Pregnancy rate per couple (all cycles)

Analysis 4.3

There was no evidence of a difference in cumulative pregnancy rate between the two treatment groups (OR 1.00, 95% CI 0.59 to 1.67; I^2 = 70%; 2 RCTs, n= 304; moderate quality evidence). To check sensitivity to the model assumptions, the random-effects model was used and a similar result was obtained (OR 1.39, 95% CI 0.37 to 5.23).

Other adverse events

4.4 Moderate or severe ovarian hyperstimulation syndrome rate per woman

One study (Deaton 1990) reported on OHSS in this comparison; no cases of OHSS were present in this study.

4.5 Miscarriage rate per couple

Analysis 4.5

There was no evidence of a difference in miscarriage rate between the two treatment groups (OR 2.28, 95% CI 0.84 to 6.20; 1 RCT, n = 253; moderate quality evidence).

4.6 Ectopic pregnancy rate per couple

Ectopic pregnancies were not reported by any of the studies.

Comparison 5. IUI in a natural cycle versus TI or expectant management in a stimulated cycle

Bhattacharya 2008 studied this comparison with IUI in a natural cycle compared to TI in a clomiphene citrate stimulated cycle.

5.1 Live birth rate per couple (all cycles)

Analysis 5.1

There was evidence of some increase in live births for IUI in a natural cycle when compared to TI in a stimulated cycle (OR 1.95, 95% CI 1.10 to 3.44; 1 RCT, n = 342: moderate quality evidence). The evidence suggested that if the chance of a live birth in TI in a stimulated cycle was assumed to be 13%, the chance of a live birth in IUI in a natural cycle would be between 14% and 34%.

5.2 Multiple pregnancy per couple

Analysis 5.2

There was no evidence of a difference in multiple pregnancy rate between women who received IUI in a natural cycle and those who underwent TI in a stimulated cycle (OR 1.05, 95% CI 0.07 to 16.90; 1 RCT, n = 342; moderate quality evidence). The evidence suggested that if the risk of a multiple pregnancy in TI in a stimulated cycle was assumed to be 1%, the risk of a multiple pregnancy in IUI in a natural cycle would be between 0% and 9%.

5.3 Pregnancy rate per couple (all cycles)

Analysis 5.3

There was evidence of a some difference in cumulative pregnancy rate between the two treatment groups (OR 1.77, 95% CI 1.01 to 3.08; 1 RCT, n = 342; moderate quality evidence).

Other adverse events

5.4 Moderate or severe ovarian hyperstimulation syndrome rate per woman

OHSS was not reported.

5.5 Miscarriage rate per couple

Analysis 5.4

There was no evidence of a difference in miscarriage rate between the two treatment groups (OR 0.91, 95% CI 0.32 to 2.58; 1 RCT, n = 342; moderate quality evidence)

5.6 Ectopic pregnancy

Analysis 5.5

Although two ectopic pregnancies occurred in the IUI group, there was no evidence of a difference in ectopic pregnancy rate between the two treatment groups(OR 5.30, 95% CI 0.25 to 111.26; 1 RCT, n = 342; moderate quality evidence).

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

IUI compared to TI or expectant management both in stimulated cycle for unexplained subfertility

Patient or population: people with unexplained subfertility
Settings:
Intervention: IUI
Comparison: TI both in stimulated cycle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI both in stimulated cycle	IUI				
Live birth rate per couple (all cycles)	255 per 1000	352 per 1000 (231 to 496)	OR 1.59 (0.88 to 2.88)	208 (2 studies)	⊕⊕⊕◯ moderate[1,2]	
Multiple pregnancy rate per couple	43 per 1000	62 per 1000 (24 to 148)	OR 1.46 (0.55 to 3.87)	316 (4 studies)	⊕⊕◯◯ low[2,3]	
Pregnancy rate per couple (all cycles)	234 per 1000	339 per 1000 (257 to 433)	OR 1.69 (1.14 to 2.53)	517 (7 studies)	⊕⊕◯◯ low[1,2,3]	
Ovarian Hyperstimulation Syndrome rate per woman	not estimable		OR 2.75 (0.11 to 69.83)	68 (1 study)	⊕⊕◯◯ low[2,3,4]	
Miscarriage rate per couple	57 per 1000	91 per 1000 (33 to 228)	OR 1.66 (0.56 to 4.88)	208 (2 studies)	⊕⊕⊕◯ moderate[1,2]	
Ectopic pregnancy rate per couple	not estimable		OR 3.06 (0.12 to 76.95)	100 (1 study)	⊕⊕⊕◯ moderate[1,2]	

*The basis for the **assumed risk** is 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; **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] Small sample size
[2] Effect estimate with wide confidence interval
[3] Most domains of risk of bias were assessed as either 'unclear' or 'high risk'
[4] Only one event in one study was reported

IUI in natural cycle compared to IUI in stimulated cycle for unexplained subfertility

Patient or population: people with unexplained subfertility
Settings:
Intervention: IUI in natural cycle
Comparison: IUI in stimulated cycle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IUI in stimulated cycle	IUI in natural cycle				
Live birth rate per couple (all cycles)	**248 per 1000**	**137 per 1000** (87 to 213)	**OR 0.48** (0.29 to 0.82)	396 (4 studies)	⊕⊕⊕◯ **moderate**[1,2]	
Multiple pregnancy rate per couple	**33 per 1000**	**11 per 1000** (0 to 229)	**OR 0.33** (0.01 to 8.7)	65 (2 studies)	⊕⊕◯◯ **low**[1,2]	
Pregnancy rate per couple (all cycles)	**300 per 1000**	**64 per 1000** (4 to 431)	**OR 0.16** (0.01 to 1.77)	26 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Ovarian Hyperstimulation Syndrome rate per woman[5] - not measured			Not estimable[3]	-		
Miscarriage rate per couple	**100 per 1000**	**21 per 1000** (1 to 366)	**OR 0.19** (0.01 to 5.2)	26 (1 study)	⊕⊕◯◯ **low**[1,2]	
Ectopic pregnancy rate per couple	**23 per 1000**	**4 per 1000** (0 to 66)	**OR 0.15** (0.01 to 3.02)	250 (2 studies)	⊕⊕⊕◯ **moderate**[1,2]	

*The basis for the **assumed risk** is 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; **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] Small sample size
[2] Effect estimate with wide confidence interval
[3] No usable data were reported

IUI in stimulated cycle compared to TI or expectant management in natural cycle for unexplained subfertility

Patient or population: people with unexplained subfertility
Settings:
Intervention: IUI in stimulated cycle
Comparison: TI or expectant management in natural cycle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI or expectant management in natural cycle	IUI in stimulated cycle				
Live birth rate per couple (all cycles)	**238 per 1000**	**204 per 1000** (123 to 318)	**OR 0.82** (0.45 to 1.49)	253 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Multiple pregnancy rate per couple	**6 per 1000**	**13 per 1000** (1 to 128)	**OR 2.00** (0.18 to 22.34)	304 (2 studies)	⊕⊕⊕◯ **moderate**[1,2]	
Pregnancy rate per couple (all cycles)	**247 per 1000**	**247 per 1000** (162 to 354)	**OR 1.00** (0.59 to 1.67)	304 (2 studies)	⊕⊕⊕◯ **moderate**[1,2]	
Ovarian Hyperstimulation rate per woman - not measured			Not estimable	-		
Miscarriage rate per couple	**48 per 1000**	**103 per 1000** (41 to 238)	**OR 2.28** (0.84 to 6.2)	253 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Ectopic pregnancy rate per couple - not reported	See comment	See comment	Not estimable	-	See comment	

*The basis for the **assumed risk** is 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; **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] Small sample size
[2] Effect estimate with wide confidence interval

IUI in natural cycle compared to TI or expectant management in stimulated cycle for unexplained subfertility

Patient or population: people with unexplained subfertility
Settings:
Intervention: IUI in natural cycle
Comparison: TI in stimulated cycle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TI in stimulated cycle	IUI in natural cycle				
Live birth rate per couple (all cycles)	**131 per 1000**	**227 per 1000** (142 to 341)	**OR 1.95** (1.1 to 3.44)	342 (1 study)	⊕⊕⊕◯ **moderate**[1]	
Multiple pregnancy rate per couple	**6 per 1000**	**6 per 1000** (0 to 88)	**OR 1.05** (0.07 to 16.9)	342 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Pregnancy rate per couple (all cycles)	**143 per 1000**	**228 per 1000** (144 to 339)	**OR 1.77** (1.01 to 3.08)	342 (1 study)	⊕⊕⊕◯ **moderate**[1]	
Ovarian Hyperstimulation Syndrome rate per woman - not reported			Not estimable	-		
Miscarriage rate per couple	**46 per 1000**	**42 per 1000** (15 to 111)	**OR 0.91** (0.32 to 2.58)	342 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	
Ectopic pregnancy rate per couple	Not estimable		**OR 5.30** (0.25 to 111.3)	342 (1 study)	⊕⊕⊕◯ **moderate**[1,2]	

*The basis for the **assumed risk** is 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; **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] Small sample size
[2] Effect estimate with wide confidence interval

DISCUSSION

Summary of main results

The aim of this review was to analyse the effectiveness of intra-uterine insemination (IUI), with or without ovarian hyperstimulation (OH), by systematically evaluating the best available evidence. Because randomised controlled trials (RCTs) are still considered to provide the best assessment of the effectiveness of treatments (Hughes 2003; Johnson 2003), we included only truly randomised trials in this review. The individual trials were contradictory and often lacked sufficient power to draw firm conclusions. In spite of these shortcomings, and also some clinical heterogeneity, we were able to pool their results and draw some conclusions.

Meta-analyses from 14 RCTs showed no conclusive evidence of a difference in live birth rates, multiple pregnancy rate and pregnancy rates for most of the comparisons.

The comparison IUI in a natural cycle with IUI in a hyperstimulated cycle revealed a more than two-fold increase in live birth rate in women treated with OH (OR 0.48, 95% CI 0.29 to 0.82). This result could be considered robust. The analysis comprised 396 couples and included high quality trials. A study with 1500 couples showing no treatment effect is needed to reduce the lower confidence limit to one. If we use these data to calculate the numbers needed to treat, with an assumed control risk of 14%, we would find that approximately nine couples need to be treated with IUI and OH for approximately four cycles to result in one additional live birth compared to the control group. These data should be interpreted with caution because the impact of OH on multiple pregnancies and other adverse effects could not be answered by this review.

All the comparisons reported data on multiple pregnancy rate and there was no evidence of a difference in this outcome between the treatment groups in all the comparisons. The quality of the evidence ranged from low to moderate. The four studies in our analysis comparing IUI versus IUI with OH all reported multiple pregnancy rates, but only two reported the rates for those with unexplained subfertility. A valid analysis could, therefore, not be performed. All studies using gonadotropins as the stimulation method reported cancellation criteria. However, the highest multiple pregnancy rate was reported by Goverde 2000 (29% in the OH group compared to 4% in the natural cycle group) despite the use of strict cancellation criteria. It should be noted that 95% of the participants included in this comparison received gonadotropin treatment, which could result in higher multiple pregnancy rates compared to CC treatment (Ombelet 2005).

The comparison of IUI versus TI, or expectant management both in stimulated cycles, showed an odds ratio for pregnancy rate per couple of 1.69 (95% CI 1.14 to 2.53) in favour of IUI. It seems appropriate, therefore, to combine IUI and OH. However, the following points need to be taken into account. Firstly, there was insufficient evidence to conclude that IUI in combination with OH improved live birth rates when compared with TI in stimulated cycles. This might be the result of insufficient power, a total of 208 couples in two trials only were included (Chung 1995; Melis 1995), or the fact that Melis included a population with a poor prognosis (all participants had previously had unsuccessful treatment with IUI and OH). Because this study makes up half of the live birth analysis it could mask the promising results from Chung 1995.

Secondly, the results varied according to whether or not one study (Agarwal 2004) was included. In the meta-analysis six studies were included, in which a total of 517 women were randomised to either treatment with OH alone or with IUI and OH. The inclusion of Agarwal 2004 (n = 140), which had been excluded due to a high risk of bias caused by losses to follow-up, in a sensitivity analysis resulted in no evidence of effect. The sensitivity of our results after inclusion of a relatively small study emphasises the fragility of our analysis. However, the trial by Agarwal 2004 showed an unexpectedly high pregnancy rate in the control group compared to the treatment group (29% higher). Because there is no reason to believe that timed intercourse would increase the pregnancy rate compared to IUI, and because of the high dropout rate, this study should not be considered representative. It would be more realistic to assume that there is no difference between IUI and TI. Our calculations indicate that it would take a trial of approximately 400 participants showing no difference between IUI and TI to reduce the lower confidence limit to one.

Thirdly, the pooled studies were clinically heterogeneous. There was, however, no evidence of statistically significant heterogeneity. This suggests that the different factors had little effect on the overall conclusions; the included studies differed markedly in terms of treatment methods and quality. The pooled studies also used different treatment protocols. The type of OH drug and dose, the treatment duration and cancellation criteria could have influenced the outcomes. For example, the highest pregnancy rate per couple was found in the study by Arcaini 1996. A reason for this could be that this study used the most aggressive stimulation method, accepted a maximum of six dominant follicles and treated couples for up to five cycles. There were also variations in the patient population among the included studies that could have influenced the outcome, such as previous treatment and the inclusion of women with endometriosis. On the other hand, our results were not sensitive to the inclusion or exclusion of trials on the basis of the above-mentioned parameters.

Fourthly, the clinical relevance of the result is questionable. The analysis shows evidence of a significant increase in pregnancy rate for cumulative cycles only. What does it clinically mean if the odds to become pregnant for a woman undergoing IUI treatment are 1.68 times higher than for a woman treated with OH alone, if the treatment duration could vary from one to up to five cycles? Stratification for treatment duration gave no evidence of an increase in pregnancy rate if only first cycle data were analysed. This implies that it takes more than one treatment cycle to signif-

icantly improve the couple's chances. However, it was not possible to give any clarity about the optimal number of treatment cycles in this review. A risk difference was calculated for the analysis of one to three treatment cycles, to extract the numbers needed to treat. Based on these results, approximately 13 couples need to be treated with one to three cycles of IUI and OH to result in one additional pregnancy.

Furthermore, the clinical relevance of the results is also dependent on the baseline fecundity of a couple. Unfortunately there were not enough data available in this meta-analysis to perform subgroup analyses for prognostic factors, such as age and duration of subfertility. Overall, we can conclude that an odds ratio of 1.68 for treatment over one to five cycles for couples with different prognoses and baseline fecundity is not specific enough to be helpful in a clinical setting.

Finally, the impact of IUI on other adverse events, such as ovarian hyperstimulation syndrome, miscarriage and ectopic pregnancy could not be adequately estimated due to a lack of information. Adverse events were often not mentioned, or mentioned per group instead of per treatment modality. The studies mentioning 'no events' were included in the meta-analyses, which might result in underestimation of the adverse events. On the other hand, these adverse events are mostly accredited to OH and not to IUI. It seems therefore unlikely that any significant difference in adverse events would be found when OH with TI is compared to OH with IUI.

Overall completeness and applicability of evidence

To adequately address the question whether IUI with or without OH is an effective treatment for couples with unexplained subfertility, our aim was to analyse the following five treatment comparisons: 1. IUI versus TI or expectant management, both in a natural cycle; 2. IUI versus TI or expectant management, both in a stimulated cycle; 3. IUI in a natural cycle versus IUI in a stimulated cycle; 4. IUI in a stimulated cycle versus TI or expectant management in a natural cycle; and 5. IUI in a natural cycle versus TI or expectant management in a stimulated cycle. Most of the comparisons were investigated in single trials, thereby making it difficult to combine data in meta-analyses. Where data were pooled in meta-analyses, the overall effect estimates usually had wide confidence intervals due to small sample size or inadequate power of the trials which contributed data to the pooled estimates. Furthermore, we were not able to assess all desired outcomes for each comparison. There were not enough data available to retrieve adequate live birth rates, and there were even fewer data available for the adverse effects of each treatment modality. Important prognostic factors such as age, duration of subfertility and previous treatment were poorly reported, making it impossible to perform subgroup analyses.

The four studies in our analysis comparing IUI versus IUI with OH all reported multiple pregnancy rates, but only two reported the rates for those with unexplained subfertility. A valid analysis could not be performed. All studies using gonadotropins as the stimulation method reported cancellation criteria. However, the highest multiple pregnancy rate was reported by Goverde 2000 (29% in the OH group compared to 4% in the natural cycle group) despite the use of strict cancellation criteria. It should be noted that 95% of the participants included in this comparison received gonadotropin treatment, which could result in higher multiple pregnancy rates compared to CC treatment..

Quality of the evidence

The overall quality of the included trials was suboptimal. This was mainly because of imprecision, with effect estimates of most of the GRADE-specific outcomes having wide confidence intervals.

The quality of fertility trials has been criticised repeatedly. One of the areas of particular concern is what statisticians refer to as the 'unit of analysis' error (Vail 2003). It is methodologically incorrect to report data per cycle when it is women or couples who are randomised because many of the women will have undergone more than one treatment cycle (Dias 2008; Johnson 2003; Vail 2003). Yet pregnancy rate per cycle is a commonly reported outcome in fertility trials and reviews.

Another methodological difficulty in fertility trials is the use of studies with a crossover design. There have been many discussions about whether a crossover design is appropriate for fertility trials, mainly because participants drop out after treatment success, which results in a selected patient population post-crossover. For this reason, it is said that the crossover design has no place in infertility trials (Daya 1993). A crossover 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 under debate (Cohlen 1998; McDonnell 2004; Vail 2003). In this systematic review we focused on live birth rates or pregnancy rates per couple. The couple being the denominator, post-crossover data could not be included because then couples would have received both treatment modalities and results per couple could not be extracted.

The more recent studies adopted expectant management as a control treatment for IUI instead of timed intercourse (Bhattacharya 2008; Steures 2006a). Because timing of intercourse (TI) interferes with the natural coital habits of a couple, expectant management has been proposed as the more appropriate comparison treatment for IUI (Wilcox 1995). A recent meta-analysis however shows no significant difference in pregnancy rate between studies comparing IUI versus TI and studies with IUI versus expectant management (Snick 2008). Whether it is appropriate to pool studies including TI and expectant management in a meta-analysis remains unclear. The data of Bhattacharya 2008 and Steures 2006a were not, however, pooled with data of trials applying TI because

these trials comprised comparisons that were not subject to many other trials.

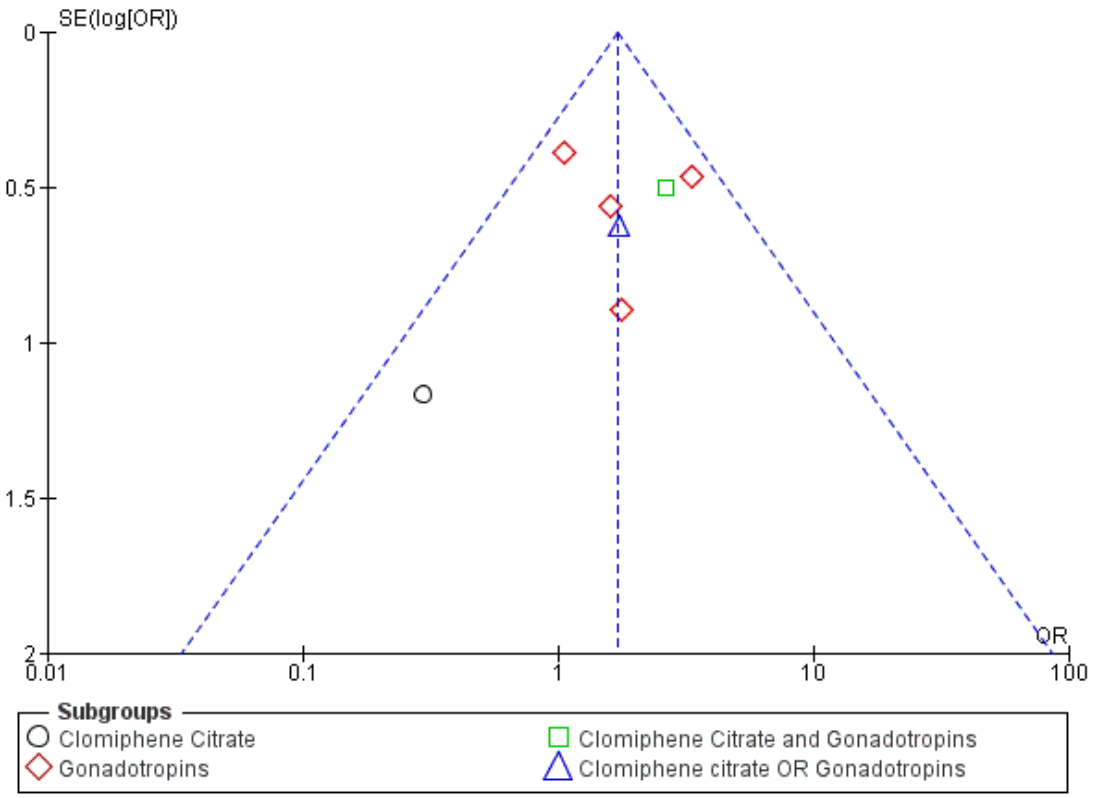
It is generally agreed that the aim of fertility treatment should be to achieve a live birth instead of inducing a pregnancy (Land 2003). Healy and others go even further by suggesting that the 'birth emphasizing a successful singleton at term' (BESST) outcome should be the standard measure of success for fertility trials (Daya 2003; Fauser 2005; Healy 2004; Min 2004). We have tried to focus on live birth as the main outcome of interest in this analysis. Unfortunately, live birth was reported by only eight of the 14 included studies. We decided to use live birth data whenever possible for the analyses. If there were not enough live birth data available we used the more often reported pregnancy rates for the main analyses.

Potential biases in the review process

To prevent selection bias, the included studies were independently selected and data extracted by two authors (Ayeleke and Verhulst for the 2015 update). Disagreements were resolved by discussion, keeping the protocol as our guideline to reduce bias. A statistician (Mr Vail) was consulted for the data extraction of complicated crossover trials. We have extracted and calculated the events per randomised couple for this meta-analysis, which resulted in the exclusion of six studies reporting only post-crossover or per-cycle data. As a consequence, the analysis is statistically less biased although a selection bias may have occurred.

A funnel plot was done only for the comparison with the most studies (IUI versus TI both in a stimulated cycle) (Figure 4). The funnel plot is reasonably symmetrical, suggesting that a publication bias is unlikely.

Figure 4. Funnel plot of comparison: 2 IUI versus TI both in stimulated cycle, outcome: 2.3 Pregnancy rate per couple (all cycles).



It should be noted that Asian countries are underrepresented in the included trials. It is not known whether Asian IUI trials have not been done or could not be found with our search.

Agreements and disagreements with other studies or reviews

Previous review articles and meta-analyses by, for example, Aboulghar 2003, Balasch 2004, Cohlen 2005, Costello 2004, Hughes 1997 and Zeyneloglu 1998 have all assessed the effectiveness of IUI and ovarian hyperstimulation. They have, however, all calculated pregnancy rates per cycle, which makes it difficult to compare with our per-couple data. Per-cycle data produce biased results that may exaggerate treatment results (Dias 2008). This could explain why the pregnancy rates found in our meta-analysis are lower than those generally reported by the above-mentioned authors.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review did not find conclusive evidence of a difference in live birth or multiple pregnancy in most of the comparisons for couples with unexplained subfertility treated with IUI when compared with timed intercourse (TI), both with and without ovarian hyperstimulation (OH). There were insufficient studies to allow for pooling of data on most of the important outcome measures for each of the comparison.

Implications for research

There is a need to investigate whether the risk of multiple pregnancy and other adverse events can be reduced to acceptable levels while still keeping acceptable live birth rates. Therefore a large randomised controlled trial is needed comparing IUI in natural cycles with low dose stimulated IUI.

Future trials are encouraged to report detailed live birth data (singleton, term) and adverse events such as multiple pregnancies, miscarriage, ectopic pregnancies and ovarian hyperstimulation syndrome.

ACKNOWLEDGEMENTS

We wish to thank all colleagues of Cochrane Gynaecology and Fertility for their help. Special thanks to Cindy Farquhar, Jane Marjoribanks, Anne Lethaby, Helen Nagels and statistician Andy Vail for all their advice and support.

Thanks are also expressed to all authors for their responses and additional information on their trials.

We acknowledge the contribution of Professor Maas Jan Heineman to previous versions of this review.

REFERENCES

References to studies included in this review

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

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

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

Bhattacharya 2008 *{published data only}*
* Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C, Harrold A, et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. *BMJ* 2008;**7**(337):a716. Wordsworth SA, Buchanan JA, Mollison JA, Harrild KA, Robertson LA, Tay C, et al. Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: Are they cost-effective?. *Human Reproduction* 2011;**26**(2):369–75.

Chung 1995 *{published data only}*
Chung CC, Fleming R, Jamieson ME, Yates RWS, Coutts JRT. Randomized comparison of ovulation induction with and without intrauterine insemination in the treatment of unexplained infertility. *Human Reproduction* 1995;**10**: 3139–41.

Crosignani 1991 *{published data only}*
Crosignani PG, Walters DE, Soliani A. The ESHRE multicentre trial on the treatment of unexplained infertility: A preliminary report (Centre 13: Willemsen, Nijmegen).

Human Reproduction 1991;**6**(7):953–8.
Crosignani PG, Walters DE, Soliani A. The ESHRE multicentre trial on the treatment of unexplained infertility: A preliminary report (Centre 16: Pellicer, Valencia). *Human Reproduction* 1991;**6**(7):953–8.
Crosignani PG, Walters DE, Soliani A. The ESHRE multicentre trial on the treatment of unexplained infertility: A preliminary report (Centre 19: Martinez, Amsterdam). *Human Reproduction* 1991;**6**(7):953–8.
* Crosignani PG, Walters DE, Soliani A. The ESHRE multicentre trial on the treatment of unexplained infertility: A preliminary report (data from centre 10: Hedon , Montpellier). *Human Reproduction* 1991;**6**(7):953–8.

Deaton 1990 ***{published data only}***
Deaton J, Gibson M, Blackmer K, Nakajima S, Badger G, Brumsted J. A randomized controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility on surgically corrected endometriosis. *Fertility and Sterility* 1990;**54**(6):1083–8.

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

Guzick 1999 ***{published data only}***
Guzick D, Carson S, Coutifaris C, Overstreet J, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. *New England Journal of Medicine* 1999;**340**(3):177–83.

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

Karlstrom 1993 ***{published data only}***
Karlstrom P, Bergh T, Lundkvist O. A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate. *Fertility and Sterility* 1993;**59**(3):554–9.

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

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

Steures 2006a ***{published data only}***
Custers IM, Van Rumste MME, Van Der Steeg JW, Van Wely MA, Hompes PGA, Bossuyt P, et al. Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. *Human Reproduction* 2012;**27**(2):444–50.
* Steures P, Van der Steeg JW, Hompes PG, Habbema JD, Eijkemans MJ, Broekmans FJ, et al. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. *Lancet* 2006;**368**(9531):216–2.

References to studies excluded from this review

Aanesen 2014 ***{published data only}***
Aanesen A, Westerbotn M. Prospective study of a Swedish infertile cohort 2005-08: Population characteristics, treatments and pregnancy rates. *Family Practice.* 2014;**31**(3):290–297.

Aboulghar 1993 ***{published data only}***
Aboulghar MA, Mansour RT, Serour GI, Amin Y, Abbas AM, Salah IM. Ovarian superstimulation and intrauterine insemination for the treatment of unexplained infertility. *Fertility and Sterility* 1993;**60**(2):303–6.

Barros Delgadillo 2008 ***{published data only}***
Barros Delgadillo JC, Martinez Barrios E, Moreno Aburto C, Godines Enriquez MS, Manzur Navarrete F, Sanchez Solis V, et al. Intrauterine insemination versus programmed intercourse in cycles of controlled ovaric hyperstimulation. *Ginecologia y Obstetricia de Mexico* 2008;**76**(1):18–31.

Barros-Delgadillo 2010 ***{published data only}***
Barros-Delgadillo JC, Trejo-Castaneda H, E-Ormsby C, Gavino-Gavino F. Differing response to GnRH antagonists in cycles of ovarian hyperstimulation plus intrauterine insemination. *Ginecologia y Obstetricia de Mexico* 2010;**78**(1):15–28.

Check 2013 ***{published data only}***
Check JH, Liss J, Bollendorf A. Intrauterine insemination (IUI) does not improve pregnancy rates in infertile couples where semen parameters are normal and postcoital tests are adequate. *Clinical and Experimental Obstetrics and Gynecology* 2013;**40**(1):33–34.

Doyle 1991 ***{published data only}***
Doyle M, DeCherney A. The value of empiric intrauterine insemination (IUI) with superovulation: a prospective-randomised clinical trial. *Fertility and Sterility* 1991;**56**:S34.

Evans 1991 ***{published data only}***
Evans J, Wells C, Gregory L, Walker S. A comparison of intrauterine insemination- intraperitoneal insemination and natural intercourse in superovulated women. *Fertility and Sterility* 1991;**56**(6):1183–7.

Gregoriou 1995 ***{published data only}***
Gregoriou O, Vitoratos N, Papadias C, Konidaris S, Gargaropoulos A, Louridas C. Controlled ovarian

hyperstimulation with or without intrauterine insemination for the treatment of unexplained infertility. *International Journal of Gynaecology and Obstetrics* 1995;**48**:55–9.

Ho 1998 ***{published data only}***
Ho P, Yeung W, So W, Lau E. A randomised trial comparing the efficacy of ovarian stimulation and intrauterine insemination versus ovarian stimulation alone in the treatment of male infertility and unexplained infertility. *British Journal of Obstetrics and Gynaecology* 1998;**105**(suppl 17):43.

Kabouk 2010 ***{published data only}***
Kabouk GB, Donadio NF, Dzik A, Freitas GC, Justen R, Cavagna M. A prospective randomized study comparing clomiphene citrate supplemented with recombinant FSH or low-dose hCG in ovarian stimulation for intrauterine insemination. *Fertility and sterility* 2010;**94 suppl 1**(4): S160 Abstract no. P-231.

Kirby 1991 ***{published data only}***
Kirby C, Flaherty S, Godfrey B, Warnes G, Matthews C. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse. *Fertility and Sterility* 1991;**56**(1):102–7.

Leanza 2014a ***{published data only}***
Leanza V, Coco L, Grasso F, Leanza G, Zarbo G, Palumbo M, et al. Ovulation induction with clomiphene citrate for infertile couple. *Minerva Ginecologica* 2014;**66**(3):309–12.

Leanza 2014b ***{published data only}***
Leanza V, Coco L, Grasso F, Leanza G, Zarbo G, Palumbo M, et al. Unexplained infertility and ovulatory induction with menopausal gonadotropins. *Minerva Ginecologica* 2014;**66**(3):303–7.

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

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

Nulsen 1990 ***{published data only}***
Randomized prospective trial of pergonal (HMG) superovulation with intrauterine insemination (IUI) versus IUI alone. Nulsen JC, Dumez S, Metzger DA. *Fertility and Sterility* 1990;**54**:S57.

Nulsen 1993 ***{published data only (unpublished sought but not used)}***
Nulsen JC, Walsh S, Dumez S, Metzger DA. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. *Obstetrics and Gynecology* 1993;**82**(5):780–6.

Peeraer 2013 ***{published data only}***
Peeraer KA, Debrock S, De Loecker P, Laenen A, Welkenhuyzen M, Spiessens C, et al. Effect of controlled ovarian stimulation with low dose human menopausal gonadotrophin or clomiphene on reproductive outcome after intrauterine insemination: a prospective, multicenter randomized trial. *Human Reproduction* 2013;**28 suppl 1**: i71-i73 O-172.

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

Serhal 1988 ***{published data only (unpublished sought but not used)}***
Serhal PF, Katz M, Little V, Woronowski H. Unexplained infertility - the value of Pergonal superovulation combined with intrauterine insemination. *Fertility and Sterility* 1988; **49**(4):602–6.

Tummon 1997 ***{published data only}***
Tummon IS, Asher LJ, Martin JS, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. *Fertility and Sterility* 1997;**68**(1):8–12.

Wadhwa 2013 ***{published data only}***
Wadhwa LA, Khanna RA, Gupta TA, Gupta SA, Arora SA, Nandwani S. Evaluation of role of GnRH antagonist in intrauterine insemination (IUI) cycles with mild ovarian hyperstimulation (MOH). *Fertility and Sterility* 2013;**100 Suppl**(3):S17–S18.

Xu 2014 ***{published data only}***
Xu BF, Wang GY, Fan WM, Chen Q, Zhang AJ. Which is the best protocol of ovarian stimulation prior to artificial insemination by donor. *Journal of Reproduction and Contraception* 2014;**25**(1):41–8.

Zikopoulos 1993 ***{published data only}***
Zikopoulos K, West C, Thong P, Kacser E, Morrison J, Wu F. Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility. *Human Reproduction* 1993;**8**(4):563–7.

Additional references

Aboulghar 2003
Aboulghar MA, Mansour RT, Serour GI, Al-Inany HG. Diagnosis and management of unexplained infertility: an update. *Archives of Gynecology and Obstetrics* 2003;**267**(4): 177–88.

Balasch 2004
Balasch J. Gonadotrophin ovarian stimulation and intrauterine insemination for unexplained infertility. *Reproductive Biomedicine online* 2004;**9**(6):664–72.

Bensdorp 2015
Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM, Koks CA, Oosterhuis GJ, Hoek A, et al. Prevention of

multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. *BMJ* 2015;**9**(350):g7771.

Besselink 2008
Besselink DE, Farquhar C, Kremer JAM, Marjoribanks J, O'Brien PA. Cervical insemination versus intra-uterine insemination of donor sperm for subfertility. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD000317.pub3]

Cantineau 2007
Cantineau AE, Cohlen BJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005356.pub2]

Cohlen 1998
Cohlen BJ, te Velde ER, Looman CW, Eijckemans R, Habbema JD. Crossover or parallel design in infertility trials? The discussion continues. *Fertility and Sterility* 1998;**70**(1):40–5.

Cohlen 2005
Cohlen B, Cantineau A, D'Hooghe T, Te Velde E. Multiple pregnancy after assisted reproduction. *Lancet* 2005;**366**(9484):452–3.

Costello 2004
Costello MF. Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2004;**44**(2):93–102.

Daya 1993
Daya S. Is there place for the crossover design in infertility trials?. *Fertility and Sterility* 1993;**59**(1):6–7.

Daya 2003
Daya S. Pitfalls in the design and analysis of efficacy trials in subfertility. *Human Reproduction* 2003;**18**(5):1005–9.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Dias 2008
Dias S, McNamee R, Vail A. Bias in frequently reported analyses of subfertility trials. *Statistics in Medicine* 2008;**27**(27):5605–19.

Dickey 2005
Dickey RP. Risk factors for high-order multiple pregnancy and multiple birth after controlled ovarian hyperstimulation: results of 4,062 intrauterine insemination cycles. *Fertility and Sterility* 2005;**83**(3):671–83.

ESHRE 2006
Andersen AN, Gianaroli L, Felberbaum R, de Mouzon J, Nygren KG. Assisted reproductive technology in Europe, 2002. Results generated from European registers by ESHRE. *Human Reproduction* 2006;**21**(7):1680–97.

Fauser 2005
Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. *Lancet* 2005;**365**(9473):1807–16.

Gleicher 2000
Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *New England Journal of Medicine* 2000;**343**(1):2–7.

Goverde 2005
Goverde AJ, Lambalk CB, McDonnell J, Schats R, Homburg R, Vermeiden JP. Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: effects on pregnancy and multiple pregnancy rates. *Human Reproduction* 2005;**20**(11):3141–6.

GRADEpro GDT 2015 [Computer program]
McMaster University (developed by Evidence Prime, Inc) available from www.gradepro.org. GRADEpro Guideline Development Tool. McMaster University (developed by Evidence Prime, Inc) available from www.gradepro.org, 2015.

Guzick 1998
Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, et al. Efficacy of treatment for unexplained infertility. *Fertility and Sterility* 1998;**70**(2):207–13.

Healy 2004
Healy D. Damaged babies from assisted reproductive technologies: focus on the BESST (birth emphasizing a successful singleton at term) outcome. *Fertility and Sterility* 2004;**81**(3):512–3.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hughes 1997
Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. *Human Reproduction* 1997;**12**(9):1865–72.

Hughes 2003
Hughes EG. Stimulated intra-uterine insemination is not a natural choice for the treatment of unexplained

subfertility.'Effective treatment' or 'not a natural choice'?. *Human Reproduction* 2003;**18**(5):912–14.

Johnson 2003
Johnson NP, Proctor M, Farquhar CM. Gaps in the evidence for fertility treatment - an analysis of the Cochrane Menstrual Disorders and Subfertility Group database. *Human Reproduction* 2003;**18**(5):947–54.

Kerin 1984
Kerin JFP, Peek J, Warnes GM, Kirby C, Jeffrey R, Matthews CD. Improved conception rate after intrauterine insemination of washed spermatozoa from men with poor quality semen. *Lancet* 1984;**1**(8376):533–5.

Khan 1996
Khan KS, Daya S, Collins JA, Walter SD. Empirical evidence of bias in infertility research: overestimation of treatment effect in crossover trials using pregnancy as the outcome measure. *Fertility and Sterility* 1996;**65**(5): 939–45.

Land 2003
Land JA, Evers JL. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. *Human Reproduction* 2003;**18**(2):455–7.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Liberati 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**:e1000100.

McDonnell 2004
McDonnell J, Goverde AJ, Vermeiden JP. The place of the crossover design in infertility trials: a maximum likelihood approach. *Human Reproduction* 2004;**19**(11):2537–44.

Min 2004
Min JK, Breheny SA, MacLachlan V, Healy DL. What is the most relevant standard of success in assisted reproduction? The singleton, term gestation, live birth rate per cycle initiated: the BESST endpoint for assisted reproduction. *Human Reproduction* 2004;**19**(1):3–7.

Nan 1994
Nan PM, Cohlen BJ, Te Velde ER, Van Kooij RJ, Eimers J, Van Zonneveld O, Habbema JDF. Intra-uterine insemination or timed intercourse after ovarian stimulation for male subfertility? A controlled study. *Human Reproduction* 1994;**9**(11):2022–6.

NICE 2013
NICE (National Institute for Health and Care Excellence). Assessment and treatment for people with fertility problems. NICE clinical guidance February 2013, issue 156:5. [guidance.nice.org.uk/cg156]

Norman 2000
Norman GR, Daya S. The alternating-sequence design (or multiple-period crossover) trial for evaluating treatment efficacy in infertility. *Fertility and Sterility* 2000;**74**(2): 319–24.

Ombelet 2005
Ombelet W, De Sutter P, Van der Elst J, Martens G. Multiple gestation and infertility treatment: registration, reflection and reaction - the Belgian project. *Human Reproduction Update* 2005;**11**(1):3–14.

Ragni 2006
Ragni G, Caliari I, Nicolosi AE, Arnoldi M, Somigliana E, Crosignani PG. Preventing high-order multiple pregnancies during controlled ovarian hyperstimulation and intrauterine insemination: 3 years' experience using low-dose recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonists. *Fertility and Sterility* 2006;**85**(3):619–24.

RCOG 1998
RCOG. The management of infertility in secondary care - evidence based guidelines No. 3. RCOG Press, London. London.

Ripps 1994
Ripps BA, Minhas BS, Carson SA, Buster JE. Intrauterine insemination in fertile women delivers larger numbers of sperm to the peritoneal fluid than intracervical insemination. *Fertility and Sterility* 1994;**61**(2):398–400.

Rumste 2006
Van Rumste MM, Den Hartog JE, Dumoulin JC, Evers JL, Land JA. Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies?. *Human reproduction* 2006;**21**(3):701–4.

Ryan 2004
Ryan GL, Zhang SH, Dokras A, Syrop CH, Van Voorhis BJ. The desire of infertile patients for multiple births. *Fertility and Sterility* 2004;**81**(3):500–4.

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Snick 2008
Snick HK, Collins JA, Evers JL. What is the most valid comparison treatment in trials of intrauterine insemination, timed or uninfluenced intercourse? A systematic review and meta-analysis of indirect evidence. *Human Reproduction* 2008;**23**(10):2239–45.

Sterne 2011
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews*

of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Steures 2006b
Steures P, Van der Steeg JW, Hompes PG, Van der Veen F, Mol BW. Results of intrauterine insemination in the Netherlands [Resultaten van intra–uteriene inseminatie in Nederland]. *Nederlands Tijdschrift der Geneeskunde* 2006; **150**(20):1127–33.

Stewart 2003
Stewart JA. Stimulated intra-uterine insemination is not a natural choice for the treatment of unexplained subfertility. Should the guidelines be changed?. *Human Reproduction* 2003;**18**(5):903–7.

Te Velde 1999
Te Velde ER, Cohlen BJ. The management of infertility. *New England Journal of Medicine* 1999;**340**(3):224–6.

Tur 2005
Tur R, Barri PN, Coroleu B, Buxaderas R, Parera N, Balasch J. Use of a prediction model for high-order multiple implantation after ovarian stimulation with gonadotropins. *Fertility and Sterility* 2005;**83**(1):116–21.

Vail 2003
Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials. *Human Reproduction* 2003;**18**(5):1000–4.

Wilcox 1995
Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *New England Journal of Medicine* 1995;**333** (23):1517–21.

Zeyneloglu 1998
Zeyneloglu HB, Arici A, Olive DL, Duleba AJ. Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis. *Fertility and Sterility* 1998;**69**(3):486–91.

References to other published versions of this review

Veltman-Verhulst 2012
Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD001838.pub4]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Agarwal 2004

Methods	Trial design: parallel Single centre Randomisation: random number table Allocation concealment: sealed opaque envelopes Nr of Pt randomised: IUI + OH 70; TI + OH 70 Nr of withdrawals: IUI + OH 26 (37%); TI + OH 1 (total 19%)
Participants	Couples with unexplained subfertility Age: IUI + OH 29.52 years (± 3.65); TI + OH 28.83 years (± 4.76) Duration of subfertility: IUI + OH 4.91 years (± 2.72); TI + OH 4.93 years (± 3.27) Basic fertility work up normal, semen normal according to WHO 1987 Previous treatment: no
Interventions	Comparison: IUI + OH versus TI + OH Stimulation method: 50 mg to 150 mg CC/day, day 3 to day 7 Ovulation: 10,000 IU hCG when not more than 4 follicles of > 16 mm were present Timing of IUI and TI: 36 hr to 40 hr after HCG Duration of treatment: 6 cycles max
Outcomes	Live birth and PR per couple and per cycle Miscarriage rate Ectopic PR Multiple pregnancies Pregnancy confirmed by USS showing gestational sac
Notes	ITT analysis: possible Author provided additional information Unbalanced groups: dropouts 37% in IUI group, 1% in TI group

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	Adequate; sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest

Agarwal 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	There was an unequal dropout in the treatment group due to financial reasons
Selective reporting (reporting bias)	Unclear risk	Reported on live birth, however authors provided additional information on ongoing pregnancies and twin pregnancies resulting in different data used for meta-analysis
Other bias	Low risk	Baseline demographic characteristics similar between the two groups

Arcaini 1996

Methods	Trial design: parallel Single centre Randomisation: method unclear Allocation concealment: unclear Nr of Pt randomised: IUI + OH 36; TI + OH 32 Nr of withdrawals: 14 (20.6%)
Participants	Couples with unexplained subfertility Age: IUI + OH 34.6 years (± 4.9); TI + OH 33.4 years (± 4.7) Duration of subfertility: IUI + OH 4.2 years (± 1.6); TI + OH 3.9 years (± 2.3) Basic fertility work up normal, semen normal, not further specified Previous treatment: not stated
Interventions	Comparison: IUI + OH versus TI + OH Stimulation method: 100 mg CC/day, day 3 to day 7 and 1 to 3 ampoule hMG/day Ovulation: 10,000 IU hCG when 2 to 6 follicles of > 17 mm were present Timing IUI or TI: 24 hr and 48 hr after hCG Duration of treatment: 5 cycles max
Outcomes	PR per couple Miscarriage rate Ectopic PR Multiple pregnancies OHSS Pregnancy confirmed by USS
Notes	ITT analysis: yes

Risk of bias

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

Arcaini 1996 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 16 cancelled treatment cycles is described and analysed according to intention to treat. People who dropped out are clearly stated in a table
Selective reporting (reporting bias)	Unclear risk	Did not report on live birth, however, did not intend to report on live birth
Other bias	Low risk	Nothing detected

Arici 1994

Methods	Trial design: crossover (after 1 cycle) Single centre Randomisation: computer-generated random number table Allocation concealment: computer system utilising locked files Nr of Pt randomised: 26 Nr of withdrawals: not clear
Participants	Couples with unexplained subfertility and couples with male factor subfertility Age: mean 33 yrs (range 24 yrs to 41 yrs) Duration of subfertility: mean 3.5 yrs (range 1 yr to 15 yrs) Unexplained subfertility: basic fertility work up normal, semen normal according to WHO 1987 criteria Previous treatment: no
Interventions	Comparison: IUI + NC versus IUI + OH Stimulation method: 50 mg CC/day, day 5 to day 9 Timing: Natural cycle: urinary LH test, IUI on day of LH peak and the next day Stimulated cycle: 10,000 IU hCG when at least 1 follicle of 18 mm was present; IUI 32 hr after hCG No cancellation criteria were given Duration of treatment: 4 cycles max
Outcomes	Live birth and PR per couple PR per 1st cycle PR per cycle

Arici 1994 (*Continued*)

	Miscarriage rate Ectopic PR Multiple pregnancies Pregnancy confirmed by USS showing gestational sac
Notes	ITT analysis: yes Author provided additional information 5 Pt with treated minimal endometriosis were included as unexplained subfertility

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Adequate; computer system utilising locked files
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	Author gave additional information on dropout rates of the couples with unexplained subfertility. Of the 26 women with unexplained subfertility, dropout occurred after one treatment cycle. Post-crossover data are not included in the meta-analysis
Selective reporting (reporting bias)	Low risk	Live birth data were obtained from the author
Other bias	Unclear risk	No sufficient information reported on baseline demographic characteristics

Bhattacharya 2008

Methods	Trial design: parallel Multi centre (four teaching hospitals, one general hospital, Scotland) Randomisation: computer-generated randomisation schedule Allocation concealment: central telephone system Nr of Pt randomised: 509 with unexplained subfertility only (total 580) Nr of withdrawals: 4
Participants	Couples with unexplained subfertility, (mild male factor infertility and minimal endometriosis)

	Age: TI + NC 32 years (± 3.4); TI + OH 32 years (± 3.5); IUI + NC 32 (± 3.7) Duration of subfertility: minimum 2 years, median 30 months all groups Basic fertility work up normal, semen normal according to WHO (sperm motility < 20% included) Previous treatment: not stated
Interventions	Comparison: TI (expectant management) + NC versus TI + OH versus IUI + NC Stimulation method: 50 mg CC/day (starting dose), day 2 to day 6 Ovulation: confirmed by progesterone measure in TI + OH group, and urinary LH surge in IUI + NC group Timing of IUI and TI: IUI 20 hr to 30 hr after LH surge, timing intercourse advised on cycle day 12 to 18 Duration of treatment: 6 cycles max
Outcomes	Live birth and PR per couple Miscarriage rate Ectopic PR Multiple pregnancies Pregnancy confirmed by USS showing gestational sac and foetal heart beat
Notes	The author provided additional data on the couples with unexplained subfertility only The baseline characteristics of the participants reported are from the group total. ITT analysis was therefore possible and performed Author provided additional information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated by independent statistician
Allocation concealment (selection bias)	Low risk	Adequate; central telephone randomisation system
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up and participants who received alternative treatment are presented in a flow-chart
Selective reporting (reporting bias)	Low risk	Live birth data and adverse events are published
Other bias	Low risk	Nothing detected

Chung 1995

Methods	Trial design: parallel Single centre Randomisation: blocked randomisation scheme Allocation concealment: numbered sealed envelopes Nr of Pt randomised: 100 Total dropouts: 12 (12%)
Participants	Couples with unexplained subfertility Age: IUI + OH 31.8 years (± 3.1); TI + OH 32.1 years (± 4.0) Duration of subfertility: IUI + OH 4.7 years (± 2.0); TI + OH 5.3 years (± 2.6) Basic fertility work up normal and semen 15 million motile per ejaculate Previous treatment: not stated
Interventions	Comparison: IUI + OH versus TI + OH Stimulation method: FSH 150 IU/day and GnRH nasal spray from day 21 on Ovulation: 5000 IU hCG when < 4 follicles > 16mm hCG post-ovulatory for luteal support Timing TI: 24 hr + 48 hr after hCG Timing IUI: 36 hr to 48 hr after hCG Duration of treatment: 3 cycles max
Outcomes	PR per couple and per cycle Total delivered Multiple pregnancies Ectopic Miscarriage rate
Notes	ITT analysis: possible IUI was not possible on Sundays

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocked randomisation scheme
Allocation concealment (selection bias)	Low risk	Adequate; numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/50 withdrawn and 6 treatment cycles cancelled in TI group, 4/50 withdrawn and 11 treatment cycles cancelled in IUI group. Reason for cycle cancellation was excessive response. Reason for withdrawal was not

Chung 1995 (*Continued*)

		stated
Selective reporting (reporting bias)	Low risk	Live birth data and complication numbers were reported.
Other bias	Low risk	Nothing detected

Crosignani 1991

Methods	Data from centre 10: Hedon, Montpellier, France Trial design: crossover (after 1 cycle) Multi centre (19 European fertility centres, 4 centres comparing IUI versus TI) Randomisation: not clear Allocation concealment: unclear Nr of Pt randomised: unclear Nr of Pt analysed: total 90 (centre 10; 18 participants) Nr of withdrawals: unclear
Participants	Couples with unexplained subfertility Age: < 38yrs Duration of subfertility: > 3yrs Basic fertility work up normal, semen normal according to WHO 1987 Previous treatment: not stated
Interventions	Comparison: IUI + OH versus TI + OH Stimulation method: not stated Ovulation: not described Timing: not described No cancellation criteria were given Duration of treatment: 2 cycles max
Outcomes	PR per 1st cycle PR per cycle
Notes	ITT analysis: not possible Author replied; could not provide additional information Multicentre ESHRE trial. Only 4 infertility centres compared IUI with superovulation alone. These centres were included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Each centre used own randomisation method. The per-centre method could not be obtained

Crosignani 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Unclear; each centre used own treatment allocation method. The per-centre method could not be obtained
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	High risk	Details on participant withdrawal or loss to follow-up were not stated
Selective reporting (reporting bias)	Unclear risk	Live birth data were not reported
Other bias	Unclear risk	Insufficient information available to evaluate this risk domain

Deaton 1990

Methods	Trial design: crossover (after 4 cycles) Single centre Randomisation: unclear Allocation concealment: unclear Nr of Pt randomised: 67 Nr of Pt analysed: 51 total, unexplained: 24 Nr of withdrawals: 4 pre-crossover (6%)
Participants	Couples with unexplained subfertility and couples with surgically treated endometriosis Age: 33 years (± 4.0) Duration of subfertility: 3.5 years (±1.7) Basic fertility work up normal, semen normal according to WHO criteria 1987 Previous treatment: not stated
Interventions	Comparison: IUI + OH versus TI + NC Stimulation method: 50 mg CC/day, day 5 to day 9 Timing: Natural cycle: urinary LH and BBT timed intercourse Stimulated cycle: 10,000 IU hCG when lead follicle was estimated to be at least 18 mm. IUI 36 hr after hCG injection No cancellation criteria were given Duration of treatment: 8 cycles max
Outcomes	Ongoing pregnancy rate Multiple pregnancies Ectopic pregnancies Miscarriage rate OHSS Pregnancy: not further defined

Deaton 1990 (*Continued*)

Notes	ITT analysis: not possible Participants with unexplained subfertility and endometriosis were included in this study; three participants with moderate and no participants with severe endometriosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	16/67 participants excluded from analysis due to anovulation, poor semen quality or inability to follow the treatment protocol. Of the remaining 51 participants, 6 couples did not complete treatment because of illness or relocation. 4/51 dropped out before cross-over
Selective reporting (reporting bias)	Unclear risk	Live birth rate was not reported
Other bias	Unclear risk	Insufficient information available to evaluate this risk domain

Goverde 2000

Methods	Trial design: parallel Single centre Randomisation: computer-generated randomisation schedule Allocation concealment: numbered, masked and sealed envelopes A power calculation was performed Nr of participants randomised: 120 (unexplained IUI + NC and IUI + TI), 258 total Nr of withdrawals: unclear
Participants	Couples with unexplained subfertility and couples with male factor subfertility Age: IUI + NC 31.6 years (± 3.7); IUI + OH 31.7 years (± 3.9) Duration of subfertility: IUI + NC 3.9 years (± 1.7); IUI + OH 4.2 years (± 1.9) Basic fertility work up normal, semen normal when > 20 million progressive motile in ejaculate Previous treatment: not stated

Goverde 2000 (*Continued*)

Interventions	Comparison: IUI + NC versus IUI + OH (versus IVF) Stimulation method: 75 IU FSH (starting dose) until 1 to 3 follicles of 18 mm were seen on USS hCG was withheld if > 3 follicles of 18 mm or > 6 of 14 mm were present Timing: Stimulated cycle: 10,000 IU hCG, IUI 40 hr to 42 hr after hCG; Natural cycle: IUI 20 hr to 30 hr after detection of urinary LH-surge Cycles were cancelled when > 3 follicles of 18 mm or > 6 follicles of 14 mm were present Duration of treatment: 6 cycles max
Outcomes	Live birth per couple OHSS
Notes	ITT analysis: yes Some dropouts because of spontaneous pregnancy

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	Adequate; numbered, masked and sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/120 withdrew before 1st treatment cycle. Details on dropout not separately available for unexplained subfertility. Some participants dropped out because of spontaneous pregnancy. It is not known whether these participants are included in the IUI unexplained subfertility group
Selective reporting (reporting bias)	Low risk	Live birth and complication data were reported
Other bias	Low risk	Nothing detected; baseline demographic characteristics similar between the two groups

Guzick 1999

Methods	Trial design: Parallel Multi centre (10 clinical sites) Randomisation: computer-generated permuted block Allocation concealment: locked computer files Nr of Pt randomised: 932 (465 treated with IUI) Nr of Pt with unexplained subfertility: 211 Nr of withdrawals: 72 total (15%)
Participants	Couples with unexplained subfertility and couples with stage I or II treated endometriosis or male factor subfertility Age: IUI + NC 32 years (± 4) IUI + OH 32 years (± 4) Duration of subfertility: IUI + NC 3.8 years (± 2.6); IUI + OH 3.5 years (± 2.2) Basic fertility work up normal, semen normal (according to WHO 1992) Previous treatment: no previous treatment. (Pt excluded if previous ART)
Interventions	Comparison: IUI + NC versus IUI + OH Stimulation method: 150 IU FSH/day, day 3 to day 7 Ovulation: IUI + OH: 10,000 IU hCG when 2 follicles of > 18 mm were present IUI + NC: urine LH testing Timing: IUI + OH: 36 hr to 40 hr after hCG IUI + NC: IUI the day after urinary LH surge Cycles were cancelled if serum E2 concentration > 3000 pg/ml Duration of treatment: 4 cycles max
Outcomes	Live birth per couple PR per couple Ectopic PR Pregnancy defined by two positive HCG tests. This is biochemical pregnancy, therefore not included in analysis
Notes	ITT analysis: not possible Author replied; provided additional information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Author could not guarantee whether or not participants were truly randomised
Allocation concealment (selection bias)	Unclear risk	Author could not guarantee whether or not participants were truly randomised
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest

Guzick 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal rates of the total group were presented: 4/465 treatment-related withdrawal, 27/465 not treatment-related. Numbers for unexplained subfertility group are not known
Selective reporting (reporting bias)	Low risk	Live birth and complication data were reported
Other bias	Low risk	Nothing detected

Janko 1998

Methods	Trial design: parallel Single centre Randomisation: not clear Allocation concealment: unclear Nr of Pt randomised: 72 Nr of withdrawals: not stated
Participants	Couples with unexplained subfertility Age: not stated Duration of subfertility: > 3 yrs Basic fertility work up normal, semen normal not further specified Previous treatment: not stated
Interventions	Comparison: IUI + OH versus TI + OH Stimulation method: hMG (10 amp per cycle) Ovulation: 10,000 IU hCG Timing: not specified No cancellation criteria were given. Duration of treatment: 3 cycles max
Outcomes	PR per cycle Pregnancy not further defined
Notes	ITT analysis: possible Abstract only. Data calculated.

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; not stated

Janko 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	High risk	Not available
Selective reporting (reporting bias)	High risk	In this abstract the reported outcome data are minimal
Other bias	Unclear risk	Insufficient information available to evaluate this risk domain

Karlstrom 1993

Methods	Trial design: parallel Single centre Randomisation: not clear Allocation concealment: unclear Nr of Pt randomised: not clear Nr of Pt analysed: 79 Nr of withdrawals: not clear
Participants	Couples with unexplained subfertility and minimal or mild endometriosis Age: 32 years (range 21 years to 38 years) Duration of subfertility: 5 years (range 2 years to 14 years) Basic fertility work up normal, semen normal according to WHO 1987 Previous treatment: no
Interventions	Comparison: IUI + OH versus TI + OH (vs DIPI + OH vs IUI and DIPI + OH) Stimulation method 1: 150 IU hMG starting dose, till one follicle of at least 17 mm was present or the detection of a LH surge in serum or urine Monitoring: USS and serum E2 Ovulation: 10,000 IU hCG Timing: IUI 36 hr to 41 hr after hCG or 24 hr after detection of LH surge. TI the two following nights after hCG injection Stimulation method 2: 100 mg CC/day for 5 days Monitoring + Ovulation: urinary LH timed Timing: IUI 20 hr to 28 hr after LH surge, TI day of LH surge and day after Cycles were cancelled according to serum E2 rise Duration of treatment: 1 cycle max
Outcomes	PR per cycle Ectopic PR Pregnancy not further defined

Karlstrom 1993 (*Continued*)

Notes	ITT analysis: not possible When ovulation occurred during the weekend, participants were transferred to TI group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four withdrawals in clomiphene group due to absent LH surge, 5 withdrawals in hMG group due to absent LH surge, fast oestrogen rise or personal reasons
Selective reporting (reporting bias)	Unclear risk	Live birth data were not reported
Other bias	Unclear risk	Insufficient information was reported on demographic characteristics to make a conclusive judgement

Melis 1995

Methods	Trial design: parallel Randomisation: computer-generated random number list Allocation concealment: numbered opaque sealed envelopes Nr of Pt randomised: 108 Nr of Pt analysed: 103 Nr of withdrawals: 5 (4.6%)
Participants	Couples with unexplained subfertility and couples with mild male factor subfertility Age: 33.1 years (± 5.2) Duration of subfertility: 4.3 years (± 1.4) Basic fertility work up normal, semen normal according to WHO 1987 criteria Previous treatment: yes, all couples
Interventions	Comparison: IUI + OH versus TI + OH Stimulation method: 3 amp FSH/day Monitoring: USS and plasma E2 Ovulation: 10,000 IU hCG when at least 2 follicles of 16 mm were present Timing: TI 12 hr after HCG, IUI 30 hr to 36 hr after HCG

Melis 1995 (*Continued*)

	Cycles cancelled when plasma E2 level > 1500 pg/ml Duration of treatment: 3 cycles max
Outcomes	Live birth per couple PR/couple Miscarriage Multiple pregnancies OHSS Pregnancy confirmed by USS showing foetal heart activity
Notes	ITT analysis: possible Author provided additional information All participants had had previous fertility treatment Pt with minor abnormalities were excluded from the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Adequate; numbered opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion numbers were published for the overall group.The author provided additional information: 1/52 (IUI + OH group) withdrew, 4/56 (TI + OH group) withdrew. Reasons for dropout were family problems, poor response or exaggerated response
Selective reporting (reporting bias)	Low risk	Live birth data and complication numbers were available for analysis
Other bias	Unclear risk	Insufficient information was reported to make a conclusive judgement on participant demographic characteristics

Murdoch 1991

Methods	Trial design: parallel Randomisation: random number sequence Allocation concealment: via sequentially numbered opaque sealed envelopes Nr of Pt randomised: 39 IUI + NC 19; IUI + OH 20 Nr of withdrawals: 5 (13%)
Participants	Couples with unexplained subfertility Age: IUI + NC 30.5 years (± 3.1); IUI + OH 30.1 years (± 2.9) Duration of subfertility: IUI + NC 5.7 years (± 2.4); IUI + OH 5.1 years (± 1.9) Basic fertility work up done, semen normal (according to WHO 1987) Previous treatment: no
Interventions	Comparison: IUI + NC versus IUI + OH (vs GIFT) Stimulation method: 75 IU hMG/day and 200 micro gram buserelin 4 times daily intranasal Ovulation: 5000 IU hCG, when < 4 follicles of > 16mm were seen. Timing: 30 hr to 36 hr after hCG Natural cycle: IUI on alternate days until ovulation confirmed on USS Cycles were cancelled if > 4 dominant follicles were present Duration of treatment: 3 cycles max
Outcomes	PR per couple and per cycle Live birth Multiple pregnancies Clinical pregnancy defined by USS showing foetal heart activity
Notes	ITT analysis: yes Author provided additional information One pregnancy between treatment cycles Ten cycles were abandoned because no treatment available at the weekend

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Adequate; numbered opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rate 3/19 (IUI + NC), and 2/20 (IUI + OH)

Murdoch 1991 (*Continued*)

Selective reporting (reporting bias)	Low risk	Live birth data were provided
Other bias	Low risk	Nothing detected

Steures 2006a

Methods	Trial design: parallel Multi centre: 26 fertility centres in the Netherlands Randomisation: computer-generated sequence in balanced blocks Allocation concealment: via opaque sealed envelopes Nr of Pt randomised: 253 IUI + OH 127; TI (expectant management) + NC 126 Nr of withdrawals: 3 (IUI + OH) and 2 (TI + NC), 2 still pregnant (TI + NC)
Participants	Couples with unexplained subfertility and an intermediate prognosis of conceiving within the next 12 months (Hunault 30% to 40%) Age: IUI + OH 33 years (± 3.4); TI + NC 33 years (± 3.19) Duration of subfertility: IUI + OH 2.0 years (± 0.5);TI + NC 1.91 years (± 0.5) Basic fertility work up done, semen analysis according to WHO 1987, normal postcoital test Previous treatment: not stated
Interventions	Comparison: IUI + OH versus TI (expectant management) + NC Stimulation method: FSH 37 to 150 IU/day or 50 mg to 150 mg CC/day Monitoring: USS Ovulation: 5000 or 10,000 IU hCG Timing: IUI 36 hr to 40 hr after hCG Cycles were cancelled when > 3 follicles of 16 mm or > 5 follicles of 12 mm were present Duration of treatment: 6 months
Outcomes	Live birth/couple PR/couple Miscarriage rate Multiple pregnancies
Notes	ITT analysis: yes Author provided additional information Only couples with an intermediate prognosis of conceiving were included, this influences the possible treatment effect

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence in balanced blocks
Allocation concealment (selection bias)	Low risk	Adequate; via opaque sealed envelopes

Steures 2006a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not possible because of the nature of the interventions and non-blinding was not likely to affect the outcomes of interest
Incomplete outcome data (attrition bias) All outcomes	Low risk	IUI + OH group, 3 participants lost to follow up, TI + NC group, 2 lost to follow up, 2 still pregnant
Selective reporting (reporting bias)	Low risk	Live birth and complications reported
Other bias	Low risk	Nothing detected

CC: clomiphene citrate
DIPI: direct intraperitoneal insemination
FSH: follicle stimulating hormone
hCG: human chorionic gonadotropin
hMG: human menopausal gonadotropin
IUI: intra-uterine insemination
OH: ovarian hyperstimulation
USS: ultrasound scan

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

Study	Reason for exclusion
Aanesen 2014	Cohort study
Aboulghar 1993	The trial was not randomised
Barros Delgadillo 2008	Not RCT
Barros-Delgadillo 2010	Did not include comparison of interest to this review
Check 2013	Not RCT
Doyle 1991	No pre-crossover data available
Evans 1991	No pre-crossover data available
Gregoriou 1995	No pre-crossover data available
Ho 1998	Abstract, full article not available. No separate data for couples with unexplained subfertility

(*Continued*)

Kabouk 2010	Did not include comparison of interest to this review
Kirby 1991	No pre-crossover data available
Leanza 2014a	Did not include comparison of interest to this review
Leanza 2014b	Did not include comparison of interest to this review
Martinez 1990	No per-woman data. Biochemical pregnancies only reported
Martinez 1991	No pre-crossover data available
Nulsen 1990	The trial (published as full paper in 1993) was not randomised
Nulsen 1993	The trial (also published as an abstract in 1990) was not randomised
Peeraer 2013	Did not include comparison of interest to this review
Prentice 1995	This trial was quasi randomised, on the basis of hospital case record number
Serhal 1988	The trial was not randomised
Tummon 1997	The participants in this trial were all diagnosed with endometriosis
Wadhwa 2013	Did not include comparison of interest to this review
Xu 2014	Study involved donor semen
Zikopoulos 1993	No pre-crossover data available

DATA AND ANALYSES

Comparison 1. IUI versus TI or expectant management both in natural cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	1	334	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.92, 2.78]
2 Multiple pregnancy rate per couple	1	334	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.04, 5.53]
3 Pregnancy rate per couple (all cycles)	1	334	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.88, 2.64]
4 Miscarriage rate per couple	1	334	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.28, 2.11]
5 Ectopic pregnancy rate per couple	1	334	Odds Ratio (M-H, Fixed, 95% CI)	5.06 [0.24, 106.21]

Comparison 2. IUI versus TI or expectant management both in stimulated cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.88, 2.88]
1.1 Gonadotropins	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.88, 2.88]
2 Multiple pregnancy rate per couple	4	316	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.55, 3.87]
2.1 Clomiphene Citrate	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.02, 11.18]
2.2 Gonadotropins	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.44, 5.89]
2.3 Clomiphene Citrate and Gonadotropins	1	68	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.32, 11.00]
3 Pregnancy rate per couple (all cycles)	6	517	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.14, 2.53]
3.1 Clomiphene Citrate	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.03, 2.93]
3.2 Gonadotropins	4	319	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [1.03, 2.75]
3.3 Clomiphene Citrate and Gonadotropins	1	68	Odds Ratio (M-H, Fixed, 95% CI)	2.62 [0.98, 6.98]
3.4 Clomiphene citrate OR Gonadotropins	1	90	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.50, 5.89]
4 Moderate or severe ovarian hyperstimulation syndrome rate per woman	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Gonadotropins	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Clomiphene Citrate and Gonadotropins	1	68	Odds Ratio (M-H, Fixed, 95% CI)	2.75 [0.11, 69.83]
5 Miscarriage rate per couple	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [0.56, 4.88]
5.1 Gonadotropins	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [0.56, 4.88]

6 Ectopic pregnancy rate per couple	1	100	Odds Ratio (M-H, Fixed, 95% CI)	3.06 [0.12, 76.95]
6.1 Gonadotropins	1	100	Odds Ratio (M-H, Fixed, 95% CI)	3.06 [0.12, 76.95]

Comparison 3. IUI in natural cycle versus IUI in stimulated cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	4	396	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.29, 0.82]
1.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.02, 3.41]
1.2 Gonadotropins	3	370	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.85]
2 Multiple pregnancy rate per couple	2	65	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.70]
2.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Gonadotropins	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.70]
3 Pregnancy rate per couple (all cycles)	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.77]
3.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.77]
4 Moderate or severe ovarian hyperstimulation syndrome per woman	3	185	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Gonadotropins	2	159	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Miscarriage rate per couple	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 5.20]
5.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 5.20]
5.2 Gonadotropins	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Ectopic pregnancy rate per couple	2	250	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.02]
6.1 Gonadotropins	2	250	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.02]

Comparison 4. IUI in stimulated cycle versus TI or expectant management in natural cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	1	253	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.45, 1.49]
2 Multiple pregnancy rate per couple	2	304	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 22.34]
2.1 Clomiphene Citrate	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Clomiphene Citrate or Gonadotropins	1	253	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 22.34]
3 Pregnancy rate per couple (all cycles)	2	304	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.59, 1.67]
3.1 Clomiphene Citrate	1	51	Odds Ratio (M-H, Fixed, 95% CI)	3.2 [0.82, 12.50]

3.2 Clomiphene Citrate or Gonadotropins	1	253	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.45, 1.42]
4 Moderate or severe ovarian hyperstimulation syndrome per woman	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Clomiphene Citrate	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Clomiphene Citrate or Gonadotropins	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Miscarriage rate per couple	1	253	Odds Ratio (M-H, Fixed, 95% CI)	2.28 [0.84, 6.20]

Comparison 5. IUI in natural cycle versus TI or expectant management in stimulated cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per couple (all cycles)	1	342	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [1.10, 3.44]
2 Multiple pregnancy rate per couple	1	342	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.90]
3 Pregnancy rate per couple (all cycles)	1	342	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.01, 3.08]
4 Miscarriage rate per couple	1	342	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.32, 2.58]
5 Ectopic pregnancy rate per couple	1	342	Odds Ratio (M-H, Random, 95% CI)	5.30 [0.25, 111.26]

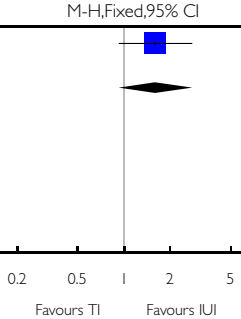
Analysis 1.1. Comparison 1 IUI versus TI or expectant management both in natural cycle, Outcome 1 Live birth rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 1 IUI versus TI or expectant management both in natural cycle

Outcome: 1 Live birth rate per couple (all cycles)

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	38/167	26/167		100.0 %	1.60 [0.92, 2.78]
Total (95% CI)	**167**	**167**		**100.0 %**	**1.60 [0.92, 2.78]**
Total events: 38 (IUI), 26 (TI)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.097)					
Test for subgroup differences: Not applicable					

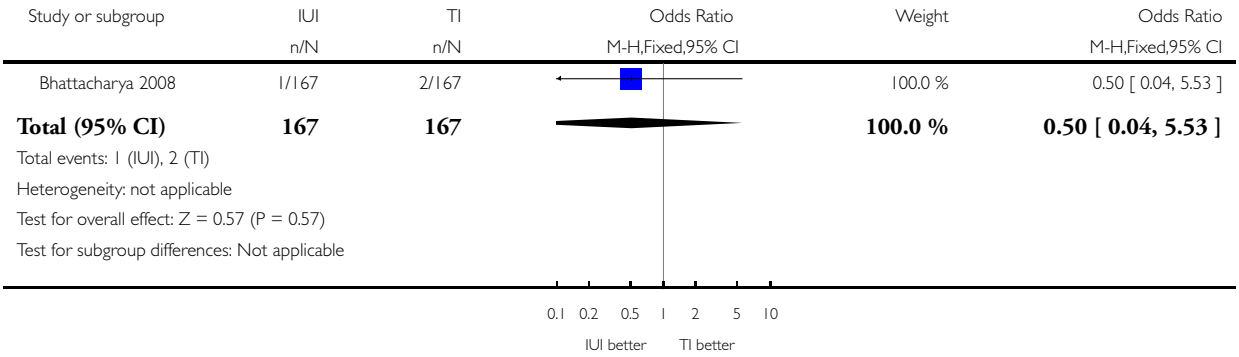


Analysis 1.2. Comparison 1 IUI versus TI or expectant management both in natural cycle, Outcome 2 Multiple pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 1 IUI versus TI or expectant management both in natural cycle

Outcome: 2 Multiple pregnancy rate per couple



Analysis 1.3. Comparison 1 IUI versus TI or expectant management both in natural cycle, Outcome 3 Pregnancy rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 1 IUI versus TI or expectant management both in natural cycle

Outcome: 3 Pregnancy rate per couple (all cycles)

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	38/167	27/167		100.0 %	1.53 [0.88, 2.64]
Total (95% CI)	**167**	**167**		**100.0 %**	**1.53 [0.88, 2.64]**
Total events: 38 (IUI), 27 (TI)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.51 (P = 0.13)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 IUI versus TI or expectant management both in natural cycle, Outcome 4 Miscarriage rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 1 IUI versus TI or expectant management both in natural cycle

Outcome: 4 Miscarriage rate per couple

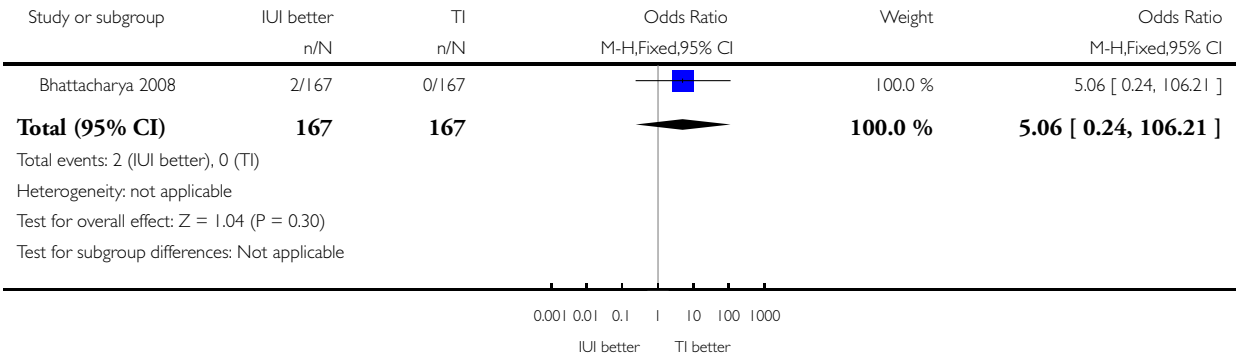
Study or subgroup	IUI n/N	TI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	7/167	9/167		100.0 %	0.77 [0.28, 2.11]
Total (95% CI)	**167**	**167**		**100.0 %**	**0.77 [0.28, 2.11]**
Total events: 7 (IUI), 9 (TI)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
Test for subgroup differences: Not applicable					

Analysis 1.5. Comparison 1 IUI versus TI or expectant management both in natural cycle, Outcome 5 Ectopic pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 1 IUI versus TI or expectant management both in natural cycle

Outcome: 5 Ectopic pregnancy rate per couple

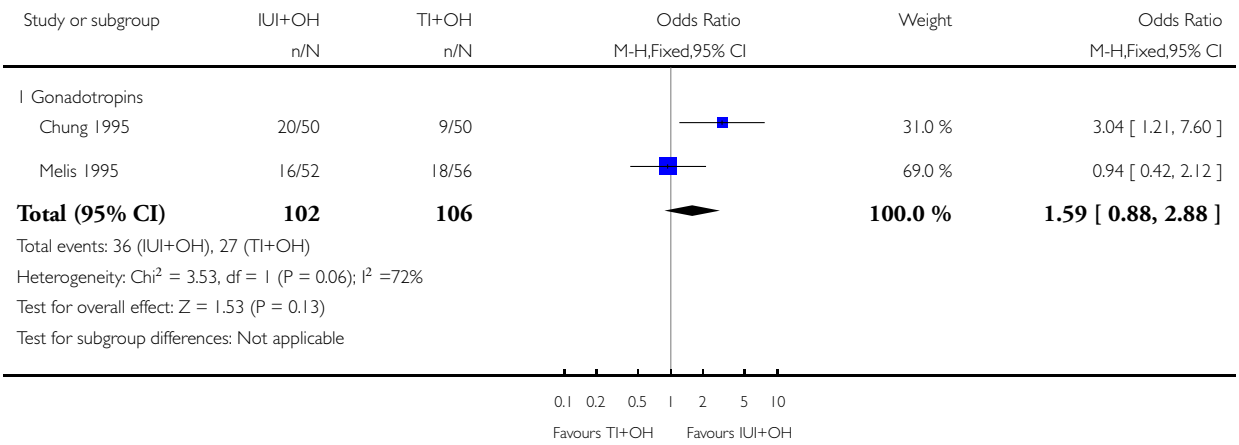


Analysis 2.1. Comparison 2 IUI versus TI or expectant management both in stimulated cycle, Outcome 1 Live birth rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 2 IUI versus TI or expectant management both in stimulated cycle

Outcome: 1 Live birth rate per couple (all cycles)

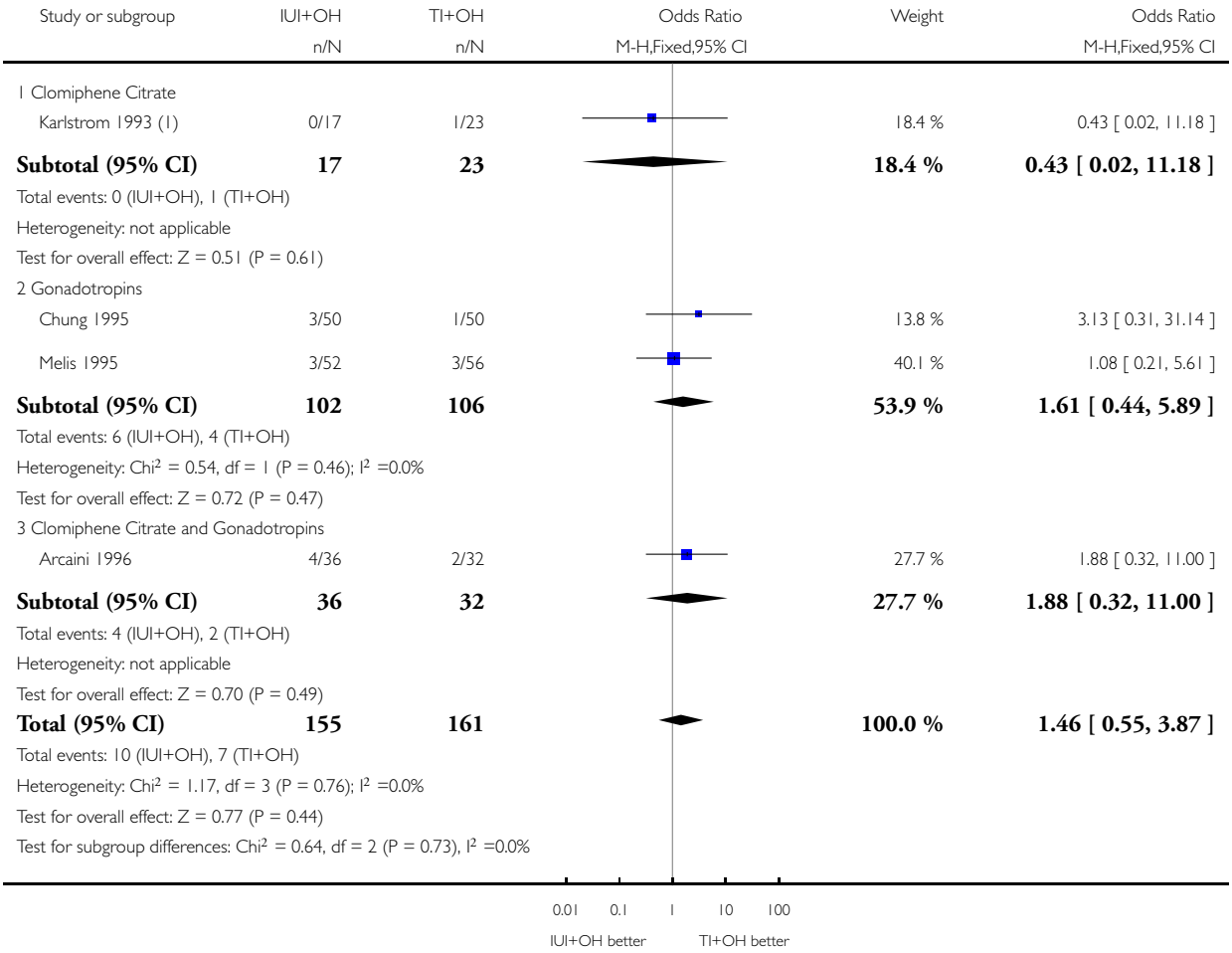


Analysis 2.2. Comparison 2 IUI versus TI or expectant management both in stimulated cycle, Outcome 2 Multiple pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 2 IUI versus TI or expectant management both in stimulated cycle

Outcome: 2 Multiple pregnancy rate per couple



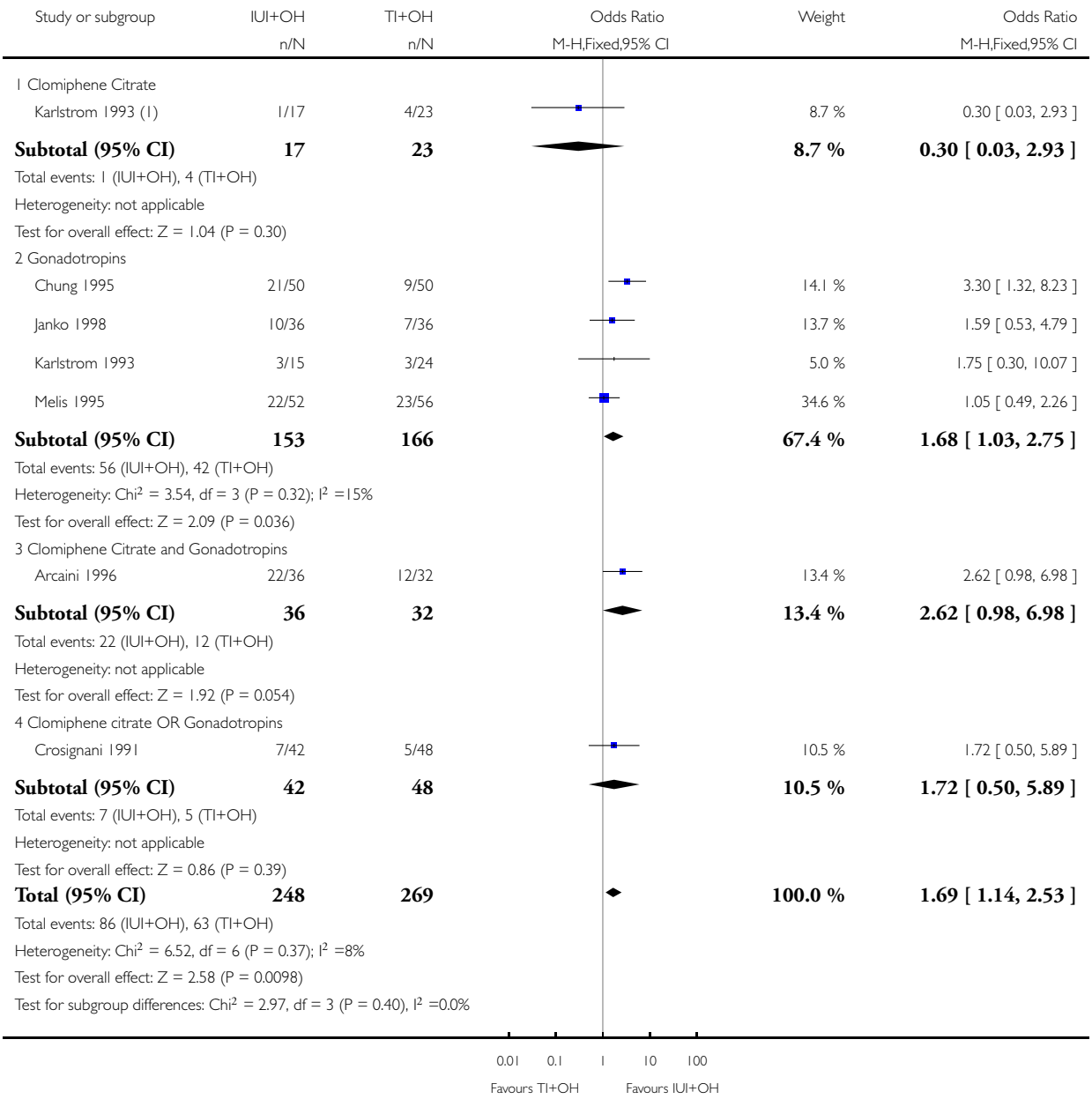
(1) Unspecified number of women moved from IUI to timed intercourse group as ovulated at weekend

Analysis 2.3. Comparison 2 IUI versus TI or expectant management both in stimulated cycle, Outcome 3 Pregnancy rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 2 IUI versus TI or expectant management both in stimulated cycle

Outcome: 3 Pregnancy rate per couple (all cycles)



(1) Unspecified number of women moved from IUI to timed intercourse group as ovulated at weekend

Analysis 2.4. Comparison 2 IUI versus TI or expectant management both in stimulated cycle, Outcome 4 Moderate or severe ovarian hyperstimulation syndrome rate per woman.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 2 IUI versus TI or expectant management both in stimulated cycle

Outcome: 4 Moderate or severe ovarian hyperstimulation syndrome rate per woman

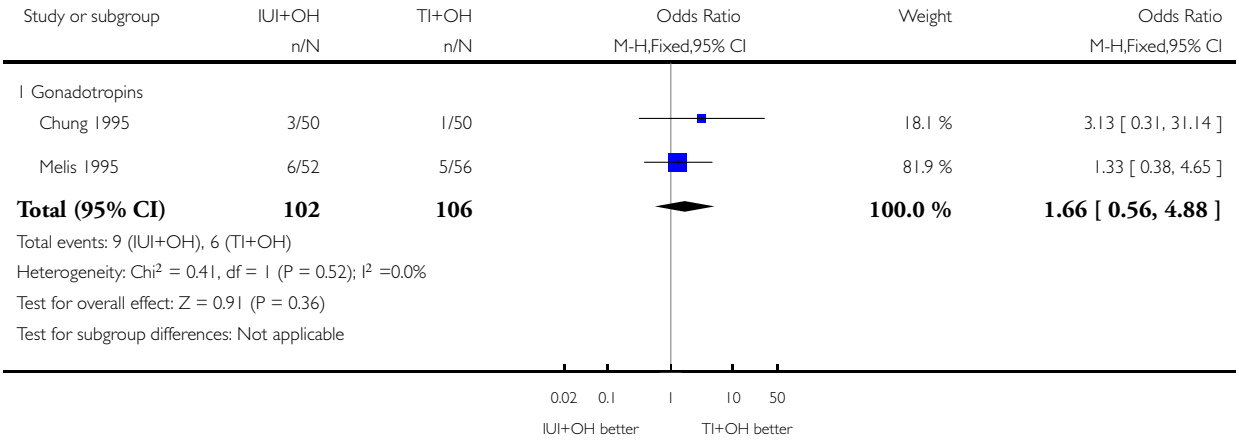
Study or subgroup	IUI+OH n/N	TI+OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Gonadotropins					
Melis 1995	0/52	0/56			Not estimable
Subtotal (95% CI)	**52**	**56**			**Not estimable**
Total events: 0 (IUI+OH), 0 (TI+OH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Clomiphene Citrate and Gonadotropins					
Arcaini 1996	1/36	0/32		100.0 %	2.75 [0.11, 69.83]
Subtotal (95% CI)	**36**	**32**		**100.0 %**	**2.75 [0.11, 69.83]**
Total events: 1 (IUI+OH), 0 (TI+OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					

Analysis 2.5. Comparison 2 IUI versus TI or expectant management both in stimulated cycle, Outcome 5 Miscarriage rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 2 IUI versus TI or expectant management both in stimulated cycle

Outcome: 5 Miscarriage rate per couple

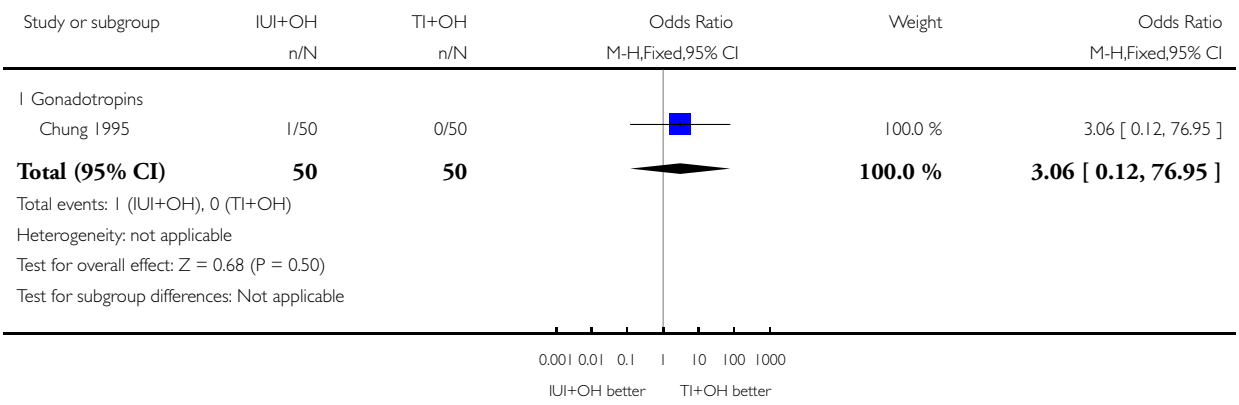


Analysis 2.6. Comparison 2 IUI versus TI or expectant management both in stimulated cycle, Outcome 6 Ectopic pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 2 IUI versus TI or expectant management both in stimulated cycle

Outcome: 6 Ectopic pregnancy rate per couple

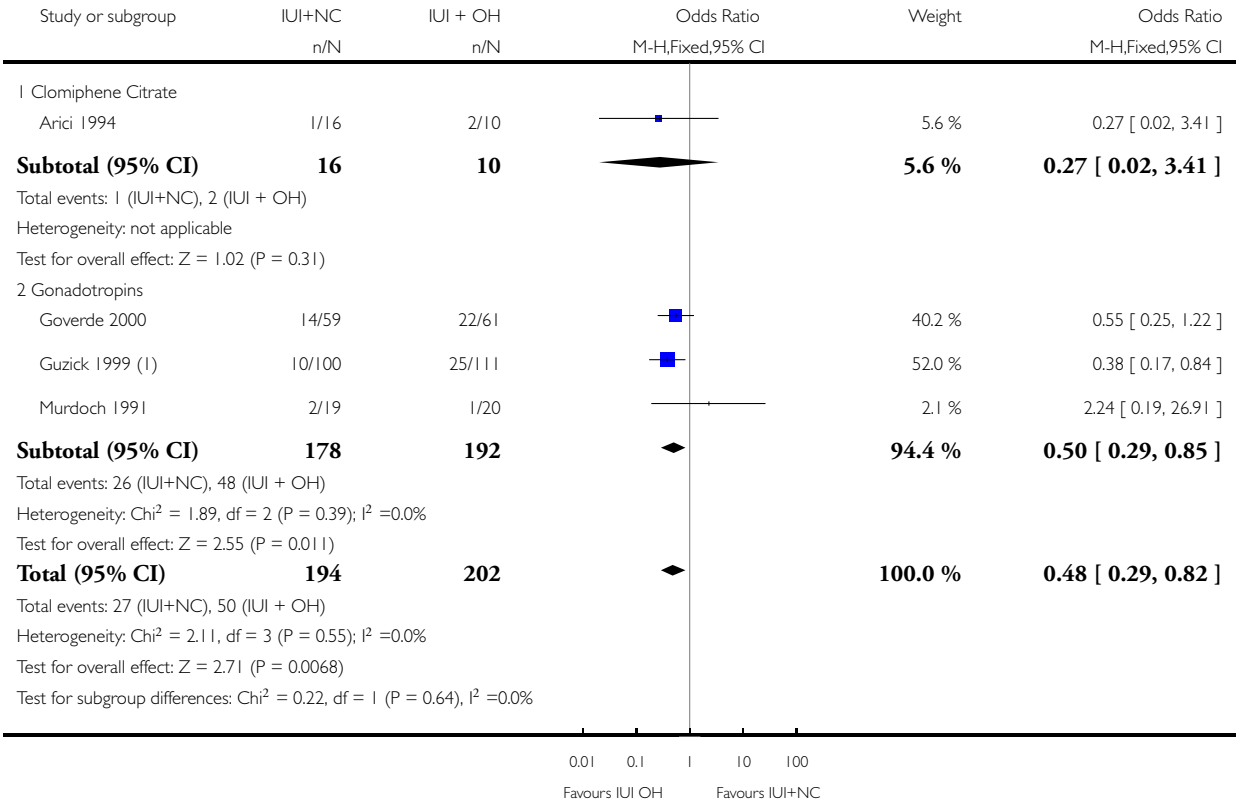


Analysis 3.1. Comparison 3 IUI in natural cycle versus IUI in stimulated cycle, Outcome 1 Live birth rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 3 IUI in natural cycle versus IUI in stimulated cycle

Outcome: 1 Live birth rate per couple (all cycles)



(1) Data are from a sub-set of trial participants meeting sperm concentration and motility criteria

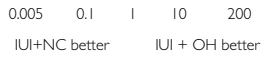
Analysis 3.2. Comparison 3 IUI in natural cycle versus IUI in stimulated cycle, Outcome 2 Multiple pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 3 IUI in natural cycle versus IUI in stimulated cycle

Outcome: 2 Multiple pregnancy rate per couple

Study or subgroup	IUI+NC n/N	IUI + OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene Citrate					
Arici 1994	0/16	0/10			Not estimable
Subtotal (95% CI)	**16**	**10**			**Not estimable**
Total events: 0 (IUI+NC), 0 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Gonadotropins					
Murdoch 1991	0/19	1/20		100.0 %	0.33 [0.01, 8.70]
Subtotal (95% CI)	**19**	**20**		**100.0 %**	**0.33 [0.01, 8.70]**
Total events: 0 (IUI+NC), 1 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Total (95% CI)	**35**	**30**		**100.0 %**	**0.33 [0.01, 8.70]**
Total events: 0 (IUI+NC), 1 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Not applicable					



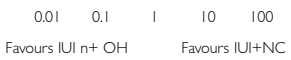
Analysis 3.3. Comparison 3 IUI in natural cycle versus IUI in stimulated cycle, Outcome 3 Pregnancy rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 3 IUI in natural cycle versus IUI in stimulated cycle

Outcome: 3 Pregnancy rate per couple (all cycles)

Study or subgroup	IUI+NC n/N	IUI + OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene Citrate					
Arici 1994	1/16	3/10		100.0 %	0.16 [0.01, 1.77]
Total (95% CI)	**16**	**10**		**100.0 %**	**0.16 [0.01, 1.77]**
Total events: 1 (IUI+NC), 3 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					
Test for subgroup differences: Not applicable					



Analysis 3.4. Comparison 3 IUI in natural cycle versus IUI in stimulated cycle, Outcome 4 Moderate or severe ovarian hyperstimulation syndrome per woman.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 3 IUI in natural cycle versus IUI in stimulated cycle

Outcome: 4 Moderate or severe ovarian hyperstimulation syndrome per woman

Study or subgroup	IUI+OH n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene Citrate					
Arici 1994	0/16	0/10			Not estimable
Subtotal (95% CI)	**16**	**10**			**Not estimable**
Total events: 0 (IUI+OH), 0 (IUI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Gonadotropins					
Goverde 2000	0/59	0/61			Not estimable
Murdoch 1991	0/20	0/19			Not estimable
Subtotal (95% CI)	**79**	**80**			**Not estimable**
Total events: 0 (IUI+OH), 0 (IUI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**95**	**90**			**Not estimable**
Total events: 0 (IUI+OH), 0 (IUI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

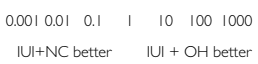
Analysis 3.5. Comparison 3 IUI in natural cycle versus IUI in stimulated cycle, Outcome 5 Miscarriage rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 3 IUI in natural cycle versus IUI in stimulated cycle

Outcome: 5 Miscarriage rate per couple

Study or subgroup	IUI+NC n/N	IUI + OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene Citrate					
Arici 1994	0/16	1/10		100.0 %	0.19 [0.01, 5.20]
Subtotal (95% CI)	**16**	**10**		**100.0 %**	**0.19 [0.01, 5.20]**
Total events: 0 (IUI+NC), 1 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
2 Gonadotropins					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IUI+NC), 0 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**16**	**10**		**100.0 %**	**0.19 [0.01, 5.20]**
Total events: 0 (IUI+NC), 1 (IUI + OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Not applicable					



Analysis 3.6. Comparison 3 IUI in natural cycle versus IUI in stimulated cycle, Outcome 6 Ectopic pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 3 IUI in natural cycle versus IUI in stimulated cycle

Outcome: 6 Ectopic pregnancy rate per couple

Study or subgroup	IUI+OH n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Gonadotropins					
Guzick 1999 (1)	0/100	3/111		100.0 %	0.15 [0.01, 3.02]
Murdoch 1991	0/19	0/20			Not estimable
Total (95% CI)	**119**	**131**		**100.0 %**	**0.15 [0.01, 3.02]**
Total events: 0 (IUI+OH), 3 (IUI)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Not applicable					

(1) Guzick 199 could be an observational study according to the author

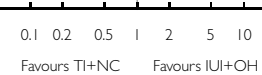
Analysis 4.1. Comparison 4 IUI in stimulated cycle versus TI or expectant management in natural cycle, Outcome 1 Live birth rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 4 IUI in stimulated cycle versus TI or expectant management in natural cycle

Outcome: 1 Live birth rate per couple (all cycles)

Study or subgroup	IUI+OH n/N	TI+NC n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Steures 2006a	26/127	30/126		100.0 %	0.82 [0.45, 1.49]
Total (95% CI)	**127**	**126**		**100.0 %**	**0.82 [0.45, 1.49]**
Total events: 26 (IUI+OH), 30 (TI+NC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Not applicable					



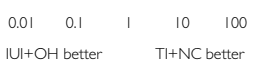
Analysis 4.2. Comparison 4 IUI in stimulated cycle versus TI or expectant management in natural cycle, Outcome 2 Multiple pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 4 IUI in stimulated cycle versus TI or expectant management in natural cycle

Outcome: 2 Multiple pregnancy rate per couple

Study or subgroup	IUI+OH n/N	TI+NC n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene Citrate					
Deaton 1990	0/23	0/28			Not estimable
Subtotal (95% CI)	**23**	**28**			**Not estimable**
Total events: 0 (IUI+OH), 0 (TI+NC)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Clomiphene Citrate or Gonadotropins					
Steures 2006a	2/127	1/126		100.0 %	2.00 [0.18, 22.34]
Subtotal (95% CI)	**127**	**126**		**100.0 %**	**2.00 [0.18, 22.34]**
Total events: 2 (IUI+OH), 1 (TI+NC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.57)					
Total (95% CI)	**150**	**154**		**100.0 %**	**2.00 [0.18, 22.34]**
Total events: 2 (IUI+OH), 1 (TI+NC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.57)					
Test for subgroup differences: Not applicable					

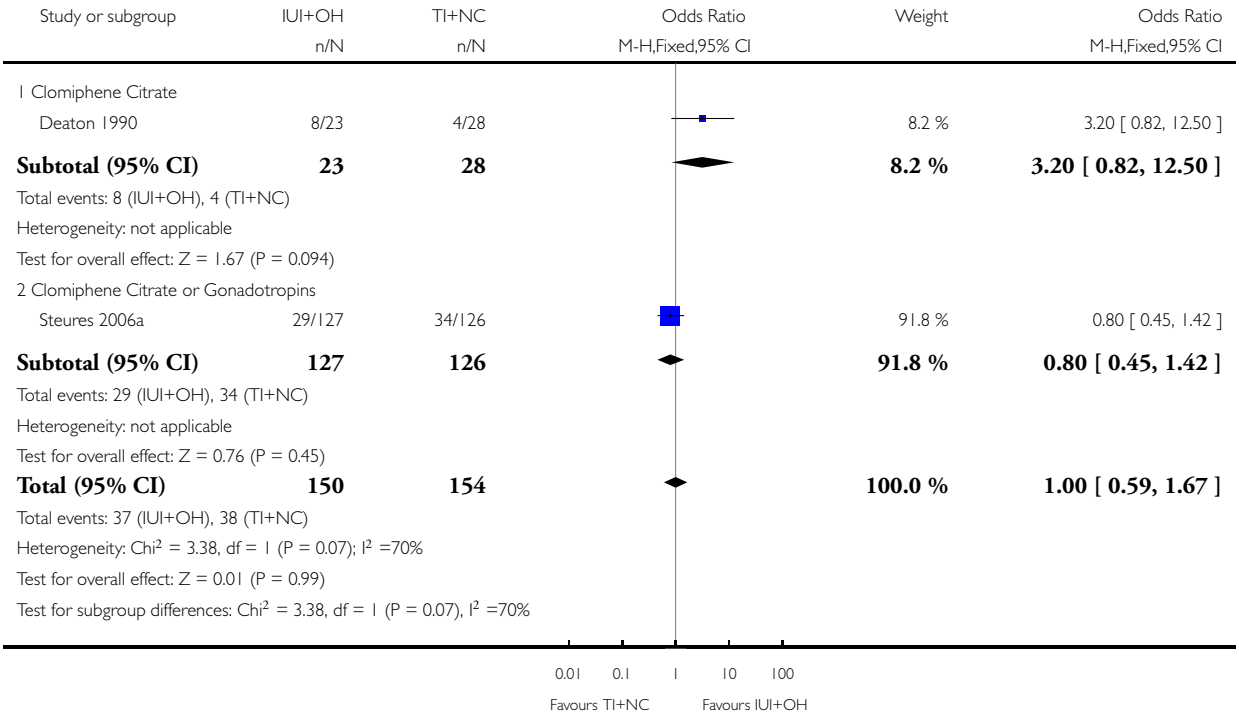


Analysis 4.3. Comparison 4 IUI in stimulated cycle versus TI or expectant management in natural cycle, Outcome 3 Pregnancy rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 4 IUI in stimulated cycle versus TI or expectant management in natural cycle

Outcome: 3 Pregnancy rate per couple (all cycles)



Analysis 4.4. Comparison 4 IUI in stimulated cycle versus TI or expectant management in natural cycle, Outcome 4 Moderate or severe ovarian hyperstimulation syndrome per woman.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 4 IUI in stimulated cycle versus TI or expectant management in natural cycle

Outcome: 4 Moderate or severe ovarian hyperstimulation syndrome per woman

Study or subgroup	IUI+OH n/N	TI+NC n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene Citrate				
Deaton 1990	0/23	0/28		Not estimable
2 Clomiphene Citrate or Gonadotropins				

Analysis 4.5. Comparison 4 IUI in stimulated cycle versus TI or expectant management in natural cycle, Outcome 5 Miscarriage rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 4 IUI in stimulated cycle versus TI or expectant management in natural cycle

Outcome: 5 Miscarriage rate per couple

Study or subgroup	IUI+OH n/N	TI+NC n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Steures 2006a	13/127	6/126		100.0 %	2.28 [0.84, 6.20]
Total (95% CI)	**127**	**126**		**100.0 %**	**2.28 [0.84, 6.20]**
Total events: 13 (IUI+OH), 6 (TI+NC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Test for subgroup differences: Not applicable					

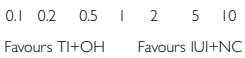
Analysis 5.1. Comparison 5 IUI in natural cycle versus TI or expectant management in stimulated cycle, Outcome 1 Live birth rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 5 IUI in natural cycle versus TI or expectant management in stimulated cycle

Outcome: 1 Live birth rate per couple (all cycles)

Study or subgroup	IUI+NC n/N	TI+OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	38/167	23/175		100.0 %	1.95 [1.10, 3.44]
Total (95% CI)	**167**	**175**		**100.0 %**	**1.95 [1.10, 3.44]**
Total events: 38 (IUI+NC), 23 (TI+OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.022)					
Test for subgroup differences: Not applicable					



Analysis 5.2. Comparison 5 IUI in natural cycle versus TI or expectant management in stimulated cycle, Outcome 2 Multiple pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 5 IUI in natural cycle versus TI or expectant management in stimulated cycle

Outcome: 2 Multiple pregnancy rate per couple

Study or subgroup	IUI+NC n/N	TI+OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	1/167	1/175		100.0 %	1.05 [0.07, 16.90]
Total (95% CI)	**167**	**175**		**100.0 %**	**1.05 [0.07, 16.90]**
Total events: 1 (IUI+NC), 1 (TI+OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.97)					
Test for subgroup differences: Not applicable					

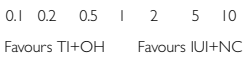
Analysis 5.3. Comparison 5 IUI in natural cycle versus TI or expectant management in stimulated cycle, Outcome 3 Pregnancy rate per couple (all cycles).

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 5 IUI in natural cycle versus TI or expectant management in stimulated cycle

Outcome: 3 Pregnancy rate per couple (all cycles)

Study or subgroup	IUI+NC n/N	TI+OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	38/167	25/175		100.0 %	1.77 [1.01, 3.08]
Total (95% CI)	**167**	**175**		**100.0 %**	**1.77 [1.01, 3.08]**
Total events: 38 (IUI+NC), 25 (TI+OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.00 (P = 0.045)					
Test for subgroup differences: Not applicable					



Analysis 5.4. Comparison 5 IUI in natural cycle versus TI or expectant management in stimulated cycle, Outcome 4 Miscarriage rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 5 IUI in natural cycle versus TI or expectant management in stimulated cycle

Outcome: 4 Miscarriage rate per couple

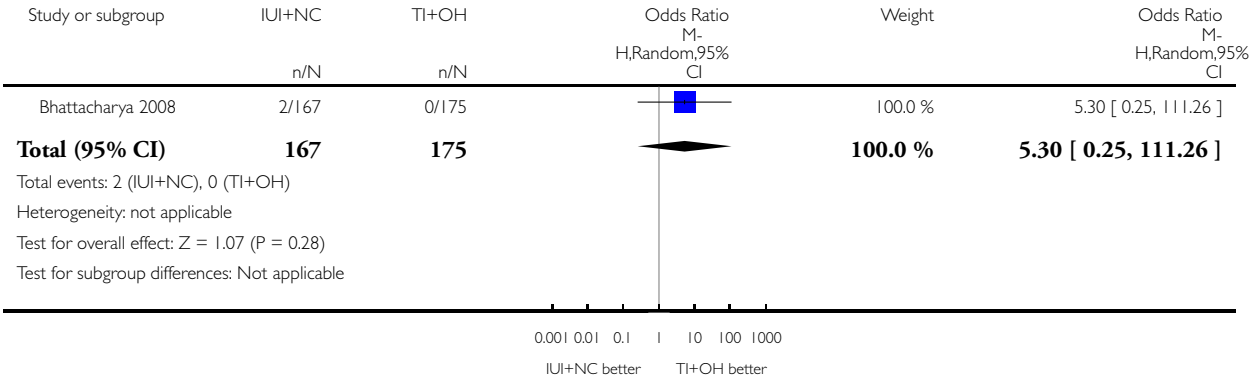
Study or subgroup	IUI+NC n/N	TI+OH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bhattacharya 2008	7/167	8/175		100.0 %	0.91 [0.32, 2.58]
Total (95% CI)	**167**	**175**		**100.0 %**	**0.91 [0.32, 2.58]**
Total events: 7 (IUI+NC), 8 (TI+OH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.86)					
Test for subgroup differences: Not applicable					

Analysis 5.5. Comparison 5 IUI in natural cycle versus TI or expectant management in stimulated cycle, Outcome 5 Ectopic pregnancy rate per couple.

Review: Intra-uterine insemination for unexplained subfertility

Comparison: 5 IUI in natural cycle versus TI or expectant management in stimulated cycle

Outcome: 5 Ectopic pregnancy rate per couple



APPENDICES

Appendix 1. MDSG search strategy

01.01.15
Keywords CONTAINS "unexplained and endometriosis related infertility" or "unexplained infertility" or "unexplained subfertility" or Title CONTAINS "unexplained and endometriosis related infertility" or "unexplained infertility" or "unexplained subfertility"
AND
Keywords CONTAINS "Intrauterine Insemination" or "intrautero tuboperitoneal insemination" or "IUI" or "artifical insemination by donor" or "artifical insemination by partner" or "artificial insemination" or Title CONTAINS "Intrauterine Insemination" or "intrautero tuboperitoneal insemination" or "IUI" or "artifical insemination by donor" or "artifical insemination by partner" or "artificial insemination"

Appendix 2. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2015>
1 exp insemination, artificial/ or exp insemination, artificial, heterologous/ or exp insemination, artificial, homologous/ (296)
2 insemination.tw. (825)
3 iui.tw. (409)
4 or/1-3 (919)
5 subfertil$.tw. (219)
6 infertil$.tw. (2489)
7 superovulation.tw. (142)
8 (unexplained adj2 sterility).tw. (3)

9 ovulation induction.tw. (557)
10 clomiphene.tw. (848)
11 exp Infertility/ (1670)
12 or/5-11 (3906)
13 4 and 12 (557)

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1950 to December 2015>
1 exp insemination, artificial/ or exp insemination, artificial, heterologous/ or exp insemination, artificial, homologous/ (10482)
2 insemination.tw. (13177)
3 iui.tw. (1347)
4 or/1-3 (17570)
5 subfertil$.tw. (4007)
6 infertil$.tw. (47182)
7 superovulation.tw. (1773)
8 (unexplained adj2 sterility).tw. (48)
9 ovulation induction.tw. (3103)
10 clomiphene.tw. (4578)
11 exp Infertility/ (56499)
12 randomized controlled trial.pt. (421692)
13 controlled clinical trial.pt. (92568)
14 randomized.ab. (343500)
15 placebo.tw. (176322)
16 clinical trials as topic.sh. (180817)
17 randomly.ab. (247477)
18 trial.ti. (151571)
19 cross over.ab. (18272)
20 or/12-19 (1027804)
21 (animals not (humans and animals)).sh. (4077418)
22 20 not 21 (947417)
23 or/5-11 (83460)
24 4 and 23 (4629)
25 24 and 22 (536)

Appendix 4. EMBASE search strategy

Database: Ovid EMBASE <1980 to December 2015>
1 exp artificial insemination/ (13129)
2 insemination.tw. (14203)
3 iui.tw. (2331)
4 or/1-3 (20211)
5 exp ovulation induction/ (11436)
6 subfertil$.tw. (5054)
7 infertil$.tw. (62456)
8 superovulation.tw. (1943)
9 unexplained.tw. (36152)
10 ovulation induction.tw. (4192)
11 clomiphene.tw. (5175)
12 exp Infertility/ (98546)
13 or/5-12 (156978)
14 4 and 13 (6953)
15 Clinical Trial/ (854455)

16 Randomized Controlled Trial/ (391145)
17 exp randomization/ (69171)
18 Single Blind Procedure/ (21435)
19 Double Blind Procedure/ (125380)
20 Crossover Procedure/ (45488)
21 Placebo/ (267953)
22 Randomi?ed controlled trial$.tw. (128448)
23 Rct.tw. (19108)
24 random allocation.tw. (1475)
25 randomly allocated.tw. (23799)
26 allocated randomly.tw. (2078)
27 (allocated adj2 random).tw. (745)
28 Single blind$.tw. (16729)
29 Double blind$.tw. (157482)
30 ((treble or triple) adj blind$).tw. (511)
31 placebo$.tw. (225354)
32 prospective study/ (317836)
33 or/15-32 (1531254)
34 case study/ (35526)
35 case report.tw. (297077)
36 abstract report/ or letter/ (947549)
37 or/34-36 (1273469)
38 33 not 37 (1490953)
39 38 and 14 (1138)

Appendix 5. PsycINFO search strategy

Database: PsycINFO <1806 to December Week 3 2015>
1 exp reproductive technology/ (1530)
2 insemination.tw. (629)
3 iui.tw. (27)
4 or/1-3 (1912)
5 subfertil$.tw. (71)
6 infertil$.tw. (2818)
7 superovulation.tw. (3)
8 (unexplained adj2 sterility).tw. (1)
9 ovulation induction.tw. (19)
10 clomiphene.tw. (46)
11 or/5-10 (2901)
12 4 and 11 (571)
13 random*.ti,ab,hw,id. (149863)
14 trial*.ti,ab,hw,id. (139796)
15 controlled stud*.ti,ab,hw,id. (10062)
16 placebo*.ti,ab,hw,id. (34029)
17 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id. (24142)
18 (cross over or crossover or factorial* or latin square).ti,ab,hw,id. (23991)
19 (assign* or allocat* or volunteer*).ti,ab,hw,id. (131093)
20 treatment effectiveness evaluation/ (19468)
21 mental health program evaluation/ (1947)
22 exp experimental design/ (50867)
23 “2000”.md. (31997)
24 or/13-23 (421988)
25 12 and 24 (21)

Appendix 6. Prognostic factors in included studies

Study ID	Age distribution	Subfertility years	Prim/Sec infertility	Previous treatment	Stimulation Method	Single insemination
1.	IUI versus Timed intercourse both in natural cycle	1 study				
Bhattacharya 2008	TI+NC: 32 (±3.4) IUI+NC: 32 (±3.7) (TI is expectant management)	TI+NC: 30 (25 - 38) IUI+NC:30 (25 - 40) months (Inter quartile range)	Mixed 117/386 (30%) Secondary	Not stated	No stimulation	Single
2.	IUI versus Timed intercourse both in stimulated cycle	7 studies				
Agarwal 2004	IUI+OH: 29.52 (±3.65) TI +OH: 28,83 (±4,76)	IUI+OH: 4.91 (±2.72) TI+OH: 4.93 (±3.27)	Mixed 32/113 (28%) secondary	No	CC 50-150 mg	Single
Arcaini 1996	IUI+OH: 34.6 (±4.9) TI+OH: 33.4 (±4.7)	IUI+OH: 4.2 (±1.6) TI+OH: 3.9 (±2.3)	Mixed 7/68 (10%) secondary	Not stated	High dose: CC100mg and hMG 75-225IU	Double
Chung 1995	IUI+OH: 31.8 (±3.1) TI+OH: 32.1 (±4.0)	IUI+OH: 4.7 (±2.0) TI+OH: 5.3 (±2.6)	Not clear	Not stated	hMG 150IU starting dose and GnRHa	IUI: Single TI: Double
Crosignani 1991	< 38 yrs	> 3 yrs	Not clear	Probably	Not stated	Not stated
Janko 1998	Not stated	> 3 yrs	Not clear	Not stated	hMG (10 amp per cycle)	Not stated
Karlstrom 1993	32 (range 21-38)	5 (range 2-14)	Mixed 49/148 (33%) secondary (incl Pt in DIPI groups)	No	hMG (low dose step up) 75 IU starting dose OR CC 100mg	IUI: Single TI: Double

(*Continued*)

Melis 1995	33.1 (±5.2)	4.3 (±1.4)	Not clear	Yes, all patients	High dose: FSH 225IU	Single
3.	IUI in natural cycle versus IUI in stimulated cycle					
Arici 1994	33 (range 24-41)	3.5 (range 1-15)	Not clear	No	CC 50 mg	IUI+NC: Double IUI+OH: Single
Goverde 2000	IUI+NC: 31.6 (±3.7) IUI+OH: 31.7 (± 3.9)	IUI+NC: 3.9 (±1.7) IUI+OH: 4.2 (±1.9)	Mixed 13.5% secondary	Not stated	hMG 75IU starting dose	Single
Guzick 1999	IUI+NC: 32 (±4) IUI+OH: 32 (±4) <40 yrs	IUI+NC: 3.8 (±2.6) IUI+OH: 3.5 (±2.2)	Mixed 40% secondary	No	FSH 150IU	Single
Murdoch 1991	IUI+NC: 30.5 (±3.1) IUI+OH: 30.1 (±2.9)	IUI+NC: 5.7 (±2.4) IUI+OH: 5.1 (±1.9)	Mixed 5/34 (15%) secondary	No	hMG (low dose) 75IU + GnRHa	IUI+OH: Single IUI+NC: till USS evidence of ovulation
4.	IUI with OH versus TI in natural cycle	1 study				
Deaton 1990	33 (±4.0)	3.5 (±1.7)	Mixed 21/51 (41%) secondary	Not stated	CC 50 mg	Single
Steures 2006	IUI+OH: 33 (±3.4) TI+NC: 33 (±3.1) (TI is expectant management)	IUI+OH: 2.0 (±0.5) TI+NC: 1.9 (±0.5)	Mixed 58/253 (23%) secondary	Not stated	FSH 37-150 IU or CC 50-150 mg	Not stated
5.	IUI in natural cycle versus TI with OH					

(*Continued*)

Bhattacharya 2008	TI+OH: 32 (±3.5) IUI+NC: 32 (±3.7)	TI+OH: 30 (24 - 38) IUI+NC: 30 (25 - 40) months (Inter quartile range)	Mixed 109/387 (28%)	Not stated	CC 25-50 mg	Single
	* Mean age in years (± SD) or range	* Mean duration in years (± SD) or range			* Daily dose	

Appendix 7. Sensitivity analyses: intra-uterine insemination (IUI) versus timed intercourse (TI) both in a stimulated cycle

	Analysis	Number of studies	OR	95% CI	Heterogeneity (P)	I^2 (%)
LIVE BIRTH RATE	Main analysis (All cycles, by ITT, fixed effect, Agarwal 2004 excluded)	2	1.59	0.88 - 2.88	0.06	72
	Not by ITT	2	1.46	0.80 - 2.66	0.06	71
	Random effect	2	1.65	0.52 - 5.23	0.06	72
	Agarwal 2004 included	3	0.81	0.51 - 1.28	0.0002	88
PREGNANCY RATE	Main analysis (All cycles, by ITT, fixed effect, Agarwal 2004 excluded)	6	1.69	1.14 - 2.53	0.37	8
	Not by ITT	6	1.65	1.10 - 2.47	0.36	10
	Random effect	6	1.72	1.11- 2.65	0.37	8
	Agarwal 2004 included	7	1.25	0.88 - 1.78	0.02	60

(*Continued*)

	Adequate methodology (Chung 1995, Melis 1995)	2	1.70	0.96 - 3.02	0.06	71.7
	Previous treatment excluded (Melis 1995 excluded)	5	2.03	1.27 - 3.26	0.50	0
	Calculated data excluded (Janko 1998 excluded)	5	1.71	1.11 - 2.63	0.26	23
	Trials including pt with endometriosis excluded (Karlstrom 1993 excluded)	5	1.83	1.20 - 2.79	0.38	4

Appendix 8. Sensitivity analyses: IUI in a natural cycle versus IUI in a stimulated cycle

	Analysis	**Number of studies**	**OR**	**95% CI**	**Heterogeneity (p)**	**I^2 (%)**
LIVE BIRTH RATE	Main analysis (All cycles, by ITT, fixed effect)	4	0.48	0.29 - 0.82	0.55	0
	Not by ITT	4	0.47	0.28 - 0.81	0.79	0
	Random effect	4	0.48	0.28 - 0.85	0.55	0
	Cross over trials excluded (Arici 1994 excluded)	3	0.50	0.29 - 0.85	0.39	0
	Adequate Methodology (Guzick 1999 excluded, Randomisation not	3	0.59	0.29 - 1.21	0.47	0

(*Continued*)

	per unexplained pt)					
	Endometriosis (Arici 1994, Guzick 1999 excl)	2	0.64	0.30 - 1.34	0.29	9

WHAT'S NEW

Last assessed as up-to-date: 22 December 2015.

Date	Event	Description
27 November 2015	New search has been performed	Update of review and literature search; no new studies added
27 November 2015	New citation required but conclusions have not changed	The conclusions of the review have not changed.

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 4, 2006

Date	Event	Description
16 August 2012	New citation required but conclusions have not changed	Recognising that new citation warranted for update in 2011.
22 June 2011	New search has been performed	Two new RCTs added: Bhattacharya 2008 and Steures 2006a.
13 June 2008	Amended	Converted to new review format.
5 August 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Susanne Veltman-Verhulst: took the lead in rewriting the protocol and writing and updating the review. She completed the literature search and selection of the trials and performed the data extraction and analyses.

Edward Hughes: performed data extraction on the included trials and contributed to drafts of the initial review.

Reuben Ayeleke: Performed the updated search, created the 'Summary of findings' tables and contributed to the writing and updating of the review

Ben Cohlen: was the primary author of the first publication of the protocol (1999). He worked as second reviewer on selection of the relevant trials and assisted with the writing of the document and updates of the draft.

DECLARATIONS OF INTEREST

Susanne Veltman-Verhulst: none known

Edward Hughes: none known

Reuben Ayeleke: none known

Ben Cohlen: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Van Harreveld Stichting, Netherlands.
- Marco Polo fonds, Netherlands.
- Stichting de Korinthiers, Netherlands.
- Jan Kornelis de Kock Stichting, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We moved multiple pregnancy rate to be a primary outcome in the 2015 update.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Rate; Coitus; Fertile Period [physiology]; Infertility [*therapy]; Insemination, Artificial [adverse effects; *methods]; Live Birth [epidemiology]; Ovulation Induction [adverse effects; *methods]; Pregnancy, Multiple; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Female; Humans; Male; Pregnancy