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Veltman-Verhulst, S. M.; Cohlen, B. J.; Hughes, Edward; Te Velde, E.; Heineman, Maas Jan

Published in:
Cochrane Database of Systematic Reviews

DOI:
[10.1002/14651858.CD001838.pub3](https://doi.org/10.1002/14651858.CD001838.pub3)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Veltman-Verhulst, S. M., Cohlen, B. J., Hughes, E., Te Velde, E., & Heineman, M. J. (2006). Intra-uterine insemination for unexplained subfertility. *Cochrane Database of Systematic Reviews*, (4), [001838]. <https://doi.org/10.1002/14651858.CD001838.pub3>

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Intra-uterine insemination for unexplained subfertility (Review)

Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ

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Intra-uterine insemination for unexplained subfertility

Susanne M Veltman-Verhulst¹, Ben J Cohlen², Edward Hughes³, Maas Jan Heineman⁴

¹University Medical Center Utrecht, Department of Reproductive Medicine and Gynecology, Utrecht, Netherlands. ²Department of Obstetrics & Gynaecology, Isala Clinics, Location Sophia, Zwolle, Netherlands. ³Department of Obstetrics and Gynaecology, McMaster University, REI Consultant, ONE Fertility, Hamilton, Canada. ⁴Department of Obstetrics & Gynaecology Academic Medical Centre, University of Amsterdam, Amsterdam, 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. veltmannerhulst@gmail.com.

Editorial group: Cochrane Menstrual Disorders and Subfertility Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2011.

Review content assessed as up-to-date: 21 July 2011.

Citation: Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD001838. DOI: 10.1002/14651858.CD001838.pub3.

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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 than 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.

Objectives

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

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (searched July 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 7), MEDLINE (1966 to July 2011), EMBASE (1980 to July 2011), PsycINFO (1806 to July 2011), SCISearch and reference lists of articles. Authors of identified studies were contacted for missing or unpublished data.

Selection criteria

Truly randomised controlled trials (RCTs) with at least one of the following comparisons were included: IUI versus TI, both in a natural cycle; IUI versus TI, both in a stimulated cycle; IUI in a natural cycle versus IUI in a stimulated cycle; IUI with OH versus TI in a natural cycle; IUI in a natural cycle versus TI with OH.

Only couples with unexplained subfertility were included.

Data collection and analysis

Quality assessment and data extraction were performed independently by two review authors. Outcomes were extracted and the data were pooled. Subgroup and sensitivity analyses were done where possible.

Main results

One trial compared IUI in a natural cycle with expectant management and showed no evidence of increased live births (334 women: odds ratio (OR) 1.60, 95% confidence interval (CI) 0.92 to 2.8). In the six trials where IUI was compared with TI, both in stimulated cycles, there was evidence of an increased chance of pregnancy after IUI (six RCTs, 517 women: OR 1.68, 95% CI 1.13 to 2.50). A significant increase in live birth rate was found for women where IUI with OH was compared with IUI in a natural cycle (four RCTs, 396 women: OR 2.07, 95% CI 1.22 to 3.50). However the trials provided insufficient data to investigate the impact of IUI with or without OH on several important outcomes including live births, multiple pregnancies, miscarriage and risk of ovarian hyperstimulation. There was no evidence of a difference in pregnancy rate for IUI with OH compared with TI in a natural cycle (two RCTs, total 304 women: data not pooled). The final comparison of IUI in natural cycle to TI with OH showed a marginal, significant increase in live births for IUI (one RCT, 342 women: OR 1.95, 95% CI 1.10 to 3.44).

Authors' conclusions

There is evidence that IUI with OH increases the live birth rate compared to IUI alone. The likelihood of pregnancy was also increased for treatment with IUI compared to TI in stimulated cycles. One adequately powered multicentre trial showed no evidence of effect of IUI in natural cycles compared with expectant management. There is insufficient data on multiple pregnancies and other adverse events for treatment with OH. Therefore couples should be fully informed about the risks of IUI and OH as well as alternative treatment options.

PLAIN LANGUAGE SUMMARY

Intra-uterine insemination for unexplained subfertility

There is evidence that intra-uterine insemination (IUI) improves the odds of becoming pregnant for couples with unexplained subfertility when combined with fertility drugs to induce ovulation.

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. The review of trials found some evidence that IUI increases the chance of pregnancy compared to correct timing of intercourse. There was also evidence of an increased live birth rate in women who underwent IUI and who were also given fertility drugs to stimulate the ovaries. However, increased multiple pregnancy rates are concerning and further studies are needed to assess the magnitude of this problem.

BACKGROUND

Description of the condition

Of all couples presenting with fertility problems 8% to 28% have no cause that can be identified (NICE 2004). 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 con-

trast to the IUI procedure, with expectant management couples 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).

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 and colleagues reported that mild ovarian hyperstimulation of IUI cycles did not yield higher pregnancy rates (Goverde 2000), 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 2009).

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 recommended IUI without OH for couples with unexplained subfertility because of the increased risk of multiple pregnancies and OHSS associated with OH (NICE 2004). 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

Only truly randomised controlled trials were included. Quasi-randomised studies where allocation, using for example alternation or chart number, was subject to manipulation were excluded. Attempts were made 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. The trial design was assessed (crossover or parallel). Crossover trials were included if pre-crossover data could be extracted.

Types of participants

1. Couples with unexplained subfertility defined as follows.

Normal ovulatory status (determined by either biphasic basal body temperature chart, normal luteal progesterone, in phase endometrial biopsy or ovulation detected with ultrasound).

Tubal patency (determined by hysterosalpingography or laparoscopy, or both).

A normal semen sample according to World Health Organization (WHO) criteria current at the time of trial.

Sperm concentration of at least 20×10^6 per ml:

- total motility of at least 50%,
- normal morphology of at least 30% (WHO 1987, at least 50%) or Kruger criteria,
- no anti-sperm antibodies.

2. Couples who had tried to conceive for at least one year.

Participants excluded were:

- 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.

Authors were contacted 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 the study was excluded. Trials that included patients with mild to moderate endometriosis only were excluded.

Types of interventions

Trials with at least one of the following comparisons:

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

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

Expectant management was included as a variant of timed intercourse.

Interventions excluded:

- 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);
- donor insemination.

Types of outcome measures

Primary outcomes

Live birth rate per couple (all cycles)

Secondary outcomes

- Live birth per couple after one treatment cycle
- Pregnancy rate per couple (all cycles)
- Pregnancy rate per couple after one treatment cycle

Adverse events:

- moderate or severe ovarian hyperstimulation syndrome (OHSS), rate per woman;
- multiple pregnancy rate per couple;
- miscarriage rate per couple;
- ectopic pregnancy rate per couple.

Clinical pregnancy was defined by the presence of an intra-uterine gestational sac or fetal heartbeat visualised by an ultrasound scan. Biochemically confirmed only pregnancies were excluded. When pregnancy was not further defined, and remained unclear even after contacting the authors, the pregnancy was assumed to

be clinical. Ongoing pregnancy was defined as a pregnancy extending beyond 12 weeks of gestation, confirmed by ultrasound or delivery.

Data on moderate or severe OHSS were collected.

Multiple pregnancies confirmed by ultrasound, with or without selective reduction, were recorded.

An intention-to-treat (ITT) analysis was used whenever possible. Women who dropped out or were excluded after randomisation were assumed not to be 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 have 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 updated in 2010. We have used the search strategy developed by the Cochrane Menstrual Disorders and Subfertility Group (see Review Group details in *the Cochrane Library* for more information).

Electronic searches

We searched the:

- Cochrane Menstrual Disorders and Subfertility Group Specialised Register (searched July 2011),
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 7),
- MEDLINE (1966 to July 2011) (Appendix 1),
- EMBASE (1980 to July 2011) (Appendix 2),
- PsycINFO (1806 to July 2011),
- SCIsearch, and
- reference lists of articles.

Searching other resources

The citation lists of relevant publications and included studies were searched. We handsearched abstracts of the American Society for Reproductive Medicine (ASRM) and European Society for Human Reproduction and Embryology (ESHRE). Authors were contacted to obtain additional information, where necessary.

Data collection and analysis

Selection of studies

Two review authors (SMV, BJC) independently selected the trials to be included according to the above-mentioned criteria. Disagreements were resolved by discussion.

Data extraction and management

Data extraction was done independently by two authors (SMV, EH). Disagreements were resolved by discussion. A statistician (AV) was consulted for data extraction and calculation of data from crossover trials, when possible.

Assessment of risk of bias in included studies

The included trials were screened by a predesigned inclusion form (by SMV, BJC) for the following quality criteria and methodological details.

Trial characteristics

1. Method of randomisation and sequence generation
2. Quality of allocation concealment (assessed according to the

Cochrane standards; studies with an adequate allocation score or where the allocation concealment was unclear were included in the meta-analysis)

3. Crossover or parallel design

4. Number of couples randomised, excluded or lost to follow up

5. Details on dropouts

6. Whether an intention-to-treat (ITT) analysis was done or could be extracted

7. Percentage of cancelled cycles

8. A power calculation performed beforehand

9. Duration, timing and location of the study

These details were summarised and entered in the 'Risk of bias' table for each included study 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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agarwal 2004	+	+	-	-	?	-
Arcaini 1996	?	?	-	+	?	
Arici 1994	+	+	-	+	+	
Bhattacharya 2008	+	+	-	+	+	
Chung 1995	+	+	-	?	+	
Crosgnani 1991	?	?	-	-	?	
Crosgnani 1991b			-			
Crosgnani 1991c			-			
Crosgnani 1991d			-			
Deaton 1990	?	?	-	+	?	
Goverde 2000	+	+	-	?	+	
Guzick 1999	+	+	-	?	+	
Janko 1998	?	?	-	-	-	
Karlstrom 1993	?	?	-	+	?	
Karlstrom 1993 b			-			
Melis 1995	+	+	-	+	+	
Murdoch 1991	+	+	-	+	+	
Steures 2006	+	+	-	+	+	

Measures of treatment effect

Statistical analysis of results followed the guidelines of the Cochrane Menstrual Disorders and Subfertility group ([Cochrane Handbook 2011](#)). Dichotomous data for each study were summarised in a two-by-two table and expressed as an odds ratio (OR) with 95% confidence interval (CI).

Unit of analysis issues

Data were analysed per randomised couple, because per treatment cycle data lead to biased results ([Dias 2008](#)). In the case of a crossover trial, only data prior to crossover were analysed.

Dealing with missing data

Authors of the published trials were contacted in the case of missing data. The newly obtained data were included in the analysis. Analyses were done according to the ITT principle when possible.

Assessment of heterogeneity

Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals, and by checking the I^2 statistic.

Assessment of reporting biases

To detect publication bias a funnel graph, plotting sample size versus effect size, was performed where possible.

Data synthesis

Where appropriate, the data were pooled and a meta-analysis was performed with RevMan software (using the Peto-modified Mantel-Haenszel method) using both a fixed-effect model and random-effects model. Published graphs display the results of the fixed-effect approach.

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

A subgroup analysis regarding methods of ovarian hyperstimulation was performed.

Heterogeneity was assessed by the I^2 statistic. An I^2 value of greater than 50% was considered as substantial heterogeneity. 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 of 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.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

Over 700 articles were found in the initial search of databases. 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 2011](#)) which relates to one of the included studies ([Bhattacharya 2008](#)): this article awaits assessment.

Attempts were made to contact all authors to retrieve unpublished details. Fifteen replies were received. Three replies resulted in the exclusion of the trial ([Nulsen 1993](#); [Prentice 1995](#); [Serhal 1988](#)). Five authors ([Agarwal 2004](#); [Arici 1994](#); [Bhattacharya 2008](#); [Guzick 1999](#); [Melis 1995](#); [Murdoch 1991](#); [Steures 2006](#)) 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

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.

Further details about the included trials are provided in the 'Characteristics of included studies' table and in the additional 'Quality features' table (Table 1) and 'Prognostic factors' table (Table 2).

Number of trials included per comparison

1. IUI versus TI both in a natural cycle: one (Bhattacharya 2008). Two other studies with this comparison were identified (Kirby 1991; Martinez 1990). These studies were excluded from the analysis because they reported post-crossover per cycle data only.

2. IUI versus TI both in a stimulated cycle: seven (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 (Arici 1994; Goverde 2000; Guzick 1999; Murdoch 1991).

4. IUI in a stimulated cycle versus TI in a natural cycle: two (Deaton 1990; Steures 2006).

5. IUI in a natural cycle versus TI in a stimulated cycle: one (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. Because the main reason for dropout was due to financial constraints this introduces a considerable bias. However, a sensitivity analysis including this study was performed, see Table 3.

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

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 2006), Slovakia (Janko 1998), Sweden (Karlstrom 1993), and different countries in Europe (ESHRE - Crosignani 1991).

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 $\pm$ 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 to 33 years (with comparable SDs). The maximum age of the participants was stated in six studies, only one of which 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 over 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. Six 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 2006). Three studies (Arici 1994; Deaton 1990; Karlstrom 1993) reported the inclusion of women with surgically corrected minimal or mild endometriosis, which we considered to be unexplained subfertility. Melis 1995 specifically excluded patients 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 patients (out of 51 patients 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. Three studies (Arcaini 1996; Janko 1998; Steures 2006) 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 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 failed fertility treatment

(Melis 1995). Five trials did not include previously treated patients (Agarwal 2004; Arici 1994; Guzick 1999; Karlstrom 1993; Murdoch 1991) and the remaining trials did not provide information regarding previous treatment.

Interventions

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-E₂). The hCG was given when the dominant follicles reached a mean diameter of 16 to 18 mm. Insemination was performed 30 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 urine tests, and intercourse was advised at 12 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 2006), couples were given general advice regarding the need for regular intercourse.

Cancellation criteria

The most serious adverse effects of ovarian hyperstimulation are multiple pregnancies and 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 patients 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-E₂ 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 pregnancy 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.

Power calculation

Bhattacharya 2008, Goverde 2000 and Steures 2006 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 clinical relevant improvement in live birth rate or pregnancy rate.

Intention to treat

An intention-to-treat (ITT) analysis was used 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 patients 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.

Excluded studies

Thirteen 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 et al (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 assessment

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

Risk of bias in included studies

The overall risk of bias was substantial (see Table 1, Figure 1, Figure 2). This was largely due to the lack of information on allocation concealment and randomisation in many of the trials.

Allocation

The randomisation or allocation concealment method was generally poorly described. Bhattacharya 2008, Chung 1995, Goverde 2000 and Steures 2006 were the only truly randomised trials that described the methods of randomisation and allocation concealment in their publication. Five authors provided the randomisation or allocation details after correspondence (Agarwal 2004; Arici 1994; Guzick 1999; Melis 1995; Murdoch 1991). The remaining five trials did not report the methods used.

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.

Incomplete outcome data

Seven of the 14 included trials clearly mentioned the number of and the reasons for dropping out (Arici 1994; Deaton 1990; Goverde 2000; Guzick 1999; Melis 1995; Murdoch 1991; Steures 2006). 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.

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 study total, which could not be included in the analysis. Multiple pregnancy rates were not reported in two trials (Crosignani 1991; Janko 1998).

Other potential sources of bias

To reduce bias introduced by a crossover study design, we included pre-crossover data only. This resulted in a selection of the eligible studies. Three studies used a crossover design (Arici 1994; Crosignani 1991; Deaton 1990). In this design patients 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 patients crossed over after one treatment cycle. In Deaton 1990 patients crossed over after four cycles. Nine studies used a parallel design, in which patients 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

This section describes the results of the meta-analyses and sensitivity analyses. The results of the two main comparisons are also presented in additional Table 3 and Table 4.

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

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

Live birth rate per couple

Analysis 1.1

Analysis comprised a total of 334 couples with unexplained subfertility only. A live birth rate of 23% was obtained in the IUI group versus 16% in the expectant management group. The live birth rates were not significantly different (OR 1.60, 95% CI 0.92 to 2.78).

Pregnancy rate per couple

Analysis 1.2

There was no evidence of a significant difference in pregnancy rates (OR 1.53, 95% CI 0.88 to 2.64). Of the 167 patients treated with IUI, 38 became pregnant compared to 27 of the 167 untreated patients.

Adverse events

Multiple pregnancy (Analysis 1.3)

Three multiple pregnancies were reported in the unexplained subfertility group, two of which occurred in the expectant management group. The multiple pregnancy rate per ongoing pregnancy was 7% for expectant management and 3% for IUI treated patients. This resulted in no significant difference between the IUI and TI groups (OR 0.50, 95% CI 0.04 to 5.53).

Miscarriage (Analysis 1.4)

Sixteen miscarriages were reported, seven in the IUI group and nine in the TI group (OR 0.77, 95% CI 0.28 to 2.11).

Ectopic pregnancies (Analysis 1.5)

Two ectopic pregnancies occurred in the IUI group (OR 5.06, 95% CI 0.24 to 106.21).

Comparison 2. IUI versus TI both in stimulated cycles

Live birth rate per couple

Analysis 2.1

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

Pregnancy rate per couple

Analysis 2.2

All six trials reported pregnancy rates per couple.

There were 517 women included in this analysis and 149 pregnancies were reported. The OR showed a statistically significant higher pregnancy rate in the IUI group (OR 1.68, 95% CI 1.13 to 2.50) if all cycles were analysed. To check sensitivity to the model assumptions, the random-effects model was used and showed a similar result (OR 1.71, 95% CI 1.11 to 2.63). There was no statistical heterogeneity ($P = 0.40$, $I^2 = 4.7\%$).

If the study by Agarwal 2004 was included in the analysis the results change markedly. The OR become 1.09 (95% CI 0.77 to 1.54),

crossing the line of no evidence of effect. Including this study also introduced a strong heterogeneity ($P = 0.001$, $I^2 = 65.4\%$). 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.

A subgroup analysis for the number of treatment cycles was performed. If we analysed the first treatment cycle only, no significant difference in pregnancy rate was seen (OR 1.48, 95% CI 0.71 to 3.11) 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.

Adverse events

Because only few studies mentioned adverse events (multiple pregnancies, miscarriage, ectopic pregnancies or OHSS) per treatment arm, no conclusions could be drawn regarding the effect of IUI compared with TI on these events.

Multiple pregnancy (Analysis 2.4)

The trials reported a total of 21 multiple pregnancies. Arcaini 1996, Chung 1995 and Karlstrom 1993 reported one high order multiple pregnancy each. Only four studies reported their multiple pregnancies per treatment arm, 11 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 significant difference (OR 1.46, 95% CI 0.55 to 3.87) and no heterogeneity ($I^2 = 0\%$).

Miscarriage (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 (OR 1.66, 95% CI 0.56 to 4.88). No heterogeneity was found ($I^2 = 0\%$).

Ectopic pregnancy (Analysis 2.6)

There were not enough data available to analyse the ectopic pregnancy rate. The occurrence of an ectopic pregnancy was reported in two studies only.

Ovarian hyperstimulation syndrome (Analysis 2.3)

With only one event of OHSS reported it appeared that OHSS rarely occurs in treatment programs of IUI in stimulated cycles.

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

Our main outcome, live birth, was reported in all included studies. For comparison reasons pregnancy rates were also calculated, if pregnancy data were not published the live birth data were used.

Live birth rate per couple

Analysis 3.1

Three trials reported the number of live births per treatment arm (Arici 1994; Goverde 2000; Murdoch 1991). The live birth data of Guzik 1999 were obtained after correspondence. A significant increase in live births was found for women treated with IUI and OH compared to women treated with IUI only (OR 2.07, 95% CI 1.22 to 3.50). The random-effects model and analysis without ITT had similar results. No statistical heterogeneity was detected ($I^2 = 0\%$).

Pregnancy rate per couple

Analysis 3.2

The pregnancy rates of Arici 1994 and Murdoch 1991 were pooled with the live birth data of Goverde 2000 and Guzik 1999 in this analysis, as Goverde and Guzik did not publish clinical pregnancy rate data. The outcome of this analysis should be interpreted as an underestimation of the real pregnancy rate because miscarriages are not included in this calculation. The OR for clinical pregnancy per woman randomised was 2.14 (95% CI 1.26 to 3.61), which was significantly in favour of IUI combined with OH. No heterogeneity was found.

Adverse events

Multiple pregnancy (Analysis 3.4)

Goverde 2000 reported an overall multiple pregnancy rate of 29% in the OH group (with both male and unexplained subfertility), Guzik 1999 reported an overall multiple pregnancy rate of 13% in the OH group. This also included patients with male subfertility and patients undergoing intra-cervical insemination. No multiple pregnancies occurred during the trial of Arici 1994, and Murdoch 1991 reported one twin pregnancy only in the OH group. A meta-analysis could not be performed.

Miscarriage (Analysis 3.5)

One miscarriage in the OH group was reported by Arici 1994. Guzik 1999 reported a total miscarriage rate of approximately 24% in all couples undergoing IUI treatment.

Ectopic pregnancy (Analysis 3.6)

Guzik 1999 reported three ectopic pregnancies in the group treated with IUI and OH.

OHSS (Analysis 3.3)

Six of the 932 women treated in Guzik 1999 required hospitalisation for OHSS. In the other three trials no women developed moderate or severe OHSS.

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 2006. Because Steures 2006 selected couples with an intermediate chance of spontaneous pregnancy only, pooling of both studies was not considered adequate.

Live birth rate per couple

Analysis 4.1

This was only reported by Steures 2006 and showed no significant difference in live birth rate (OR 0.82, 95% CI 0.45 to 1.49); 20% of the IUI combined with OH treatments resulted in a live birth while 24% of the patients in the expectant management group had a live born child.

Pregnancy rate per couple

Analysis 4.2

There was no evidence of a significant difference in pregnancy rates for both Deaton 1990 (OR 4.05, 95% CI 0.39 to 41.87) as for Steures 2006 (OR 0.61, 95% CI 0.25 to 1.47).

Adverse events

Analysis 4.4

No multiple pregnancies occurred in Deaton 1990 and there were three in Steures 2006, two of which occurred in the IUI with OH group (OR 2.00, 95% CI 0.18 to 22.34). No women developed OHSS. Miscarriage rates were not significantly different between the groups (Analysis 4.5). Ectopic pregnancies were not reported.

Comparison 5. IUI in a natural cycle versus TI in a stimulated cycle

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

Live birth rate per couple

Analysis 5.1

Live birth rates were 23% and 13% for women treated with IUI compared to TI in a stimulated cycle, respectively. There was a small but significant difference in favour of IUI in a natural cycle (OR 1.95, 95% CI 1.10 to 3.44) for couples with unexplained subfertility.

Pregnancy rate per couple

Analysis 5.2

A marginal significant effect was found in the ongoing pregnancy rate (OR 1.77, 95% CI 1.01 to 3.08).

Adverse events

Multiple pregnancy ([Analysis 5.3](#))

There were two multiple pregnancies, one in each group.

Miscarriage ([Analysis 5.4](#))

The miscarriage rate was evenly distributed among groups (OR 0.91, 95% CI 0.32 to 2.58).

Ectopic pregnancies ([Analysis 5.5](#))

Two ectopic pregnancies occurred in the IUI group resulting in a non-significant difference with a wide CI (OR 5.30, 95% CI 0.25 to 111.26).

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.

This meta-analysis of 14 RCTs showed a significant increase in pregnancy rates for treatment with both intrauterine insemination (IUI) and ovarian hyperstimulation (OH). We can therefore conclude that in couples with unexplained subfertility the combination of OH and IUI seems to be the most effective treatment modality.

The comparison of IUI versus TI, both in stimulated cycles, showed an odds ratio for pregnancy rate per couple of 1.68 (95% CI 1.13 to 2.50) 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 patients had previously failed 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 unexpected 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 is 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 significantly 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 multiple pregnancies, ovarian hyperstimulation syndrome, miscarriage and ectopic pregnancy could not be 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.

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 2.07, 95% CI 1.22 to 3.50). 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.

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, even though it is associated with higher pregnancy rates, because it carries a risk of multiple pregnancy" (NICE 2004).

The absence of a known reason for not getting pregnant in unexplained subfertility makes it difficult to target treatment. 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 matu-

ration and fertilisation and may improve the endometrial quality (Guzick 1998).

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 is being collected that mild ovarian hyperstimulation with strict cancellation criteria minimizes the risk of achieving multiple pregnancies to approximately 10%, without compromising pregnancy rates (ESHRE 2006; Ragni 2006; Rumste 2006; Steures 2006a). 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 unacceptable 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 patients (Dickey 2005; Tur 2005); te Velde 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 (te Velde 1999). 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 could be argued that IVF will become a safer treatment option than IUI with OH. However, Goverde et al found IUI to be a more cost-effective treatment than IVF for couples with unexplained or male subfertility (Goverde 2000).

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 (Ombelet

2005). On the contrary, meta-analyses showed higher pregnancy rates in couples treated with gonadotropins as compared to CC treatment (OR 1.8, 95% CI 1.2 to 2.7) without a significant increase in multiple pregnancies (4% for gonadotropin treatment versus 2% for CC) (Cantineau 2009). It should be noted though that data on multiple pregnancies could only be obtained from three of the seven studies included in the meta-analysis.

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, 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; and 5. IUI in a natural cycle versus TI in a stimulated cycle. Unfortunately, we were able to perform a meta-analysis for two of these comparisons only, because of the lack of comparable RCTs available for the other comparisons. Therefore, we were not able to answer all questions posed.

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 less data available for the adverse effects of each treatment modality. Important prognostic factor such as age, duration of subfertility and previous treatment were poorly reported, making it impossible to perform subgroup analyses.

Quality of the evidence

The overall quality of the included trials was suboptimal. This was mainly because of the poorly reported randomisation and allocation methods.

The quality of fertility trials has been criticized 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 patients 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 over-

estimation 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 2006). 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 2006 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 seven of the 12 included studies. We have 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 (Cohlen, Verhulst; Hughes and Verhulst respectively). Disagreements were resolved by discussion, keeping the protocol as our guideline to reduce bias. A statistician (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 3). The funnel plot is reasonably symmetrical, suggesting that a publication bias is unlikely.

Figure 3.

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 shows evidence that the addition of ovarian hyperstimulation (OH) to intrauterine insemination (IUI) treat-

ment improves live birth rates in couples with unexplained subfertility. A smaller but statistically significant rise in pregnancy rate was found for IUI when compared with time intercourse (TI) in stimulated cycles.

The results of this analysis should be interpreted with caution for daily practice as we could not adequately assess the multiple pregnancy rates and other adverse effects.

Despite the limitations of this review, it shows evidence that IUI with OH is more effective than no treatment at all and could be considered an effective treatment for couples with unexplained subfertility. In couples with a moderate to good prognosis of spontaneously conceiving, abstaining from treatment for several months should be considered. The multiple pregnancy rates should be kept to a minimum by using mild stimulation protocols and strict cancellation criteria. Couples should be fully informed about the risks of IUI and OH and alternative treatment options should also be offered.

Implications for research

There is a need to investigate whether the multiple pregnancy risk 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 the Cochrane Menstrual Disorders and Subfertility Group for their help. Special thanks to Cindy Farquhar, Jane Marjoribanks, Anne Lethaby and statistician Andy Vail for all their advice and support. Thanks also to Egbert te Velde, who contributed to the first publication of the protocol in 1999.

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

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* *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 (±3.65); TI+OH 28.83 (±4.76) Duration of subfertility: IUI+OH 4.91 (±2.72); TI+OH 4.93 (±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: 50-150 mg CC/day, day 3-7 Ovulation: 10000 IU hCG when not more than 4 follicles of >16mm were present Timing of IUI and TI: 36-40hr 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	A - Adequate; sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions

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	High risk	The financial constraints causing unbalanced groups could also have influenced patient selection, follow-up and treatment compliance

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 (± 4.9); TI+OH 33.4 (± 4.7) Duration of subfertility: IUI+OH 4.2 (± 1.6); TI+OH 3.9 (± 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: 100mg CC/day, day 3-7 and 1-3 ampoule hMG/day Ovulation: 10000 IU hCG when 2-6 follicles of >17 mm were present Timing IUI or TI: 24hr 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
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Arcaini 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
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. Patients 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

Arici 1994

Methods	<p>Trial design: crossover (after 1 cycle)</p> <p>Single centre</p> <p>Randomisation: computer generated random number table</p> <p>Allocation concealment: computer system utilising locked files</p> <p>Nr of Pt randomised: 26</p> <p>Nr of withdrawals: not clear</p>
Participants	<p>Couples with unexplained subfertility and couples with male factor subfertility</p> <p>Age: mean 33 yrs (range 24-41)</p> <p>Duration of subfertility: mean 3.5 yrs (range 1-15 yr)</p> <p>Unexplained subfertility: basic fertility work up normal, semen normal according to WHO 1987 criteria</p> <p>Previous treatment: no</p>
Interventions	<p>Comparison: IUI+NC versus IUI+OH</p> <p>Stimulation method: 50 mg CC/day, day 5-9</p> <p>Timing:</p> <p>Natural cycle: urinary LH test, IUI on day of LH peak and the next day</p> <p>Stimulated cycle: 10000 IU hCG when at least 1 follicle of 18mm was present; IUI 32 hr after hCG</p> <p>No cancellation criteria were given</p> <p>Duration of treatment: 4 cycles max</p>
Outcomes	<p>Live birth and PR per couple</p> <p>PR per 1st cycle</p> <p>PR per cycle</p> <p>Miscarriage rate</p> <p>Ectopic PR</p> <p>Multiple pregnancies</p>

	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	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number table
Allocation concealment (selection bias)	Low risk	A - Adequate; computer system utilizing locked files
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
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 1 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

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 (± 3.4); TI+OH 32 (± 3.5); IUI+NC 32 (± 3.7) Duration of subfertility: minimal 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 2-6 Ovulation: confirmed by progesterone measure in TI+OH group, and urinary LH surge in IUI+NC group Timing of IUI and TI: IUI 20-30hr after LH surge, Timing intercourse advised on cycle day 12-18 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 fetal hart beat	
Notes	The author provided additional data on the couples with unexplained subfertility only The baseline characteristics of the patients reported are from the group total. ITT analysis was therefore possible and performed Author provided additional information.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated by independent statistician
Allocation concealment (selection bias)	Low risk	A - Adequate; central telephone randomisation system
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up and patients who received alternative treatment are presented in a flow-chart
Selective reporting (reporting bias)	Low risk	Live birth data and adverse events are published

Chung 1995

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

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	A - Adequate; numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
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 stated

Chung 1995 (Continued)

Selective reporting (reporting bias)	Low risk	Live birth data and complication numbers were reported.
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Crosignani 1991

Methods	Data from centre 10: Hedon, Montpellier, France Trial design: cross over (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 patients) 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
Allocation concealment (selection bias)	Unclear risk	B - Unclear; each centre used own treatment allocation method. The per centre method could not be obtained

Crosignani 1991 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) All outcomes	High risk	Details on patient withdrawal or loss to follow-up were not stated
Selective reporting (reporting bias)	Unclear risk	Live birth data were not reported

Crosignani 1991b

Methods	Data from centre 13: Willemsen, Nijmegen, the Netherlands Nr of Pt analysed: 7	
Participants		
Interventions		
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) All outcomes	High risk	

Crosignani 1991c

Methods	Data from centre 16: Pellicer, Valencia, Italy Nr of Pt analysed: 35	
Participants		
Interventions		
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Croignani 1991c (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	
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Croignani 1991d

Methods	Data from centre 19: Martinez, Amsterdam, the Netherlands Nr of Pt analysed: 30	
Participants		
Interventions		
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) All outcomes	High risk	

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 (± 4.0) Duration of subfertility: 3.5 (± 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 5-9 Timing: Natural cycle: urinary LH and BBT timed intercourse Stimulated cycle: 10000 IU hCG when lead follicle was estimated to be at least 18mm. IUI 36hr after hCG injection. No cancellation criteria were given	

Deaton 1990 (Continued)

	Duration of treatment: 8 cycles max	
Outcomes	Ongoing pregnancy rate Multiple pregnancies Ectopic pregnancies Miscarriage rate OHSS Pregnancy: not further defined	
Notes	ITT-analysis: not possible Patients with unexplained subfertility and endometriosis were included in this study; three patients with moderate and no patients with severe endometriosis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	16/67 patients excluded from analysis due to anovulation, poor semen quality or inability to follow the treatment protocol. Of the remaining 51 patients, 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.

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 patients 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 (± 3.7); IUI+OH 31.7 (± 3.9) Duration of subfertility: IUI+NC 3.9 (± 1.7); IUI+OH 4.2 (± 1.9)	

	Basic fertility work up normal, semen normal when >20 million progressive motile in ejaculate Previous treatment: not stated
Interventions	Comparison: IUI+NC versus IUI+OH (versus IVF) Stimulation method: 75 IU FSH (starting dose) until 1-3 follicles of 18mm were seen on USS hCG was withheld if >3 follicles of 18mm or > 6 of 14 mm were present Timing: Stimulated cycle: 10000 IU hCG, IUI 40-42 hr after hCG; Natural cycle: IUI 20-30 hr after detection of urinary LH-surge. Cycles were cancelled when >3 follicles of 18mm 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	A - Adequate; numbered, masked and sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
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 patients dropped out because of spontaneous pregnancy. It is not known whether these patients are included in the IUI unexplained subfertility group
Selective reporting (reporting bias)	Low risk	Live birth and complication data were reported

Guzick 1999

Methods	<p>Trial design: Parallel</p> <p>Multi centre (10 clinical sites)</p> <p>Randomisation: computer generated permuted block</p> <p>Allocation concealment: locked computer files</p> <p>Nr of Pt randomised: 932 (465 treated with IUI)</p> <p>Nr of Pt with unexplained subfertility: 211</p> <p>Nr of withdrawals: 72 total (15%)</p>
Participants	<p>Couples with unexplained subfertility and couples with stage I or II treated endometriosis or male factor subfertility</p> <p>Age: IUI+NC 32 (± 4)</p> <p>IUI+OH 32 (± 4)</p> <p>Duration of subfertility: IUI+NC 3.8 (± 2.6); IUI+OH 3.5 (± 2.2)</p> <p>Basic fertility work up normal, semen normal (according to WHO 1992)</p> <p>Previous treatment: No previous treatment. (Pt excluded if previous ART)</p>
Interventions	<p>Comparison: IUI+NC versus IUI+OH</p> <p>Stimulation method: 150 IU FSH/day, day 3-7</p> <p>Ovulation: IUI+OH: 10000 IU hCG when 2 follicles of > 18mm were present</p> <p>IUI+NC: urine LH testing</p> <p>Timing: IUI+OH: 36-40 hr after hCG</p> <p>IUI+NC: IUI the day after urinary LH surge</p> <p>Cycles were cancelled if serum E2 concentration >3000pg/ml</p> <p>Duration of treatment: 4 cycles max</p>
Outcomes	<p>Live birth per couple</p> <p>PR per couple</p> <p>Miscarriage rate</p> <p>Ectopic PR</p> <p>Multiple pregnancies</p> <p>OHSS</p> <p>Pregnancy defined by two positive HCG tests. Confirmed by live birth</p>
Notes	<p>ITT-analysis: not possible</p> <p>Author replied; provided additional information</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated permuted block
Allocation concealment (selection bias)	Low risk	A - Adequate; locked computer files
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions

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

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: 10000 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	B - Unclear; not stated

Janko 1998 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
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

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 (range 21-38) Duration of subfertility: 5 (range 2-14) 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: 150IU 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: 10000 IU hCG Timing: IUI 36-41 hr after hCG or 24 hr after detection of LH surge. TI the two following nights after hCG injection Cycles were cancelled according to serum E2 rise. Duration of treatment: 1 cycle max	
Outcomes	PR per cycle Ectopic PR Pregnancy not further defined	
Notes	ITT-analysis: not possible When ovulation occurred during the weekend, Pt were transferred to TI group	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Karlstrom 1993 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	B - Unclear; not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 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

Karlstrom 1993 b

Methods	See Karlstrom 1993a Group underwent different stimulation method	
Participants		
Interventions	Stimulation method 2: 100mg CC/day for 5 days Monitoring + Ovulation: urinary LH timed. Timing: IUI 20-28 hr after LH surge, TI day of LH surge and day after	
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) All outcomes	High risk	

Melis 1995

Methods	<p>Trial design: parallel</p> <p>Randomisation: computer generated random number list</p> <p>Allocation concealment: numbered opaque sealed envelopes</p> <p>Nr of Pt randomised: 108</p> <p>Nr of Pt analysed: 103</p> <p>Nr of withdrawals: 5 (4.6%)</p>
Participants	<p>Couples with unexplained and couples with mild male factor subfertility</p> <p>Age: 33.1 (± 5.2)</p> <p>Duration of subfertility: 4.3 (± 1.4)</p> <p>Basic fertility work up normal, semen normal according to WHO 1987 criteria</p> <p>Previous treatment: yes, all couples</p>
Interventions	<p>Comparison: IUI+OH versus TI+OH</p> <p>Stimulation method: 3 amp FSH/day</p> <p>Monitoring: USS and plasma E2</p> <p>Ovulation: 10000 IU hCG when at least 2 follicles of 16mm were present</p> <p>Timing: TI 12 hr after HCG, IUI 30-36 hr after HCG</p> <p>Cycles cancelled when plasma E2 level > 1500pg/ml</p> <p>Duration of treatment: 3 cycles max</p>
Outcomes	<p>Live birth per couple</p> <p>PR/couple</p> <p>Miscarriage</p> <p>Multiple pregnancies</p> <p>OHSS</p> <p>Pregnancy confirmed by USS showing fetal heart activity</p>
Notes	<p>ITT analysis: possible</p> <p>Author provided additional information</p> <p>All patients have had previous fertility treatment</p> <p>Pt with minor abnormalities were excluded from the study</p>

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	A - Adequate; numbered opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions

Melis 1995 (Continued)

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

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 (± 3.1); IUI+OH 30.1 (± 2.9) Duration of subfertility: IUI+NC 5.7 (± 2.4); IUI+OH 5.1 (± 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: 30-36 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 fetal heart activity	
Notes	ITT analysis: yes Author provided additional information 1 pregnancy between treatment cycles 10 cycles were abandoned because no treatment available at the weekend	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Murdoch 1991 (Continued)

Random sequence generation (selection bias)	Low risk	Computer generated random number sequence
Allocation concealment (selection bias)	Low risk	A - Adequate; numbered opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rate 3/19 (IUI+NC), and 2/20 (IUI+OH). Reasons not stated. Data on cycle cancellation are reported
Selective reporting (reporting bias)	Low risk	Live birth data were provided

Steures 2006

Methods	<p>Trial design: parallel</p> <p>Multi centre: 26 fertility centres in the Netherlands</p> <p>Randomisation: computer generated sequence in balanced blocks</p> <p>Allocation concealment: via opaque sealed envelopes</p> <p>Nr of Pt randomised: 253</p> <p>IUI+OH 127; TI (expectant management)+NC 126</p> <p>Nr of withdrawals: 3 (IUI+OH) and 2 (TI+NC), 2 still pregnant (TI + NC)</p>
Participants	<p>Couples with unexplained subfertility and an intermediate prognosis of conceiving within the next 12 months (Hunault 30-40%)</p> <p>Age: IUI+OH 33 (± 3.4); TI+NC 33 (± 3.19)</p> <p>Duration of subfertility: IUI+OH 2.0 (± 0.5); TI+NC 1.91 (± 0.5)</p> <p>Basic fertility work up done, semen analysis according to WHO 1987, normal postcoital test</p> <p>Previous treatment: not stated</p>
Interventions	<p>Comparison: IUI+OH versus TI (expectant management)+NC</p> <p>Stimulation method: FSH 37-150 IU/day or 50-150 mg CC/day</p> <p>Monitoring: USS</p> <p>Ovulation: 5000 or 10000 IU hCG</p> <p>Timing: IUI 36-40 hr after hCG</p> <p>Cycles were cancelled when >3 follicles of 16mm or >5 follicles of 12mm were present</p> <p>Duration of treatment: 6 months</p>
Outcomes	<p>Live birth/couple</p> <p>PR/couple</p> <p>Miscarriage rate</p> <p>Multiple pregnancies</p>

Notes	ITT analysis: yes Author provided additional information. Only couples with an intermediate prognosis of conceiving were included, this influences the possible treatment effect	
<i>Risk of bias</i>		
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	A - Adequate; via opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	IUI+OH group 3 patients 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

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
Aboulghar 1993	The trial was not randomised
Doyle 1991	No pre-crossover data available
Evans 1991	No pre-crossover data available
Gregoriou 1995	No pre-crossover data available

(Continued)

Ho 1998	Abstract, full article not available. No separate data for couples with unexplained subfertility
Kirby 1991	No pre-crossover data available
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
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
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		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pregnancy rate per couple (all cycles)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Multiple pregnancy rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Miscarriage rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Ectopic pregnancy rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. IUI versus TI 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 Pregnancy rate per couple (all cycles)	10	517	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [1.13, 2.50]
2.1 Clomiphene Citrate	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.03, 2.93]
2.2 Gonadotropins	4	319	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [1.03, 2.75]
2.3 Clomiphene Citrate and Gonadotropins	1	68	Odds Ratio (M-H, Fixed, 95% CI)	2.62 [0.98, 6.98]
2.4 Clomiphene citrate OR Gonadotropins	4	90	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.52, 5.05]
3 Ovarian Hyperstimulation Syndrome rate per women	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Gonadotropins	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Clomiphene Citrate and Gonadotropins	1	68	Odds Ratio (M-H, Fixed, 95% CI)	2.75 [0.11, 69.83]
4 Multiple pregnancy rate per couple	4	316	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.55, 3.87]
4.1 Clomiphene Citrate	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.02, 11.18]
4.2 Gonadotropins	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.44, 5.89]
4.3 Clomiphene Citrate and Gonadotropins	1	68	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.32, 11.00]
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	Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Gonadotropins	1	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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)	2.07 [1.22, 3.50]
1.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	3.75 [0.29, 47.99]
1.2 Gonadotropins	3	370	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.18, 3.45]
2 Pregnancy rate per couple (all cycles)	4	396	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [1.26, 3.61]
2.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	6.43 [0.56, 73.35]
2.2 Gonadotropins	3	370	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.18, 3.45]
3 Ovarian Hyperstimulation Syndrome rate per women	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Gonadotropins	2	159	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Multiple pregnancy rate per couple	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Gonadotropins	1	39	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.11, 78.27]
5 Miscarriage rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Clomiphene Citrate	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Gonadotropins	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Ectopic pregnancy rate per couple	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Clomiphene Citrate	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Gonadotropins	2	250	Odds Ratio (M-H, Fixed, 95% CI)	6.48 [0.33, 127.09]

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		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pregnancy rate per couple (all cycles)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Clomiphene Citrate	1	51	Odds Ratio (M-H, Fixed, 95% CI)	3.2 [0.82, 12.50]
2.2 Clomiphene Citrate or Gonadotropins	1	253	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.45, 1.42]
3 Ovarian Hyperstimulation Syndrome rate per women	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected