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[Intervention Review]

Intrauterine insemination versus intracervical insemination in donor sperm treatment

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ABSTRACT

Background

The first-line treatment in donor sperm treatment consists of inseminations that can be done by intrauterine insemination (IUI) or by intracervical insemination (ICI).

Objectives

To compare the effectiveness and safety of intrauterine insemination (IUI) and intracervical insemination (ICI) in women who start donor sperm treatment.

Search methods

We searched the Cochrane Gynaecology and Fertility Group Trials Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL in October 2016, checked references of relevant studies, and contacted study authors and experts in the field to identify additional studies. We searched PubMed, Google Scholar, the Grey literature, and five trials registers on 15 December 2017.

Selection criteria

We included randomised controlled trials (RCTs) reporting on IUI versus ICI in natural cycles or with ovarian stimulation, and RCTs comparing different cointerventions in IUI and ICI. We included cross-over studies if pre-cross-over data were available.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. We collected data on primary outcomes of live birth and multiple pregnancy rates, and on secondary outcomes of clinical pregnancy, miscarriage, and cancellation rates.

Main results

We included six RCTs (708 women analysed) on ICI and IUI in donor sperm treatment. Two studies compared IUI and ICI in natural cycles, two studies compared IUI and ICI in gonadotrophin-stimulated cycles, and two studies compared timing of IUI and ICI. There was very low-quality evidence; the main limitations were risk of bias due to poor reporting of study methods, and serious imprecision.

IUI versus ICI in natural cycles

There was insufficient evidence to determine whether there was any clear difference in live birth rate between IUI and ICI in natural cycles (odds ratio (OR) 3.24, 95% confidence interval (CI) 0.12 to 87.13; 1 RCT, 26 women; very low-quality evidence). There was only one live birth in this study (in the IUI group). IUI resulted in higher clinical pregnancy rates (OR 6.18, 95% CI 1.91 to 20.03; 2 RCTs, 76 women; $I^2 = 48\%$; very low-quality evidence).

No multiple pregnancies or miscarriages occurred in this study.

IUI versus ICI in gonadotrophin-stimulated cycles

There was insufficient evidence to determine whether there was any clear difference in live birth rate between IUI and ICI in gonadotrophin-stimulated cycles (OR 2.55, 95% CI 0.72 to 8.96; 1 RCT, 43 women; very low-quality evidence). This suggested that if the chance of a live birth following ICI in gonadotrophin-stimulated cycles was assumed to be 30%, the chance following IUI in gonadotrophin-stimulated cycles would be between 24% and 80%. IUI may result in higher clinical pregnancy rates than ICI (OR 2.83, 95% CI 1.38 to 5.78; 2 RCTs, 131 women; $I^2 = 0\%$; very low-quality evidence). IUI may be associated with higher multiple pregnancy rates than ICI (OR 2.77, 95% CI 1.00 to 7.69; 2 RCTs, 131 women; $I^2 = 0\%$; very low-quality evidence). This suggested that if the risk of multiple pregnancy following ICI in gonadotrophin-stimulated cycles was assumed to be 10%, the risk following IUI would be between 10% and 46%.

We found insufficient evidence to determine whether there was any clear difference between the groups in miscarriage rates in gonadotrophin-stimulated cycles (OR 1.97, 95% CI 0.43 to 9.04; 2 RCTs, overall 67 pregnancies; $I^2 = 50\%$; very low-quality evidence).

Timing of IUI and ICI

We found no studies that reported on live birth rates.

We found a higher clinical pregnancy rate when IUI was timed one day after a rise in blood levels of luteinising hormone (LH) compared to IUI two days after a rise in blood levels of LH (OR 2.00, 95% CI 1.14 to 3.53; 1 RCT, 351 women; low-quality evidence). We found insufficient evidence to determine whether there was any clear difference in clinical pregnancy rates between ICI timed after a rise in urinary levels of LH versus a rise in basal temperature plus cervical mucus scores (OR 1.31, 95% CI 0.42 to 4.11; 1 RCT, 56 women; very low-quality evidence).

Neither of these studies reported multiple pregnancy or miscarriage rates as outcomes.

Authors' conclusions

There was insufficient evidence to determine whether there was a clear difference in live birth rates between IUI and ICI in natural or gonadotrophin-stimulated cycles in women who started with donor sperm treatment. There was insufficient evidence available for the effect of timing of IUI or ICI on live birth rates. Very low-quality data suggested that in gonadotrophin-stimulated cycles, IUI may be associated with a higher clinical pregnancy rate than ICI, but also with a higher risk of multiple pregnancy rate. We concluded that the current evidence was too limited to choose between IUI or ICI, in natural cycles or with ovarian stimulation, in donor sperm treatment.

PLAIN LANGUAGE SUMMARY

Intrauterine insemination versus intracervical insemination in donor sperm treatment

Review question

We reviewed the evidence on the effectiveness and safety of intrauterine insemination (IUI) compared to intracervical insemination (ICI) in women who started donor sperm treatment.

Background

The first-line treatment in donor sperm treatment consists of inseminations that can be done by placing sperm inside a woman's uterus to facilitate fertilisation (IUI) or by inserting sperm into the vagina using a small, needleless syringe or a cervical cap (ICI). Both IUI and ICI can be performed in natural cycles or following ovarian stimulation.

Ovarian stimulation can be performed with gonadotrophins, which are injected, or clomiphene citrate, which is available as a tablet. One of the risks of ovarian stimulation is multiple pregnancies. Therefore, the first few cycles of IUI and ICI are usually performed without ovarian stimulation.

It is important that IUI and ICI are performed at a specific time in the woman's menstrual cycle (as close to ovulation as possible). Various techniques of determining the best timing for IUI and ICI in natural cycles are available, such as keeping basal temperature charts, checking cervical mucus scores, testing blood or urine levels of luteinising hormone (LH), or monitoring with ultrasounds.

We compared IUI and ICI with each other, and also compared different types of each technique.

Study characteristics

We found six randomised controlled trials, including 708 women. Two studies compared IUI and ICI in natural cycles. Two studies compared IUI and ICI in gonadotrophin-stimulated cycles. Two studies compared the timing of IUI and ICI. The evidence is current to December 2017.

Key results

There was insufficient evidence to determine whether there was any clear difference between IUI and ICI in live birth rates, in either natural cycles or in gonadotrophin-stimulated cycles. As there was only one live birth in the small study using natural cycles, we could not make any meaningful comparison between the groups. The evidence on gonadotrophin-stimulated cycles suggested that if the live birth rate following ICI was assumed to be 30%, the chance of live birth rate following IUI in gonadotrophin-stimulated cycles would be between 24% and 80%. For IUI and ICI in natural cycles, no multiple pregnancies were reported. In gonadotrophin-stimulated cycles, IUI was associated with higher multiple pregnancy rates than ICI. The evidence suggested that if the risk of multiple pregnancy following ICI in gonadotrophin-stimulated cycles was assumed to be 10%, the risk of multiple pregnancy following IUI would be between 10% and 46%.

We concluded that the evidence was too limited to encourage or discourage either IUI or ICI, in natural cycles or with ovarian stimulation in donor sperm treatment.

Quality of the evidence

Following GRADE assessment, we found that the evidence for all outcomes was of very low quality. The main limitations were risk of bias, due to poor reporting of study methods, and serious imprecision, due to the limited number of studies and small study sizes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Intrauterine insemination versus intracervical insemination in natural cycles

Intrauterine insemination (IUI) versus intracervical insemination (ICI) in donor sperm treatment in natural cycles

Patient or population: women starting donor sperm treatment

Settings: outpatient clinic

Intervention: IUI in natural cycles

Control: ICI in natural cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ICI	IUI				
Live birth rate	Not estimable		OR 3.24 (0.12 to 87.13)	26 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	There was only one live birth in this study (in the IUI group)
Multiple pregnancy rate	No events		Not estimable	26 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	
Clinical pregnancy rate	143 per 1000	507 per 1000 (241 to 769)	OR 6.18 (1.91 to 20.03)	76 (2 studies)	⊕⊕⊕⊕ very low ^{1,2}	
Miscarriage rate	No events			26 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	
Cancellation rate - natural cycles	No available data					

*The basis for the **assumed risk** is the mean rate in the study population. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ Downgraded one level for serious risk of bias associated with poor reporting of study methods (unclear selection and other biases in the individual study)
² Downgraded two levels for very serious imprecision (effect estimate with an extremely wide confidence interval (wider than the interval (wider than the interval 0.5 to 2), or low event rate)

Summary of findings 2. Intrauterine insemination versus intracervical insemination in gonadotropin-stimulated cycles

Intrauterine insemination (IUI) versus intracervical insemination (ICI) in gonadotropin-stimulated cycles

Patient or population: women who are starting donor sperm treatment

Settings: outpatient clinic

Intervention: IUI in gonadotropin-stimulated cycles

Control: ICI in gonadotropin-stimulated cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ICI	IUI				
Live birth rate	300 per 1000	522 per 1000 (236 to 793)	OR 2.55 (0.72 to 8.96)	43 (1 study)	⊕○○○ very low ^{1,2}	
Multiple pregnancy rate	98 per 1000	232 per 1000 (98 to 456)	OR 2.77 (1 to 7.69)	131 (2 studies)	⊕○○○ very low ^{1,2}	
Clinical pregnancy rate	377 per 1000	631 per 1000 (455 to 778)	OR 2.83 (1.38 to 5.78)	131 (2 studies)	⊕○○○ very low ^{1,2}	
Miscarriage rate	33 per 1000	63 per 1000 (14 to 235)	OR 1.97 (0.43 to 9.04)	131 (2 studies)	⊕○○○ very low ^{1,2}	
Cancellation rate	No studies reported this outcome					

*The basis for the **assumed risk** is the mean rate in the study population. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ Downgraded one level for serious risk of bias associated with poor reporting of study methods (unclear selection and other biases in the individual study)
² Downgraded two levels for very serious imprecision (effect estimate with an extremely wide confidence interval, low event rate, or both)

Summary of findings 3. Timing of insemination for intrauterine insemination with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days

Timing of intrauterine insemination (IUI) with donor sperm: insemination one day after the luteinising hormone (LH) surge versus insemination two days after the LH surge.

Patient or population: women starting donor sperm treatment

Settings: outpatient clinic

Intervention: IUI with donor sperm one day after the LH surge (LH + 1)

Control: IUI with donor sperm two days after the LH surge (LH + 2)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	LH + 2	LH + 1				
Live birth rate	No studies reported this outcome					
Multiple pregnancy rate	No studies reported this outcome					
Clinical pregnancy rate	130 per 1000	230 per 1000 (146 to 346)	OR 2 (1.14 to 3.53)	351 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	
Miscarriage rate	No studies reported this outcome					
Cancellation rate	No studies reported this outcome					

*The basis for the **assumed risk** is the mean rate in the study population. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ Downgraded one level for serious risk of bias associated with poor reporting of study methods (unclear selection and other biases in the individual study)
² Downgraded two levels for very serious imprecision (low event rate)

Summary of findings 4. Timing of intrauterine insemination with donor sperm: urinary luteinising hormone test versus temperature curve and cervical mucus score

Timing for intrauterine insemination (ICI) with donor sperm: urinary luteinising hormone (LH) test versus temperature curve and cervical mucus score

Patient or population: women starting donor sperm treatment

Settings: outpatient clinic

Intervention: urinary LH test

Control: temperature curve and cervical mucus score

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	temperature curve and cervical mucus score	urinary LH test				
Live birth rate	No studies reported this outcome					
Multiple pregnancy rate	No studies reported this outcome					
Clinical pregnancy rate	276 per 1000	333 per 1000 (138 to 610)	OR 1.31 (0.42 to 4.11)	56 (1)	⊕⊕⊕⊕ very low ^{1,2}	
Miscarriage rate	No studies reported this outcome					
Cancellation rate	No studies reported this outcome					

*The basis for the **assumed risk** is the mean rate in the study population.. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ Downgraded one level for serious risk of bias associated with poor reporting of study methods (unclear selection and other biases in the individual study).
- ² Downgraded two levels for very serious risk associated with serious imprecision and indirectness (effect estimate with wide confidence interval (wider than the interval 0.5 to 2)).

BACKGROUND

Description of the condition

Donor sperm treatment, or donor insemination, is the oldest fertility treatment for couples with involuntary childlessness due to male infertility ([Seymour 1941](#)).

Since the introduction of intracytoplasmic sperm injection (ICSI) with or without surgical sperm extraction, semen washing to prevent the transmission of human immunodeficiency virus, and preimplantation genetic diagnosis, it is possible for couples with male infertility, human immunodeficiency virus, or those who are carriers of a genetic defect to become parents of a child genetically related to both parents ([Liebaers 1998](#); [Palermo 1992](#); [Semprini 1992](#); [Silber 1996](#); [Tournaye 1994](#)).

These newer types of medically-assisted reproduction have rendered donor sperm treatment a treatment option in couples after failure of surgical sperm retrieval, or ICSI. They may also be used to prevent transmission of human immunodeficiency virus after sperm washing has failed, and to prevent vertical transmission of a genetic defect. In lesbian couples or single women, it is a commonly used technique to achieve pregnancy ([NICE 2013](#); [Vernaev 2004](#)).

Description of the intervention

Donor sperm can be introduced by intrauterine insemination (IUI) or by intracervical insemination (ICI). For both insemination techniques, the use of cryo-preserved sperm is mandatory to prevent transmission of sexually transmitted diseases, such as human immunodeficiency virus, and Hepatitis B and C, although pregnancy rates are lower compared to fresh sperm ([ARSM 2012](#); [Subak 1992](#)).

The sperm can be inseminated in natural cycles or in cycles with ovarian stimulation.

In natural cycles, the timing of insemination may be determined with a basal body temperature chart in combination with cervical mucus scores ([Insler 1977](#)). Another method to detect ovulation is by measuring urinary luteinising hormone (LH). The advantage of this test is that women can perform the urinary LH tests at home. Detection of a rise in the LH level can also be done in the clinic, with daily blood samples. Finally, transvaginal ultrasound, in combination with ovulation induction by the administration of human chorionic gonadotropin (hCG), may be used to time the insemination ([Cantineau 2014](#)).

In cycles with ovarian stimulation, women receive clomiphene citrate, an anti-oestrogen, or gonadotrophins to induce the growth of up to three follicles. The timing of insemination is determined by transvaginal ultrasound, combined with hCG-triggered ovulation.

The main difference between IUI and ICI is the processing of the sperm. In IUI, the sperm is processed. There are two preparation techniques; one is to freeze the sperm without processing, thaw the sperm when needed, and process the sperm against a density gradient centrifugation, wash it with culture medium, or both. The other is to process the sperm against a density gradient centrifugation, wash it with culture medium, or both, before freezing the sperm, and then thaw the sperm when needed. There is no evidence that one technique is superior to the other ([Boomsma](#)

[2007](#)). After thawing, the sperm is inseminated into the uterine cavity.

In ICI, the sperm is cryo-preserved without processing, and thawed when needed. After thawing, the sperm is inseminated at the external cervical os, using a cap or a straw. The cervical cap acts as an ectocervical reservoir, placed in the cervical canal for a few hours ([Coulson 1996](#); [Flierman 1997](#)).

How the intervention might work

In IUI, the sperm is processed and inseminated into the uterine cavity. In ICI, the sperm is not processed, and is inseminated at the external cervical os. The inseminated sperm then has to fertilize the released oocyte. Both IUI and ICI are often combined with ovarian stimulation; multiple pregnancies are a side effect, occurring in between 10% and 40% of women ([Fauser 2005](#)).

Why it is important to do this review

The present review is an update and extension of a previous Cochrane review ([Besselink 2008](#)). [Besselink 2008](#) had compared IUI with ICI, and pooled the data of natural cycles with cycles with ovarian stimulation. In this update, we disentangled ovarian stimulation from the natural cycle, and added other cointerventions that might influence pregnancy rates in donor sperm treatment.

It is unclear which insemination technique, IUI or ICI, is more effective in terms of live birth rate. Summarising the evidence on the effectiveness and safety of IUI and ICI in donor sperm treatment will help women and gynaecologists to make informed decisions about their choices for donor sperm treatment.

OBJECTIVES

To compare the effectiveness and safety of intrauterine insemination (IUI) and intracervical insemination (ICI) in women who start donor sperm treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. We analysed only the pre-cross-over data from cross-over trials. We excluded quasi-randomised controlled trials.

Types of participants

- women starting donor sperm treatment
- women undergoing donor sperm treatment who received treatment for anovulation

Types of interventions

- IUI or ICI in natural cycles
- IUI or ICI with ovarian stimulation
- cointerventions in IUI
- cointerventions in ICI

Types of outcome measures

Primary outcomes

1. Live birth rates - defined as delivery of a live fetus after 20 completed weeks of gestation.

2. Multiple pregnancy rates

Secondary outcomes

3. Ongoing pregnancy rates - defined as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed with ultrasound

4. Clinical pregnancy rates - defined as evidence of a gestational sac, confirmed by ultrasound

5. Miscarriage rates

6. Adverse effects, cancellation rates

If a study compared multiple cycles the cumulative outcomes were registered.

Search methods for identification of studies

We searched for all published and unpublished RCTs of IUI and ICI in donor sperm treatment, without language restriction.

We carried out all searches in consultation with the Gynaecology and Fertility Group (formerly Menstrual Disorders and Subfertility Group) Information Specialist.

Electronic searches

Marian Showell, Information Specialist, The Gynaecology and Fertility Group, developed the search strategies. See [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#)

We searched the following electronic databases:

- The Cochrane Gynaecology and Fertility Group Trials Register, PROCITE platform (5 October 2016);
- The Cochrane Central Register of Controlled trials, via the Cochrane Register of Studies Online (CRSO Web platform) (5 October 2016);
- MEDLINE Ovid (1946 to 5 October 2016);
- Embase Ovid (1974 to 5 October 2016);
- PsycINFO Ovid (1806 to 5 October 2016);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature, 1982 to 5 October 2016).

- EU Clinical Trials Register - www.clinicaltrialsregister.eu/; World Health Organization International Trials Registry Platform search portal (WHO ICTRP; apps.who.int/trialsearch/); (5 October 2016).

On 15 December 2017, we searched the following databases and trials registers. See [Appendix 7](#); [Appendix 8](#); [Appendix 9](#) for our search strategies.

Databases:

- PubMed and Google Scholar;
- Conference abstracts on the Web of Knowledge;
- Grey literature on Greylit.org;
- OpenGrey for unpublished literature for Europe at www.opengrey.eu.

Trial registers:

- U.S. National Library of Medicine - www.clinicaltrials.gov/;
- EU Clinical Trials Register - www.clinicaltrialsregister.eu/;
- World Health Organization International Trials Registry Platform search portal (WHO ICTRP; apps.who.int/trialsearch/);
- BioMed Central register - www.isrctn.com/;
- Dutch trial register - www.trialregister.nl/.

Searching other resources

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

Data collection and analysis

Selection of studies

Marian Showell conducted the initial screening of titles and abstracts retrieved by the search. We tried to retrieve the full text of all potentially eligible studies. If full texts were not available, we contacted the authors for further information. Two review authors (PK, MvW) independently examined the full text of articles for compliance with the inclusion criteria and selected eligible studies. We corresponded with study investigators as required, to clarify study eligibility. Disagreements were resolved by discussion. We planned that if any report required translation, we would describe the process used for data collection. We documented the selection process with a 'PRISMA' flow chart ([Figure 1](#)).

Figure 1. Study flow diagram

Data extraction and management

Two review authors (PK and MvW) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. Any disagreements were resolved by discussion. We entered details of the studies into the 'Characteristics of included studies' table. We presented studies that appeared to meet the inclusion criteria but were excluded from the review in the 'Characteristics of excluded studies' table, briefly stating the reason for exclusion, but giving no further information. We corresponded with study investigators for further data on methods or results, as required.

Assessment of risk of bias in included studies

Two review authors (PK, MvW) independently extracted information regarding the risk of bias (threats to internal validity) under six domains (see the Cochrane 'Risk of Bias' assessment tool in [Appendix 10 \(Higgins 2011\)](#)). We resolved any differences by discussion.

1. Sequence generation. Evidence that an unpredictable random process was used.
2. Allocation concealment. Evidence that the allocation list was not available to anyone involved in the recruitment process.
3. Blinding of participants, clinicians, and outcome assessors. Evidence that knowledge of allocation was not available to those involved in subsequent treatment decisions or follow-up efforts.
4. Completeness of outcome data. Evidence that any losses to follow-up were low and comparable between groups.
5. Selective outcome reporting. Evidence that major outcomes had been reported in sufficient detail to allow analysis, independent of their apparent statistical significance. When data were obtained, but not reported in the paper, this was considered to be internal reporting bias.
6. Other potential sources. Evidence of miscellaneous errors or circumstances that might influence internal validity of trial results.

We sought missing details from the authors of the original publications. We present all details in the 'Risk of bias' table following each included study.

Measures of treatment effect

For dichotomous data, we used the number of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). We presented 95% confidence intervals for all outcomes.

Unit of analysis issues

We expressed all outcomes per woman randomised. Where only data 'per cycle' were available without the number of women included, analysis was not possible, and we did not include the data. In the case of cross-over trials, we only included data from the first phase.

Dealing with missing data

We analysed the data on an intention-to-treat basis as often as possible. When there was insufficient information in the published report, we attempted to contact the authors for clarification. If missing data became available, the data were included in

the analysis. Where randomised participants were missing from outcome assessment, we first contacted the authors for additional data. If further data were not available, we assumed that missing participants had failed to achieve pregnancy, and had not experienced any of the reported adverse events. We anticipated that trials conducted over 10 years ago may not have data on live birth rates for the study participants.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. The presence of statistical heterogeneity of treatment effect among trials was determined using the I^2 statistic ([Higgins 2011](#)). We took an I^2 measurement greater than 50% to indicate substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. We had planned that if we included 10 or more studies in an analysis, we would use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

When multiple studies were available on a similar comparison, we used Review Manager 5 software ([Review Manager 2014](#)) to perform the meta-analyses, using the Mantel-Haenszel method with a fixed-effect model. For reporting purposes, we translated primary outcomes to absolute risks.

Subgroup analysis and investigation of heterogeneity

We had not pre-planned subgroup analyses. If substantial heterogeneity ($I^2 > 50\%$) existed among studies, we planned to explore this informally using the clinical and design details recorded in the table 'Characteristics of included studies'.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding study eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

- eligibility had been restricted to studies without high risk of bias;
- a random-effects model had been adopted;
- the summary effect measure had been risk ratio rather than odds ratio.

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

We prepared a 'Summary of findings' table using GRADEpro GDT and Cochrane methods ([GRADEpro GDT](#); [Higgins 2011](#)). This table evaluates the overall quality of the body of evidence for the main review outcomes (live births, multiple pregnancy, clinical pregnancy, miscarriages, cancellation rate) for the main review comparison (IUI versus ICI). We prepared additional 'Summary of findings' tables for the main review outcomes for other important

comparisons (timing of IUI, and timing of ICI). We assessed the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness, and publication bias). Two review authors independently made judgements about the quality of the evidence (high, moderate, low, or very low), resolving disagreements by discussion. They justified, documented, and incorporated judgments into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The search retrieved 456 references. We assessed 19 studies as potentially eligible and retrieved them in full text. We found six studies that met our inclusion criteria. We excluded 13 studies.

See [Figure 1](#); 'Characteristics of included studies' table; 'Characteristics of excluded studies' table.

Included studies

We included six studies, all single centre randomised trials, that compared first-line treatment strategies in women who started with donor sperm treatment.

Design

All trials analysed more than one cycle per woman, with a maximum of six cycles. One study was a cross-over study, in which the cross-over was performed after one cycle. Therefore, we only used the first cycle for analysis ([Hurd 1993](#)).

Only one study performed a power calculation ([Blockeel 2014](#)).

Participants

[Robinson 1992](#) and [Matorras 1996](#) included couples with azoospermia or oligospermia. [Patton 1992](#) and [Hurd 1993](#)

also included single women. [Wainer 1995](#) included men with azoospermia, and men with a genetic defect. [Blockeel 2014](#) also included lesbian couples.

Interventions

Two studies compared intrauterine insemination (IUI) to intracervical insemination (ICI) in natural cycles, including the use of clomiphene citrate in cases of anovulation due to polycystic ovarian syndrome (PCOS; ([Hurd 1993](#); [Patton 1992](#)). Two studies compared IUI to ICI in gonadotrophin-stimulated cycles ([Matorras 1996](#); [Wainer 1995](#)). One study reported on the timing of ICI ([Robinson 1992](#)), and one study reported on the timing of IUI ([Blockeel 2014](#)).

Outcomes

Two studies reported data on live births ([Hurd 1993](#); [Wainer 1995](#)), and three trials reported on multiple pregnancy rates ([Hurd 1993](#); [Matorras 1996](#); [Wainer 1995](#)). Four studies reported clinical pregnancy rates as the primary outcome ([Blockeel 2014](#); [Matorras 1996](#); [Patton 1992](#); [Robinson 1992](#)). [Hurd 1993](#), [Matorras 1996](#), and [Wainer 1995](#) reported miscarriage rates. Cancellation rates were not reported.

Excluded studies

We excluded thirteen trials: 11 trials because they were unable to provide pre-cross-over data ([Alexander 1994](#); [Byrd 1990](#); [Carroll 2001](#); [Coulson 1996](#); [Flierman 1997](#); [Patton 1990](#); [Peters 1993](#); [Pistorius 1996](#); [Ract 1992](#); [Urry 1988](#); [Williams 1995](#)); two studies because they made no distinction between natural cycles and gonadotrophin-stimulated cycles ([Le Lannou 1989](#); [Walker 1993](#)).

Risk of bias in included studies

We summarised the risks of bias in the included studies in [Figure 2](#) and [Figure 3](#).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias domain 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
Blockeel 2014	+	?	+	+	+	?
Hurd 1993	?	?	?	+	+	-
Matorras 1996	+	?	?	+	+	?
Patton 1992	?	?	+	-	+	-
Robinson 1992	?	?	+	?	+	?
Wainer 1995	?	?	?	+	+	?

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

Allocation

We rated two studies at low risk of selection bias for sequence generation, since they used computer randomisation or random number tables for sequence generation. In four studies, the method used for sequence generation was not fully described, and we rated them at unclear risk of selection bias in relation to sequence generation.

All studies failed to describe methods used for allocation concealment, and we rated these at unclear risk of bias for this domain.

Blinding

Blinding was not performed in any of the studies. We did not consider that blinding was likely to influence findings for the primary review outcomes (live birth and multiple pregnancy). Blinding might influence outcomes for other adverse events, but no studies reported relevant data for this outcome.

Incomplete outcome data

One trial had a high risk of attrition bias (Patton 1992). For one trial, this was unclear (Robinson 1992). The other four trials had a low risk of bias for this domain.

Selective reporting

We rated all six studies at low risk of selective reporting bias. All outcomes planned in the methods sections were reported.

Other potential sources of bias

We rated this as high for two studies, as these trials included some women with anovulation due to PCOS, who received ovulation induction with clomiphene citrate (Hurd 1993; Patton 1990). The number of women receiving clomiphene citrate was not

described, and outcomes were not reported separately for this group, therefore, we could not perform subgroup analyses. We rated the risk of other potential biases as unclear for the other four studies. Baseline characteristics were not always provided, and were not perfectly balanced over the two treatment groups. Only one study mentioned the duration of the trial (Blockeel 2014). Other studies did not report on study duration. Studies with a long duration can induce bias by creating heterogeneity in the study group.

Blockeel 2014 included women after one to six failed IUI attempts. This may have caused bias since women who became pregnant in the first cycles were not included in this study.

Effects of interventions

See: [Summary of findings for the main comparison](#) Intrauterine insemination versus intracervical insemination in natural cycles; [Summary of findings 2](#) Intrauterine insemination versus intracervical insemination in gonadotropin-stimulated cycles; [Summary of findings 3](#) Timing of insemination for intrauterine insemination with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days; [Summary of findings 4](#) Timing of intrauterine insemination with donor sperm: urinary luteinising hormone test versus temperature curve and cervical mucus score

1. Intrauterine insemination (IUI) versus intracervical insemination (ICI)

See [Summary of findings for the main comparison](#), [Summary of findings 2](#).

Primary outcomes

1.1 Live birth rate

(Figure 4)

Figure 4. Forest plot of comparison: 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), outcome: 1.1 Live birth rate.

Two randomised controlled trials (RCT), including 69 women, reported on live births (Hurd 1993; Wainer 1995). There was insufficient evidence to determine whether there was any clear difference in live birth rates in natural cycles after IUI or ICI (OR 3.24, 95% CI 0.12 to 87.13; 1 RCT, 26 women; Analysis 1.1; very low-quality evidence (Hurd 1993)).

There was also insufficient evidence to determine whether there was any difference in live birth rates in gonadotrophin-stimulated cycles after IUI or ICI (OR 2.55, 95% CI 0.72 to 8.96; 1 RCT, 43 women; Analysis 1.1; very low-quality evidence (Wainer 1995)).

This suggested that if the chance of a live birth following ICI in gonadotrophin-stimulated cycles was assumed to be 30%, the chance following IUI in gonadotrophin-stimulated cycles would be between 24% and 80%.

Sensitivity analyses - as only one study reported on live birth the only sensitivity analysis possible was to determine the risk ratio. The RR for live birth was 1.83 (95% CI 0.86 to 3.91) for IUI versus IC.

1.2 Multiple pregnancy rate (Figure 5)

Figure 5. Forest plot of comparison: 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), outcome: 1.2 Multiple pregnancy rate.

Test for subgroup differences: Not applicable

Risk of bias legend

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

For IUI and ICI in natural cycles, no multiple pregnancies were reported. ICI in gonadotrophin-stimulated cycles was associated with lower multiple pregnancy rates than IUI in gonadotrophin-stimulated cycles (OR 2.77, 95% CI 1.00 to 7.69; 2 RCTs, 131 women; I² = 0%; Analysis 1.2; very low-quality evidence). This suggested that if the risk of a multiple pregnancy following ICI in gonadotrophin-stimulated cycles was assumed to be 10%, the risk following IUI gonadotrophin-stimulated cycles would be between 11% and 35%.

Sensitivity analyses - as only two studies reported on multiple pregnancy per woman we used a random effect model and determined the risk ratio. Pooling data using a random effect model

resulted in exactly the same OR of 2.77 (95% CI 1.00 to 7.69). The risk ratio for multiple pregnancy per woman was 2.32 (95% CI 0.98 to 5.53) for IUI versus IC.

Secondary outcomes

1.3 Ongoing pregnancy rate

No studies reported on ongoing pregnancy rate.

1.4. Clinical pregnancy rate

(Figure 6)

Figure 6. Forest plot of comparison: 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), outcome: 1.3 Clinical pregnancy rate

Four studies, including 207 women, reported on clinical pregnancy (Hurd 1993; Matorras 1996; Patton 1992; Wainer 1995).

There was a higher clinical pregnancy rate after IUI compared to ICI in natural cycles (OR 6.18, 95% CI 1.91 to 20.03; 2 RCTs, 76 women; $I^2 = 48\%$; Analysis 1.3; very low-quality evidence (Hurd 1993; Patton 1992)).

There was a higher clinical pregnancy rate after IUI compared to ICI in gonadotrophin-stimulated cycles (OR 2.83, 95% CI 1.38 to 5.78; 2 RCTs, 131 women; $I^2 = 0\%$; Analysis 1.3; very low-quality evidence (Matorras 1996; Wainer 1995)).

1.5 Miscarriage rate

Three studies, including 157 women, reported on miscarriage (Hurd 1993; Matorras 1996; Wainer 1995).

In natural cycles, no miscarriages were reported (Hurd 1993).

There was insufficient evidence to determine whether there was any clear difference in miscarriage rates after IUI compared to ICI in gonadotrophin-stimulated cycles (OR 1.97, 95% CI 0.43 to 9.04; 2 RCTs, overall 67 pregnancies; $I^2 = 50\%$; Analysis 1.4; very low-quality evidence (Matorras 1996; Wainer 1995)).

1.6 Adverse effects, cancellation rate

Cancellation rates were not reported.

2. Timing of intrauterine insemination (IUI)

See Summary of findings 3.

One study reported on the timing of IUI (Blockeel 2014). IUI was performed one day after a rise in luteinising hormone (LH) blood levels compared to two days after a rise in LH blood levels.

Primary outcomes

2.1. Live birth rate

No studies reported on live birth rates.

2.2. Multiple pregnancy rate

No studies reported on multiple pregnancy rates.

Secondary outcomes

2.3. Ongoing pregnancy rate

No studies reported on ongoing pregnancy rates.

2.4. Clinical pregnancy rate

(Figure 7)

Figure 7. Forest plot of comparison: 2 Timing of intrauterine insemination (IUI) with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days, outcome: 2.3 Clinical pregnancy rate **Risk of bias legend**

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

One study, including 351 women, reported on clinical pregnancy rate and the timing of IUI (Blockeel 2014).

We found a higher clinical pregnancy rate when IUI was performed one day after a rise in LH blood levels compared to two days after a rise in LH blood levels (OR 2.00, 95% CI 1.14 to 3.53; 1 RCT, 351 women; Analysis 2.3; low-quality evidence (Blockeel 2014)).

2.5. Miscarriage rate

No studies reported on miscarriage rates.

2.6 Adverse effects, cancellation rate

No studies reported these outcomes.

3. Timing of intracervical insemination (ICI)

See Summary of findings 4.

One study reported on the timing of ICI (Robinson 1992). ICI performed following a rise in urinary luteinising hormone (LH)

levels was compared to ICI performed after a rise in basal temperature in combination with cervical mucus scores.

Primary outcomes**3.1. Live birth rate**

No studies reported on live birth rates.

3.2. Multiple pregnancy rate

No studies reported on multiple pregnancy rates.

Secondary outcomes**3.3. Ongoing pregnancy rate**

No studies reported on ongoing pregnancy rates.

3.4. Clinical pregnancy rate

(Figure 8)

Figure 8. Forest plot of comparison: 3 Timing of intracervical insemination (ICI) with donor sperm: urinary luteinising hormone (LH) test versus temperature curve and cervical mucus score, outcome: 3.2 Clinical pregnancy rate **Risk of bias legend**

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

One study, including 56 women, reported on clinical pregnancy rate and timing of ICI (Robinson 1992).

There was insufficient evidence to determine whether there was any clear difference in clinical pregnancy rate after ICI was performed following a rise in urinary LH levels compared to a rise in

basal temperature in combination with cervical mucus scores (OR 1.31, 95% CI 0.42 to 4.11; 1 RCT, 56 women; [Analysis 3.2](#); very low-quality evidence ([Robinson 1992](#))).

3.5. Miscarriage rate

No studies reported on miscarriage rates.

3.6 Adverse effects, cancellation rates

No studies reported on these outcomes.

Assessment of reporting biases

We were unable to assess the risk of reporting biases because there were insufficient data to construct a funnel plot.

DISCUSSION

Summary of main results

In this systematic review, we selected studies that provided data on the effectiveness and safety of intrauterine insemination (IUI) and intracervical insemination (ICI) in donor sperm treatment. We found four studies that compared IUI and ICI, two of which performed IUI and ICI in natural cycles, and two performed IUI and ICI in gonadotrophin-stimulated cycles.

There was insufficient evidence to determine whether there was any real difference in live birth rates between IUI and ICI in natural cycles. There were more clinical pregnancies following IUI in natural cycles compared to ICI in natural cycles. There were no multiple pregnancies reported following IUI or ICI in natural cycles. Also, there was insufficient evidence to determine whether there was any clear difference in live birth rates between IUI and ICI in gonadotrophin-stimulated cycles. There were more clinical pregnancies following IUI than ICI in gonadotrophin stimulated cycles. IUI was associated with higher multiple pregnancy rates than ICI in gonadotrophin-stimulated cycles.

We found two studies on timing of insemination; one on timing of ICI and one on timing of IUI. None of the studies reported on the primary outcomes of live birth and multiple pregnancy rates.

Overall completeness and applicability of evidence

The studies included in this review were clinically heterogeneous. Studies differed in population, intervention, and laboratory techniques, and used different inclusion criteria. Two studies included couples with azoospermia or oligospermia, one study included couples with azoospermia and men with a genetic defect, two studies included single women, and one study included lesbian couples. This may have biased outcomes, since it is known that in heterosexual couples, partners of azoospermic men conceive more quickly after donor sperm treatment, compared to partners of men with spermatozoa in their ejaculates, suggesting that in heterosexual couples, unknown female factors also contribute to subfertility of these couples ([NICE 2013](#)).

One study included women after one to six failed IUI attempts. This may have caused bias, since women who became pregnant in the first cycles were not included in this study ([Blockeel 2014](#)).

The studies also differed in treatment regimens. One study started ovarian stimulation on the second day of the menstrual cycle with 150 IU of recombinant human follicle stimulating hormone

(recFSH ([Matorras 1996](#))), while one study started on the fourth or fifth day of the menstrual cycle with 75 IU of human menopausal gonadotrophin (hMG) followed by 150 IU of hMG on the sixth and seventh day ([Wainer 1995](#)). Human chorionic gonadotropin (hCG) was administered on the day that two or more follicles were larger than 17 mm and oestrogen levels were higher than 400 pg/mL, and IUI was performed 36 hours after ovulation was triggered ([Matorras 1996](#)). Another study administered hCG if one to three follicles were larger than 15 mm, and IUI was performed 38 hours after ovulation was triggered ([Wainer 1995](#)). In ICI with ovarian stimulation, insemination was performed twice, with a cervical cap — 12 and 36 hours after ovulation was triggered. Cancellation of the cycle was mentioned in one study when more than six follicles reached 17 mm or more ([Matorras 1996](#)). Studies on IUI and ICI in natural cycles performed one insemination, on the day after the urinary luteinising hormone (LH) level surge. In ICI, inseminations were performed with a straw. The number of motile sperm used for insemination differed between studies, from 1.58 million post wash to 43.7 million. It was difficult to assess if differences in sperm count influenced pregnancy outcomes, since studies on the effect of sperm count on pregnancy rates in donor sperm treatment are lacking.

One study in natural cycles, and one study in gonadotrophin-stimulated cycles did report on live births, and one study in natural cycles and two studies in gonadotrophin-stimulated cycles did report on multiple pregnancy rates. Most of these trials were published between 1992 and 1993, when clinical pregnancy rate was still an accepted endpoint. Nowadays, it is common to use live birth as a primary outcome, and multiple pregnancies as a reflection of the quality of care or safety.

Finally, studies on IUI or ICI that compared natural cycles with gonadotrophin-stimulated cycles were lacking.

In conclusion, it was uncertain which insemination technique, IUI or ICI, resulted in higher live birth rates. Differences in inclusion criteria, treatment regimens, number of motile sperm used for insemination, primary outcomes, and small study sizes made it difficult to compare studies on the effectiveness and safety of IUI and ICI in natural cycles. Moreover, studies on IUI and ICI in gonadotrophin-stimulated cycles used differences in stimulation protocols, cancellation rates for the number of follicles, and number of motile sperm used for insemination.

Quality of the evidence

Following the GRADE assessment, we found that evidence for all outcomes was of very low quality; the main limitations were risk of bias, mainly due to poor reporting of study methods, and serious imprecision. None of the studies described the method they used for allocation concealment, we judged one study to have a high attrition bias, and two to have high risk of potential bias associated with the inclusion of anovulatory women receiving clomiphene citrate.

Potential biases in the review process

Strengths of this review included a comprehensive systematic search for eligible studies, rigid inclusion criteria for RCTs, and independent data extraction and analysis by two review authors. The possibility of publication bias was minimized by searching for both published and unpublished studies, such as abstracts from

meetings. We may have introduced bias in our assumptions about missing data. We assumed that if further data were not available, missing participants had failed to achieve pregnancy. This may have caused under-reporting of pregnancies and adverse events. As with any review, we cannot guarantee that we found all eligible studies.

One of our peer reviewers noted that our review did not include studies of cointerventions associated with donor sperm treatment, apart from comparisons of the timing. Potential cointerventions are luteal support, type of trigger, and single versus double insemination. These comparisons were outside the planned scope of the current review, and we were not aware of any relevant randomised evidence. However, we may consider extending the scope of the review in future updates.

Agreements and disagreements with other studies or reviews

We added RCTs on the timing of IUI and ICI to the previous Cochrane review, which focused their conclusions on clinical pregnancy ([Besselink 2008](#)). Our results concerning pregnancy outcomes were comparable.

A previous non-Cochrane review and meta-analysis suggested that IUI resulted in higher clinical pregnancy rates than ICI ([Goldberg 1999](#)). The authors pooled data of the four RCTs that were also included in our review with the results of three cross-over studies. As pre-cross-over data were not retrievable, these results could not validly be used.

AUTHORS' CONCLUSIONS

Implications for practice

There was insufficient evidence to determine whether there was a clear difference in live birth rates between intrauterine insemination (IUI) and intracervical insemination (ICI) in natural or gonadotrophin-stimulated cycles in women who started donor sperm treatment. There was no evidence available for the effect of timing on live birth following either IUI or ICI. Very low-quality evidence suggested that in gonadotrophin-stimulated cycles, ICI may be associated with a higher clinical pregnancy rate than IUI, but also with a higher risk of multiple pregnancy.

We concluded that the evidence was too limited to choose between IUI or ICI, in natural cycles or with ovarian stimulation, in donor sperm treatment.

Implications for research

We suggest that further research is needed. Most women requiring donor sperm treatment are fertile women. In these women, primary treatment should be aimed at facilitating conception leading to a live birth without increasing the risks of multiple pregnancy rates. Therefore, we suggest that further research should focus on (cost) effectiveness of IUI versus ICI in natural cycles in women who are starting donor sperm treatment.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Blockeel 2014

Methods	<p>Prospective open label, randomised trial, single centre</p> <p>Randomisation: random by using an open computer-generated list</p> <p>Power calculation: In order to detect a difference of 10% to 20% in pregnancy rate with a power of 80% and a two-sided significance level of 5%, a total of 420 cycles were needed.</p>
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • male factor infertility or severe oligoasthenoteratozoospermia; • presence of inheritable genetic disorders of the male partner; • lesbian couples or single women; • age between 18 and 39 years old; • regular menstrual cycle, ranging from 21 to 35 days; • had undergone no more than six unsuccessful IUI attempts. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • presence of tubal factor infertility, endometriosis classified as American Fertility Society II or higher • patients with a serum progesterone > 1.2 ng/mL on the day of LH rise or > 3 follicles > 15 mm on the day of the LH rise. <p>Basic characteristics:</p> <ul style="list-style-type: none"> • age: IUI LH + 1 = 32.0 ± 4.1; IUI LH + 2 = 32.1 ± 3.8 • previous pregnancy: IUI LH + 1 = 55 (25.8%); IUI LH + 2 = 62 (31.2%) • number of previous IUI cycles: IUI LH + 1 = 1 (0 to 3); LH + 2 = 1 (0 to 3)
Interventions	<p>Timing of IUI was performed by blood sampling LH levels, combined with transvaginal ultrasound from day 11 of the menstrual cycle onward. IUI was performed one day or two days after the LH rise.</p> <p>After the IUI, 10 minutes of bedrest were prescribed.</p>
Outcomes	<p>Primary Outcome: clinical pregnancy rate per IUI cycle</p> <p>Secondary outcome: the rate of positive BHCG results, endocrine profile of included women.</p> <p>Adverse outcome: biochemical pregnancy</p>
Notes	<p>Total women randomised = 315</p> <p>211 women underwent a single treatment cycle</p> <p>93 women underwent more than one treatment cycle</p> <p>182 women in LH + 1 group</p>

Blokeel 2014 (Continued)

169 women in LH + 2 group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by using an open computer-generated list. The randomisation procedure took place during the daily monitoring sessions at the clinic, when an LH rise was observed. It was done on IUI cycle level.
Allocation concealment (selection bias)	Unclear risk	Study failed to describe methods of allocation concealment, and we rated this as unclear risk of bias for this domain.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was not performed, but we did not consider blinding of participants or assessors could have affected pregnancy outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appeared all couples completed the study.
Selective reporting (reporting bias)	Low risk	Preplanned outcome reported
Other bias	Unclear risk	Not sure why there were more previous IUI cycles done in the LH + 2 group Results on IUI cycle basis and not on patient level. IUI was not performed exactly 12 to 24 hours after the LH surge.

Hurd 1993

Methods	<p>Prospective, open label, cross-over randomised, single centre trial.</p> <p>Randomisation: random number lists, allocation concealment unclear.</p> <p>Power analysis not performed</p> <p>Only pre-cross-over data were used.</p>
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> azoospermia, severe oligospermia and single women. <p>All patients had an ovulatory cycle. Abnormalities in ovulatory dysfunction were treated with clomiphene citrate (50 mg to 100 mg for 5 days). All women underwent a hysterosalpingography, and 15 women also had laparoscopy, and 7 of those had laser treatment for tubal adhesions or endometriosis grade I or II.</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> patients with ovulatory dysfunction not corrected by clomiphene citrate <p>Basic characteristics:</p> <ul style="list-style-type: none"> Age: not stated per intervention group (all women = 23 ± years)
Interventions	IUI versus ICI in natural cycles

Hurd 1993 (Continued)

In all groups, insemination was planned by use of urinary LH tests. Inseminations were performed the day after the LH surge.

In case of ICI, insemination was performed by straw, after the insemination, remained 15 minutes in supine position.

Ovulatory dysfunction was treated with clomiphene citrate

A maximum of four inseminations per technique were performed, resulting in a maximum of 10 cycles per woman.

Outcomes	<p>Primary outcome: live birth</p> <p>Secondary outcome: pregnancy rate</p> <p>Adverse outcomes: miscarriage rate, multiple pregnancy rate, ectopic pregnancy rate</p>
Notes	<p>Total women randomised: 26</p> <p>13 women to IUI; 13 women to ICI</p> <p>A third treatment in this three-way study was transcervical intratubal insemination combined with IUI</p> <p>Pregnancy defined by serum hCG + ultrasound (gestation sac)</p> <p>Donor sperm was purchased from International Cryogenics</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A random number list was used. Before the start of the study, six possible combinations of techniques, with either a different initial technique or a different order of techniques, were arranged in a random order.
Allocation concealment (selection bias)	Unclear risk	Study failed to describe methods of allocation concealment, and we rated this as unclear risk of bias for this domain.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not performed, but we did not consider blinding of participants or assessors could have affected pregnancy outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study.
Selective reporting (reporting bias)	Low risk	Appeared to report pre-specified outcomes.
Other bias	High risk	Some women were treated with clomiphene citrate

Matorras 1996

Methods	<p>Prospective, open label, randomised trial, single centre.</p> <p>Randomisation: random number table, with unclear allocation concealment.</p> <p>Power analysis was not performed</p>
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Matorras 1996 (Continued)

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> male infertility, stated as a sperm count of $<1.5 \times 10^6$ motile sperm after Percoll preparation. all patients had a history of subfertility > 2 years, at least one patent tube, younger than 40 years, an abnormal sperm analysis according to WHO criteria, and < 1.5 million motile sperm after Percoll preparation. <p>Only cryopreserved donor sperm was used.</p> <p>Exclusion criteria: not specified</p> <p>Baseline characteristics:</p> <ul style="list-style-type: none"> age: ICI = 31.89 ± 3.71 years; IUI = 30.78 ± 3.71 years duration of infertility: ICI = 5.97 ± 3.13 years; IUI = 7.81 ± 3.75 years proportion of couples with azoospermia: ICI = 56.10%; IUI = 65.96% proportion of couples with normal infertility studies: ICI = 48.78%; IUI = 59.57%
Interventions	<p>IUI versus ICI in gonadotrophin-stimulated cycles</p> <p>In both groups, gonadotrophin stimulation was started at 2nd day of the menstrual cycle, with hMG two ampoules (pergonal 500) or 150 IU recFSH. Monitoring was carried out by transvaginal ultrasound and E2 monitoring. Gonadotrophin dosage was adjusted according to the response.</p> <p>HCG was given on the day that two or more follicles > 17 mm and $E2 > 400$ pg/mL. A cycle was cancelled if more than six follicles > 17 mm were present or $E2 > 2000$ pg</p> <p>In IUI, insemination was performed 36 hours after administering hCG. After insemination, the patient stayed in supine position for 20 minutes.</p> <p>Pericervical insemination was performed by cap; the cap was positioned and remained in place for 16 to 18 hours. Two inseminations were performed 12 and 36 hours after hCG administration.</p> <p>Luteal phase support was given if $E2$ levels were < 1500 pg/mL A maximum of 6 insemination cycles were performed</p>
Outcomes	<p>Primary outcome: pregnancy rate</p> <p>Secondary outcome: Pregnancy rate with azoospermic partner, pregnancy rate with or without fertility problems after all cycles</p> <p>Adverse outcomes: miscarriage rate, multiple pregnancy rate</p>
Notes	<p>Total 88 women randomised: 47 IUI, 41 ICI</p> <p>Pregnancy defined by the visualisation of a gestational sac at 6th to 7th week of amenorrhoea</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table was used. "Patients were assigned randomly to one of the two following groups using an aleatory number table: pericervical insemination donor (41 women) and IUI donor (47 women)."
Allocation concealment (selection bias)	Unclear risk	Study failed to describe methods of allocation concealment, and we rated this as unclear risk of bias for this domain.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not performed, but we did not consider blinding of participants or assessors could have affected pregnancy outcomes.

Matorras 1996 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	It appeared all women completed the study
Selective reporting (reporting bias)	Low risk	It appeared that all outcomes were reported
Other bias	Unclear risk	Study groups differed slightly in age, duration of infertility, and diagnosis.

Patton 1992

Methods	<p>Prospective, open label, randomised trial, single centre.</p> <p>Randomisation: unclear, allocation concealment unclear.</p> <p>Power analysis was not performed.</p>
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • azoospermia or severe oligospermia or single women • all patients had an ovulatory cycle. • abnormalities in ovulatory dysfunction were treated with clomiphene citrate (50 mg to 150 mg for 5 days). An optimal cycle was defined as follicular phase of 10 days and luteal phase of 12 days. Tubal patency was tested in women with a historical risk. <p>Exclusion criteria: women with an abnormal hysterosalpingogram.</p> <p>Baseline characteristics:</p> <p>Age: ICI = 32.0 ± 5; IUI = 30.7 ± 5</p> <p>Number of drop-outs: 9 IUI dropouts and 10 ICI dropouts; 7 women dropped out before the first insemination; 12 were eliminated from analyses for the following reasons: more than a single route of insemination (4), more than one insemination per cycle (2), uterine structural anomalies (4), gonadotropin use (2)</p>
Interventions	<p>IUI versus ICI in the natural cycle</p> <p>In both groups, insemination was planned by use of LH levels in urine.</p> <p>Inseminations were performed on the day after the positive LH test, expect on Friday, when the inseminations were performed the same day.</p> <p>For IUI, the patient remained recumbent for 10 to 15 minutes.</p> <p>In ICI, insemination was performed by straw, and was pooled against the cervix for 20 minutes.</p> <p>Abnormalities in ovulatory function were treated with clomiphene citrate, this was when the basal body temperature chart showed anovulation or the luteal phase was < 12 days.</p> <p>A maximum of 6 insemination cycles were performed</p>
Outcomes	<p>Primary outcome: pregnancy rate</p> <p>Secondary outcome: Pregnancy rate after one cycle, pregnancy rate after all cycles</p> <p>Adverse outcome: study does not report on this</p>
Notes	Total 50 women randomised: 28 IUI; 22 ICI

Patton 1992 (Continued)

Pregnancies were confirmed by standard serum assays of human chorionic gonadotropin and ultra-sound evidence of a gestational sac.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided, only that patients were placed into one of two treatment groups by random assignment.
Allocation concealment (selection bias)	Unclear risk	Study failed to describe methods of allocation concealment, and we rated this as unclear risk of bias for this domain.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was not performed, but we did not consider blinding of participants or assessors could have affected pregnancy outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	69 women enrolled Number of dropouts: 9 IUI dropouts and 10 ICI dropouts; 7 women dropped out before the first insemination; 12 were eliminated from analyses for the following reasons: more than a single route of insemination (4), more than one insemination per cycle (2), uterine structural anomalies (4), gonadotropin use (2)
Selective reporting (reporting bias)	Low risk	It appeared that all outcomes were reported
Other bias	High risk	Differences in age at baseline. Some women were treated with clomiphene citrate.

Robinson 1992

Methods	Prospective, open label, randomised trial, single centre Randomisation: randomly allocated and stratified Power analysis was not performed
Participants	Inclusion criteria: <ul style="list-style-type: none">• azoospermia and oligozoospermia.• all patients were < 38 years old, had normal baseline gonadotrophins, normal thyroid function, and no sign of polycystic ovarian syndrome. An optimal cycle was defined as a cycle between 24 and 36 days, and if ovulation was detected once by a mid-luteal progesterone. Exclusion criteria: not specified Baseline characteristics: Age was not specified per group.
Interventions	Inseminations were planned by using urinary LH tests or basal temperature charts and Insler cervical scoring. Inseminations were performed by ICI, not clear if it was by cap or by straw. Inseminations were performed twice a cycle, except when the ovulation test was positive on Friday, than one insemination was performed. A maximum of six insemination cycles were performed.

Robinson 1992 (Continued)

Outcomes	Total 56 women randomised: 27 LH tests; 29 basal temperature curve with cervical mucus score
	Primary Outcome: pregnancy rate
	Secondary outcome: visits per cycle
	Adverse events: not specified

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were provided.
Allocation concealment (selection bias)	Unclear risk	Study failed to describe methods of allocation concealment, and we rated this as unclear risk of bias for this domain.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was not performed, but we did not consider blinding of participants or assessors could have affected pregnancy outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	drop-outs were mentioned, but not how many patients dropped out of the study
Selective reporting (reporting bias)	Low risk	it appeared that all outcomes were reported
Other bias	Unclear risk	baseline characteristics not specified

Wainer 1995

Methods	Prospective, open label, randomised, single centre trial Randomisation: randomised list, allocation concealment was unclear Power analysis was not performed
Participants	Inclusion criteria: <ul style="list-style-type: none"> the male partner was sterile or the partner had a genetic defect. all patients had an ovulatory cycle, patients with ovulation dysfunction were treated with hMG. all patients' cervical mucus was analysed, including a post-coital test with control spermatozoa, normal hysterosalpingography, normal hormonal concentrations; a laparoscopy was performed if hysterosalpingography results were ambiguous. Exclusion criteria: <ul style="list-style-type: none"> women who had any infertility factors Baseline characteristics: <p>Age: ICI = 30 ± 0.3 years; IUI = 31 ± 0.4 years</p> <p>Previous treatment: ICI = 1 birth after ICI; IUI = 1 birth and 1 miscarriage after ICI</p>

Wainer 1995 (Continued)

Interventions	<p>In both groups, gonadotrophin stimulation was started at 4th or 5th day of the menstrual cycle with 75 IU of hMG, followed by 150 IU of hMG on the 6th and 7th day. Thereafter, the dose was adjusted according to plasma E2 and LH. HCG was given on the day that one to three follicles were > 15 mm, or according to plasma E2 levels. In IUI, insemination was performed 38 ± 4 hours after hCG injection.</p> <p>ICI was performed by cap, inseminations were performed 12 and 36 hours after hCG administration. For the first cycles, sometimes one insemination was performed.</p> <p>Luteal support was given by progesterone pessaries in both IUI and ICI groups.</p> <p>Women were inseminated for two successive menstrual cycles, followed by a rest cycle, to a maximum of six inseminations.</p>
Outcomes	<p>Primary outcome: pregnancy rate after all cycles</p> <p>Secondary outcome: pregnancy rate after one cycle</p> <p>Adverse outcomes: multiple pregnancy rate and miscarriage rate</p>
Notes	<p>Pregnancy defined as being visible by ultrasound</p> <p>Donor sperm was supplied by three different centres</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were provided.
Allocation concealment (selection bias)	Unclear risk	Study failed to describe methods of allocation concealment, and we rated this as unclear risk of bias for this domain.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information supplied
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appeared all couples completed the study
Selective reporting (reporting bias)	Low risk	It appeared all planned outcome were reported
Other bias	Unclear risk	Difficult to judge. For the first cycles, sometimes one insemination was performed, and this might have influenced the results.

ICI - intracervical insemination

IUI - intrauterine insemination

LH - luteinising hormone

BHCG - beta-human chorionic gonadotropin

E2 - estradiol

hCG - human chorionic gonadotropin

hMG - human menopausal gonadotrophin

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alexander 1994	1. Cross-over; no pre-cross-over data available 2. Appeared as an abstract only
Byrd 1990	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated
Carroll 2001	1. Randomisation by alternation 2. Cross-over; no pre-cross-over data available 3. Allocation concealment not stated
Coulson 1996	1. Crossover: no pre-crossover data available 2. allocation concealment not stated
Flierman 1997	1. Cross-over: no pre-cross-over data available
Le Lannou 1989	1. Pseudo-randomised 2. No distinction between natural and ovarian stimulation cycles in control group.
Patton 1990	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated 3. Randomisation method not stated
Peters 1993	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated 3. Randomisation by alternation
Pistorius 1996	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated 3. Randomisation method not stated
Ract 1992	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated 3. Randomisation method not stated
Urry 1988	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated 3. Randomisation method not stated
Walker 1993	1. Stated to be RCT but all patients received ICI in the first treatment cycle 2. ICI cycles that some patients had undergone before the trial were included in the results 3. Ovarian stimulation cycles versus natural cycles
Williams 1995	1. Cross-over; no pre-cross-over data available 2. Allocation concealment not stated

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

NTR4462

Trial name or title	Artificial insemination with donor sperm: intrauterine or intracervical insemination?
Methods	RCT multi-centre
Participants	women who apply for donor sperm treatment, without a history of subfertility

Intrauterine insemination versus intracervical insemination in donor sperm treatment (Review)

NTR4462 (Continued)

Interventions	Six cycles of IUI or six cycles of ICI in the natural cycle with cryopreserved donor sperm
Outcomes	ongoing pregnancy leading to live birth
Starting date	01 February 2014
Contact information	m.h.mochtar@amc.nl
Notes	

DATA AND ANALYSES
Comparison 1. Intrauterine insemination (IUI) versus intracervical insemination (ICI)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Natural cycle	1	26	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [0.12, 87.13]
1.2 Gonadotrophin-stimulated cycle	1	43	Odds Ratio (M-H, Fixed, 95% CI)	2.55 [0.72, 8.96]
2 Multiple pregnancy rate	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Natural cycle	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Gonadotrophin-stimulated cycle	2	131	Odds Ratio (M-H, Fixed, 95% CI)	2.77 [1.00, 7.69]
3 Clinical pregnancy rate	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Natural cycle	2	76	Odds Ratio (M-H, Fixed, 95% CI)	6.18 [1.91, 20.03]
3.2 Gonadotrophin-stimulated cycle	2	131	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [1.38, 5.78]
4 Miscarriage rate	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Natural cycle	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Gonadotrophin-stimulated cycle	2	131	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [0.43, 9.04]

Analysis 1.1. Comparison 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), Outcome 1 Live birth rate.

Analysis 1.2. Comparison 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), Outcome 2 Multiple pregnancy rate.

Analysis 1.3. Comparison 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), Outcome 3 Clinical pregnancy rate.

Analysis 1.4. Comparison 1 Intrauterine insemination (IUI) versus intracervical insemination (ICI), Outcome 4 Miscarriage rate.

Comparison 2. Timing of intrauterine insemination (IUI) with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	1	351	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Multiple pregnancy rate	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Clinical pregnancy rate	1	351	Odds Ratio (M-H, Fixed, 95% CI)	2.00 [1.14, 3.53]

Analysis 2.1. Comparison 2 Timing of intrauterine insemination (IUI) with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days, Outcome 1 Live birth rate.

Study or subgroup	LH+1 n/N	LH+2 n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Blockeel 2014	0/182	0/169			Not estimable
Total (95% CI)	182	169			Not estimable
Total events: 0 (LH+1), 0 (LH+2)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Analysis 2.2. Comparison 2 Timing of intrauterine insemination (IUI) with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days, Outcome 2 Multiple pregnancy rate.

Study or subgroup	LH+1 n/N	LH+2 n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Blockeel 2014	0/42	0/22			Not estimable
Total (95% CI)	42	22			Not estimable
Total events: 0 (LH+1), 0 (LH+2)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Analysis 2.3. Comparison 2 Timing of intrauterine insemination (IUI) with donor sperm: luteinising hormone (LH) + 1 day versus LH + 2 days, Outcome 3 Clinical pregnancy rate.

Study or subgroup	LH+1 n/N	LH+2 n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Blockeel 2014	42/182	22/169		100%	2[1.14,3.53]
Total (95% CI)	182	169		100%	2[1.14,3.53]
Total events: 42 (LH+1), 22 (LH+2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.41(P=0.02)

Comparison 3. Timing of intracervical insemination (ICI) with donor sperm: urinary luteinising hormone (LH) test versus temperature curve and cervical mucus score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multiple pregnancy rate	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical pregnancy rate	1	56	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.42, 4.11]

Analysis 3.1. Comparison 3 Timing of intracervical insemination (ICI) with donor sperm: urinary luteinising hormone (LH) test versus temperature curve and cervical mucus score, Outcome 1 Multiple pregnancy rate.

Analysis 3.2. Comparison 3 Timing of intracervical insemination (ICI) with donor sperm: urinary luteinising hormone (LH) test versus temperature curve and cervical mucus score, Outcome 2 Clinical pregnancy rate.

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register search strategy

From inception to 5 October 2016

Procite platform

Keywords CONTAINS "insemination" or "insemination-artificial by donor" or "artificial insemination by donor" or "artificial insemination by partner" or "artificial insemination" or "donor insemination" or "donor semen" or "donors" or "insemination-donor" or Title CONTAINS "insemination" or "insemination-artificial by donor" or "artificial insemination by donor" or "artificial insemination by partner" or "artificial insemination" or "donor insemination" or "donor semen" or "donors" or "insemination-donor"

AND

Keywords CONTAINS "insemination-cervical cap" or "insemination, intracervical" or "insemination-pericervical" or "cervical" or "cervical cap" or "cervix" or "pericervical" or "pericervical insemination" or "intracervical" or "intracervical insemination" or "cervical cap reservoir" or "insemination-intrauterine" or "insemination techniques" or Title CONTAINS "insemination-cervical cap" or "insemination, intracervical" or "insemination-pericervical" or "cervical" or "cervical cap" or "cervix" or "pericervical" or "pericervical insemination" or "intracervical" or "intracervical insemination" or "cervical cap reservoir" or "insemination-intrauterine" or "insemination techniques" (178 hits)

Appendix 2. Central Register of Studies Online search strategy

From inception to 5 October 2016

CRSO web platform

#1 MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES 324

#2 inseminat*:TI,AB,KY 985

#3 #1 OR #2 985

#4 intrauterine:TI,AB,KY 2737

#5 intra-uterine:TI,AB,KY 190

#6 intracervical:TI,AB,KY 427

#7 intra-cervical:TI,AB,KY 32

#8 pericervical:TI,AB,KY 12

#9 peri-cervical:TI,AB,KY 0

#10 (cervix or cervical):TI,AB,KY 10819

#11 (cup or cap):TI,AB,KY 2218

#12 ICI:TI,AB,KY 359

#13 straw:TI,AB,KY 74

#14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 16048

#15 #3 AND #14 679

#16 MESH DESCRIPTOR Insemination, Artificial, Heterologous EXPLODE ALL TREES 39

#17 (Heterologous adj5 Inseminat*):TI,AB,KY 4

#18 donor*:TI,AB,KY 5746

#19 (sperm* adj5 donat*):TI,AB,KY 5

#20 (semen adj5 donat*):TI,AB,KY 1

#21 #16 OR #17 OR #18 OR #19 OR #20 5757

#22 #15 AND #21 45

Appendix 3. MEDLINE search strategy

1946 to 5 October 2016

Ovid platform

1 exp Insemination, Artificial/ (10658)

2 inseminat\$.tw. (16412)

3 euteleogenesis.tw. (6)

4 or/1-3 (20081)
 5 IUI.tw. (1429)
 6 intrauterine.tw. (45130)
 7 intra-uterine.tw. (4231)
 8 intracervical.tw. (807)
 9 intra-cervical.tw. (68)
 10 pericervical.tw. (64)
 11 peri-cervical.tw. (9)
 12 (cervix or cervical).tw. (212205)
 13 (cup or cap).tw. (48778)
 14 ICI.tw. (7123)
 15 straw.tw. (6998)
 16 or/5-15 (321428)
 17 4 and 16 (3340)
 18 exp Insemination, Artificial, Heterologous/ (1506)
 19 (Heterologous adj5 Inseminat\$).tw. (115)
 20 donor\$.tw. (257425)
 21 (sperm\$ adj5 donat\$).tw. (374)
 22 (semen adj5 donat\$).tw. (124)
 23 or/18-22 (258230)
 24 17 and 23 (314)
 25 randomized controlled trial.pt. (432375)
 26 controlled clinical trial.pt. (91772)
 27 randomized.ab. (372212)
 28 randomised.ab. (76436)
 29 placebo.tw. (184362)
 30 clinical trials as topic.sh. (179773)
 31 randomly.ab. (264844)
 32 trial.ti. (163027)
 33 (crossover or cross-over or cross over).tw. (71410)
 34 or/25-33 (1124241)
 35 exp animals/ not humans.sh. (4323394)
 36 34 not 35 (1036540)
 37 24 and 36 (50)

Appendix 4. Embase search strategy

1974 to 5 October 2016

Ovid platform

1 exp artificial insemination/ (16958)
 2 inseminat\$.tw. (17699)
 3 euteleogenesis.tw. (3)
 4 or/1-3 (23413)
 5 IUI.tw. (2460)
 6 intrauterine.tw. (57192)
 7 intra-uterine.tw. (5601)
 8 intracervical.tw. (974)
 9 intra-cervical.tw. (95)
 10 pericervical.tw. (97)
 11 peri-cervical.tw. (12)
 12 (cervix or cervical).tw. (252399)
 13 (cup or cap).tw. (61244)
 14 ICI.tw. (13529)
 15 straw.tw. (8052)
 16 or/5-15 (394288)
 17 4 and 16 (4521)
 18 (Heterologous adj5 Inseminat\$).tw. (101)
 19 donor\$.tw. (335280)
 20 (sperm\$ adj5 donat\$).tw. (546)
 21 (semen adj5 donat\$).tw. (154)
 22 or/18-21 (335690)

23 17 and 22 (424)
24 Clinical Trial/ (970336)
25 Randomized Controlled Trial/ (450491)
26 exp randomization/ (82635)
27 Single Blind Procedure/ (25645)
28 Double Blind Procedure/ (134838)
29 Crossover Procedure/ (52902)
30 Placebo/ (317470)
31 Randomized controlled trial\$.tw. (145345)
32 Rct.tw. (21721)
33 random allocation.tw. (1600)
34 randomly allocated.tw. (26146)
35 allocated randomly.tw. (2188)
36 (allocated adj2 random).tw. (837)
37 Single blind\$.tw. (18313)
38 Double blind\$.tw. (170634)
39 ((treble or triple) adj blind\$.tw. (619)
40 placebo\$.tw. (243788)
41 prospective study/ (376485)
42 or/24-41 (1734183)
43 case study/ (90742)
44 case report.tw. (317914)
45 abstract report/ or letter/ (978017)
46 or/43-45 (1377711)
47 42 not 46 (1684913)
48 23 and 47 (47)

Appendix 5. PsycINFO search strategy

1806 to 5 October 2016

Ovid platform

1 exp Reproductive Technology/ (1306)
2 inseminat\$.tw. (743)
3 eutelegensis.tw. (1)
4 or/1-3 (1802)
5 IUI.tw. (20)
6 intrauterine.tw. (1383)
7 intrauterine.tw. (152)
8 intracervical.tw. (3)
9 (cervix or cervical).tw. (5403)
10 (cup or cap).tw. (2521)
11 ICI.tw. (483)
12 straw.tw. (599)
13 or/5-12 (10511)
14 4 and 13 (28)
15 random.tw. (40620)
16 control.tw. (315260)
17 double-blind.tw. (17867)
18 clinical trials/ (7614)
19 placebo/ (3778)
20 exp Treatment/ (580009)
21 or/15-20 (885819)
22 14 and 21 (12)

Appendix 6. CINAHL search strategy

1982 to 5 October 2016

EBSCO platform

#	Query	Results
S23	S10 AND S22	37
S22	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	1,078,367
S21	TX allocat* random*	5,276
S20	(MH "Quantitative Studies")	14,878
S19	(MH "Placebos")	9,823
S18	TX placebo*	39,610
S17	TX random* allocat*	5,276
S16	(MH "Random Assignment")	41,649
S15	TX randomi* control* trial*	110,479
S14	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	854,497
S13	TX clinic* n1 trial*	189,861
S12	PT Clinical trial	79,719
S11	(MH "Clinical Trials+")	203,253
S10	S3 AND S9	150
S9	S4 OR S5 OR S6 OR S7 OR S8	18,645
S8	TX semen N2 donat*	9
S7	TX sperm* N2 donat*	208
S6	TX donor*	18,535
S5	TX Heterologous N2 inseminat*	3
S4	(MM "Sperm Donation")	113
S3	S1 OR S2	643
S2	TX inseminat*	643
S1	(MM "Insemination, Artificial")	256

Appendix 7. Trial registers search strategy

We searched five trial registers on 15 December 2017, using the terms 'insemination and sperm' and 'insemination and donor'.

- U.S. National Library of Medicine - www.clinicaltrials.gov

- EU Clinical Trials Register - www.clinicaltrialsregister.eu/
- World Health Organization International Trials Registry Platform search portal (WHO ICTRP; apps.who.int/trialsearch/)
- BioMed Central register - www.isrctn.com/
- Dutch trial register - www.trialregister.nl/

We found one ongoing trial evaluating ICI versus IUI (METC AMC 2013_364/ NL 4733001813/ NTR 16798/ ZonMw 80-83700-98-42063)

Appendix 8. Grey literature search strategy

We searched the grey literature on 15 December 2017, using the terms 'insemination and donor semen'. We found no studies.

- New York Academy of Medicine - www.greylit.org/
- Grey Literature in Europe - www.opengrey.eu

Appendix 9. PubMed and Google Scholar search strategy

We searched PubMed and Google Scholar on 15 December 2017, using the keywords as text: insemination AND donor AND random*. We did not find any recent studies (over the last 18 months).

Appendix 10. Cochrane's 'Risk of bias' assessment tool

Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel (Assessments should be made for each main outcome (or class of outcomes)).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment (Assessments should be made for each main outcome (or class of outcomes)).	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data (Assessments should be made for each	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group	Attrition bias due to amount, nature, or handling of incomplete outcome data.

(Continued)

main outcome (or class of outcomes)).

(compared with total randomised participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses performed by the review authors.

Reporting bias

Selective reporting

State how the possibility of selective outcome reporting was examined by the review authors, and what was found.

Reporting bias due to selective outcome reporting.

Other bias

Other sources of bias

State any important concerns about bias not addressed in the other domains in the tool.

If particular questions or entries were prespecified in the review's protocol, responses should be provided for each question or entry.

Bias due to problems not covered elsewhere in the table.

WHAT'S NEW

Date	Event	Description
5 February 2018	Amended	Correction of Author's conclusions text and forest plot for outcome 1.2 Multiple pregnancy rate (Figure 5)

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1998

Date	Event	Description
19 January 2018	New citation required and conclusions have changed	With the addition of two studies we concluded that current evidence was too limited to choose between IUI or ICI, in natural cycles or with ovarian stimulation, in donor sperm treatment.
15 December 2017	New search has been performed	Main databases were searched on 5 October 2016 and 2 studies identified for inclusion (Blockeel 2014 and Robinson 1992). On 15 December 2017 we searched in PubMed, Google Scholar, the grey literature, and in five trial registers. We found no further studies.
4 December 2016	Amended	The first versions of the protocol and review were published in 1998. In 2000, the review was due for updating but significant methodological changes within the Cochrane Menstrual Disorders and Subfertility Group mandated a complete redrafting of the protocol to support an updated review. This review was withdrawn from The Cochrane Library and the updated protocol was published in 2007. This new version of the review found one new study, which was excluded.
22 February 2011	Review declared as stable	The findings of this review are deemed to be conclusive therefore this review is now regarded as stable.

Date	Event	Description
6 November 2008	Amended	Converted to new review format.
17 February 2008	New citation required and conclusions have changed	Substantive amendment
17 May 2007	New search has been performed	This review was updated May 2007

CONTRIBUTIONS OF AUTHORS

2018 update:

Femke PAL Kop: took the lead in updating the review - completed the literature search, selected trials, extracted data, conducted the analyses, and wrote the review.

Madelon van Wely: as the second review author, assisted with updating the review - did the final literature search for the update, selected trials, extracted data, conducted the analyses, and wrote the review.

Monique H Mochtar: assisted in updating the review, and acted as referee when the first and second review authors disagreed on inclusion of trials.

Fulco van der Veen: acted as a clinical expert, and assisted in updating the review.

Paul O'Brien: was the original author of the review and assisted in updating the review.

DECLARATIONS OF INTEREST

Femke PAL Kop, Madelon van Wely, Monique H. Mochtar, and Fulco van der Veen are conducting an RCT on ICI versus IUI in natural cycles in donor sperm treatment.

SOURCES OF SUPPORT

Internal sources

- We received no internal sources of support, Other.

External sources

- We received no external sources of support, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2018 update we analysed IUI and ICI in natural cycles separately from IUI and ICI in ovarian stimulation cycles. We extended the search for cointerventions concerning donor sperm treatment.

INDEX TERMS

Medical Subject Headings (MeSH)

Body Temperature; Cervix Mucus; Gonadotropins [therapeutic use]; Insemination, Artificial, Heterologous [*methods]; Live Birth [epidemiology]; Luteinizing Hormone [blood]; Menstrual Cycle [drug effects]; Pregnancy Rate; Pregnancy, Multiple; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy