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[Intervention Review]

Synchronised approach for intrauterine insemination in subfertile couples

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ABSTRACT

Background

In many countries intrauterine insemination (IUI) is the treatment of first choice for a subfertile couple when the infertility work up reveals an ovulatory cycle, at least one open Fallopian tube and sufficient spermatozoa. The final goal of this treatment is to achieve a pregnancy and deliver a healthy (singleton) live birth. The probability of conceiving with IUI depends on various factors including age of the couple, type of subfertility, ovarian stimulation and the timing of insemination. IUI should logically be performed around the moment of ovulation. Since spermatozoa and oocytes have only limited survival time correct timing of the insemination is essential. As it is not known which technique of timing for IUI results in the best treatment outcome, we compared different techniques for timing IUI and different time intervals.

Objectives

To evaluate the effectiveness of different synchronisation methods in natural and stimulated cycles for IUI in subfertile couples.

Search methods

We searched for all publications which described randomised controlled trials of the timing of IUI. We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL) (1966 to October 2014), EMBASE (1974 to October 2014), MEDLINE (1966 to October 2014) and PsycINFO (inception to October 2014) electronic databases and prospective trial registers. Furthermore, we checked the reference lists of all obtained studies and performed a handsearch of conference abstracts.

Selection criteria

Randomised controlled trials (RCTs) comparing different timing methods for IUI were included. The following interventions were evaluated: detection of luteinising hormone (LH) in urine or blood, single test; human chorionic gonadotropin (hCG) administration; combination of LH detection and hCG administration; basal body temperature chart; ultrasound detection of ovulation; gonadotropin-releasing hormone (GnRH) agonist administration; or other timing methods.

Data collection and analysis

Two review authors independently selected the trials, extracted the data and assessed study risk of bias. We performed statistical analyses in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration. The overall quality of the evidence was assessed using GRADE methods.

Main results

Eighteen RCTs were included in the review, of which 14 were included in the meta-analyses (in total 2279 couples). The evidence was current to October 2013. The quality of the evidence was low or very low for most comparisons . The main limitations in the evidence were failure to describe study methods, serious imprecision and attrition bias.

Ten RCTs compared different methods of timing for IUI. We found no evidence of a difference in live birth rates between hCG injection versus LH surge (odds ratio (OR) 1.0, 95% confidence interval (CI) 0.06 to 18, 1 RCT, 24 women, very low quality evidence), urinary hCG versus recombinant hCG (OR 1.17, 95% CI 0.68 to 2.03, 1 RCT, 284 women, low quality evidence) or hCG versus GnRH agonist (OR 1.04, 95% CI 0.42 to 2.6, 3 RCTS, 104 women, I^2 = 0%, low quality evidence).

Two RCTs compared the optimum time interval from hCG injection to IUI, comparing different time frames that ranged from 24 hours to 48 hours. Only one of these studies reported live birth rates, and found no difference between the groups (OR 0.52, 95% CI 0.27 to 1.00, 1 RCT, 204 couples). One study compared early versus late hCG administration and one study compared different dosages of hCG, but neither reported the primary outcome of live birth.

We found no evidence of a difference between any of the groups in rates of pregnancy or adverse events (multiple pregnancy, miscarriage, ovarian hyperstimulation syndrome (OHSS)). However, most of these data were very low quality.

Authors' conclusions

There is insufficient evidence to determine whether there is any difference in safety and effectiveness between different methods of synchronization of ovulation and insemination. More research is needed.

PLAIN LANGUAGE SUMMARY

What is the best timing technique for intrauterine insemination in subfertile couples

Review question. Cochrane authors reviewed the evidence about the effectiveness of different timing techniques for intrauterine insemination in subfertile couples.

Background. Couples that have not reached pregnancy after trying for at least a year are defined as subfertile. This affects approximately 10% of couples trying to have a baby. A procedure that may assist couples is intrauterine insemination (IUI). This is an assisted reproduction procedure where sperm are placed directly into the uterus at a specific time in the woman's menstrual cycle (as close to ovulation as possible). It remains unclear which technique of timing for IUI results in the best treatment outcome, a healthy live birth. Timing of IUI is most frequently performed with hormone (luteinising hormone (LH)) detection in urine or blood, or human chorionic gonadotropin (hCG) injection. The usefulness of urinary LH monitoring is hampered by the possibility of false-negative results which can cause inaccurate timing and significantly reduce pregnancy rates. On the other hand, the ease of performing a test at home, the lower costs and the non-invasiveness are advantages. Limitations of timing by ultrasound and hCG administration are frequent hospital visits and the occurrence of premature LH surges or the possibility of triggering ovulation in the presence of an immature follicle. The major advantage of this hCG method is the clinical predictability of the ovulation.

Study characteristics. We found 18 randomised controlled trials, all comparing different timing methods in one treatment cycle for IUI, with a total of 2279 couples. The evidence was current to October 2013.

Key results. We found no evidence of a difference in live birth rates between timing methods. We also found no evidence of a difference between any of the groups in rates of pregnancy or adverse events (multiple pregnancy, miscarriage, ovarian hyperstimulation syndrome (OHSS)).

Quality of the evidence. Most of the evidence was of low or very low quality. The main limitations were poor reporting of study methods, imprecision and losses to follow up. More research is needed.

Summary of findings for the main comparison. hCG compared to LH surge for intrauterine insemination in subfertile couples

hCG compared to LH surge for intrauterine insemination in subfertile couples

Population: women undergoing intrauterine insemination
Intervention: hCG
Comparison: LH surge

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 surge	HCG				
Live birth rate per couple	**83 per 1000**	**83 per 1000** (5 to 621)	**OR 1** (0.06 to 18.08)	24 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Pregnancy rate per couple	**146 per 1000**	**185 per 1000** (110 to 295)	**OR 1.33** (0.72 to 2.45)	275 (4 studies)	⊕⊕⊖⊖ **low** [1,3]	
Multiple pregnancy rate per pregnancy	**59 per 1000**	**66 per 1000** (11 to 323)	**OR 1.12** (0.17 to 7.6)	42 (2 studies)	⊕⊖⊖⊖ **very low** [1,2]	

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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]Methods used for random sequence generation and/or allocation concealment were unclear.
[2]There was very serious imprecision, with small sample sizes and very few events.
[3]There was serious imprecision: findings were compatible with substantial benefit in either group, or with no effect.

Summary of findings 2. u-hCG compared to r-hCG for intrauterine insemination in subfertile couples

u-hCG compared to r-hCG for intrauterine insemination in subfertile couples

Population: women undergoing intrauterine insemination
Intervention: u-hCG
Comparison: r-hCG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	R-hCG	U-hCG				
Live birth rate per couple	**221 per 1000**	**249 per 1000** (162 to 365)	**OR 1.17** (0.68 to 2.03)	284 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Pregnancy rate per couple	**261 per 1000**	**265 per 1000** (187 to 357)	**OR 1.02** (0.65 to 1.57)	409 (2 studies)	⊕⊕⊝⊝ **low** [2,3]	
Multiple pregnancy rate per pregnancy	**184 per 1000**	**182 per 1000** (83 to 358)	**OR 0.99** (0.4 to 2.47)	109 (2 studies)	⊕⊕⊝⊝ **low** [2,3]	
Miscarriage rate per pregnancy	**84 per 1000**	**50 per 1000** (12 to 185)	**OR 0.57** (0.13 to 2.47)	109 (2 studies)	⊕⊝⊝⊝ **very low** [2,3,4]	
OHSS rate per cycle	See comment	See comment	Not estimable	468 (2 studies)	⊕⊕⊕⊝ **moderate** [3]	There were no events in either study

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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]Methods used for random sequence generation and/or allocation concealment were unclear.
[2]There was serious imprecision: findings were compatible with substantial benefit in either group, or with no effect.
[3]One study did not report the method of allocation concealment used.

[4]There was very serious imprecision, with very few events and wide confidence intervals.

Summary of findings 3. Short interval compared to long interval for intrauterine insemination in subfertile couples

Short interval compared to long interval for intrauterine insemination in subfertile couples

Population: women undergoing intrauterine insemination
Intervention: short interval
Comparison: long interval

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long interval	Short interval				
Live birth rate per couple - 24 hours versus 34 to 36 hours	**298 per 1000**	**181 per 1000 (103 to 298)**	**OR 0.52** (0.27 to 1)	204 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Pregnancy rate per couple - 24 hours versus 34 to 36 hours	**397 per 1000**	**266 per 1000** (170 to 392)	**OR 0.55** (0.31 to 0.98)	234 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pregnancy rate per couple - 24 hours versus 48 hours	**600 per 1000**	**398 per 1000** (130 to 742)	**OR 0.44** (0.1 to 1.92)	30 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Pregnancy rate per couple - 34 to 36 hours versus 48 hours	**600 per 1000**	**465 per 1000** (174 to 788)	**OR 0.58** (0.14 to 2.48)	30 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Miscarriage rate per pregnancy - 24 hours versus 34 to 36 hours	**116 per 1000**	**172 per 1000** (44 to 484)	**OR 1.58** (0.35 to 7.16)	67 (2 studies)	⊕⊖⊖⊖ **very low** [1,3]	
Miscarriage rate per pregnancy - 24 hours versus 48 hours	**111 per 1000**	**333 per 1000** (33 to 880)	**OR 4** (0.27 to 58.56)	15 (1 study)	⊕⊖⊖⊖ **very low** [1,3]	
Miscarriage rate per pregnancy - 34 to 36 hours versus 48 hours	**111 per 1000**	**142 per 1000** (9 to 764)	**OR 1.33** (0.07 to 25.91)	16 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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]Methods used for random sequence generation or allocation concealment were unclear.
[2]There was serious imprecision: findings were compatible with substantial benefit in the long interval group, or with no effect. **(See comment)**
[3]There was very serious imprecision, with very few events and wide confidence intervals

Summary of findings 4. hCG compared to GnRH-a for intrauterine insemination in subfertile couples

hCG compared to GnRH-a for intrauterine insemination in subfertile couples

Population: women undergoing intrauterine insemination
Intervention: hCG
Comparison: GnRH-a

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a	HCG				
Live birth rate per couple	**200 per 1000**	**206 per 1000** (95 to 390)	**OR 1.04** (0.42 to 2.56)	104 (3 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pregnancy rate per couple	**315 per 1000**	**344 per 1000** (225 to 489)	**OR 1.14** (0.63 to 2.08)	206 (4 studies)	⊕⊕⊖⊖ **low** [1,2]	
Multiple pregnancy rate per pregnancy	**33 per 1000**	**5 per 1000** (1 to 45)	**OR 0.15** (0.02 to 1.38)	74 (4 studies)	⊕⊖⊖⊖ **very low** [1,3]	
Miscarriage rate per pregnancy	**124 per 1000**	**196 per 1000** (64 to 467)	**OR 1.72** (0.48 to 6.2)	74 (4 studies)	⊕⊖⊖⊖ **very low** [1,3]	
OHSS per cycle	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 2.27** (0.65 to 7.91)	456 (3 studies)	⊕⊕⊖⊖ **low** [1,2]	

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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]Methods used for random sequence generation and allocation concealment were unclear.
[2]There was serious imprecision: findings were compatible with substantial benefit in either group, or with no effect.
[3]There was very serious imprecision, with very few events and wide confidence intervals.

Summary of findings 5. Early hCG compared to late hCG for intrauterine insemination in subfertile couples

Early hCG compared to late hCG for intrauterine insemination in subfertile couples

Population: women undergoing intrauterine insemination
Intervention: Early hCG
Comparison: Late hCG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Late hCG	Early hCG				
Pregnancy rate per couple	**86 per 1000**	**110 per 1000** (68 to 175)	**OR 1.32** (0.77 to 2.25)	612 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Miscarriage rate	**103 per 1000**	**55 per 1000** (9 to 274)	**OR 0.51** (0.08 to 3.28)	65 (1 study)	⊕⊖⊖⊖ **very low** [1,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

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]Unclear risk of attrition bias.
[2]There was serious imprecision: findings were compatible with substantial benefit in the early hCG group, or with no effect.
[3]There was very serious imprecision, with very few events and wide confidence intervals.

Summary of findings 6. Differing dosages of hCG for intrauterine insemination in subfertile couples

Differing dosages of hCG for intrauterine insemination in subfertile couples

Population: women undergoing intrauterine insemination
Intervention: differing dosages of hCG: 500 µg hCG versus 250 µg hCG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	250 µg hCG	500 µg hCG				
Pregnancy rate per couple	**91 per 1000**	**121 per 1000** (27 to 402)	**OR 1.38** (0.28 to 6.71)	66 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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]Methods of random sequence generation and allocation concealment were unclear, high risk of attrition bias.
[2]There was very serious imprecision, with very few events and wide confidence intervals.

BACKGROUND

Description of the condition

Subfertility is usually defined as the inability of a couple to conceive after at least one year of unprotected intercourse. This is approximately 10% of couples who try to conceive. Subfertility is considered to be unexplained when an infertility work up consisting of cycle analysis, semen analysis and analysis of at least one patent Fallopian tube was unable to detect any abnormality. Couples with male subfertility have repeated semen analyses below the criteria for normal semen as defined by the World Health Organization (WHO) (WHO 2010). Couples suspected of cervical hostility used to be diagnosed by a well-timed non-progressive postcoital test, defined as the absence of spermatozoa moving in a straight direction and at a functional speed. However, nowadays the accuracy of this test and the existence of the diagnosis have been questioned. Finally, mild endometriosis is defined as grade I or II at diagnostic laparoscopy. When one of these causes for subfertility has been identified and the probability of a spontaneous pregnancy is low, the first treatment option is often intrauterine insemination (IUI), although couples with a good prognosis might benefit from expectant management (Steures 2006). The final goal of this treatment is to achieve a pregnancy and deliver a healthy (singleton) live birth. The probability of conceiving with IUI depends on various confounding factors including age of the couple, type of subfertility, ovarian stimulation and the timing of insemination (Rahman 2011).

As spermatozoa and oocytes survive for only a limited period of time, correct timing of IUI seems essential. Therefore, IUI should logically be performed as close to ovulation as possible.

Description of the intervention

There are several options for timing IUI including luteinising hormone (LH) testing, ultrasound scanning, human chorionic gonadotropin (hCG) injection, recombinant LH and gonadotropin-releasing hormone (GnRH) agonist administration, and basal body temperature (BBT) charts.

LH levels in urine or blood are one of the most precise predictors of ovulation. According to the WHO, ovulation in natural cycles takes place from 24 to 56 hours after the onset of the LH surge, with a mean time of 32 hours (WHO 1980).

In stimulated cycles, when the dominant follicle(s) reaches a certain mean diameter hCG is given to induce ovulation; which occurs approximately 36 to 40 hours after hCG injection (Andersen 1995).

GnRH agonist can also be used for final oocyte maturation and ovulation. GnRH agonists induce an endogenous surge of LH and follicle-stimulating hormone (FSH), giving a more physiologic approach than with exogenous hCG. The use of GnRH agonists is less widespread because of the high costs (Andrés-Oros 2008).

How the intervention might work

Each of these interventions is seeking to predict or synchronise ovulation, or both, in order to time the IUI to provide the best pregnancy outcomes.

Why it is important to do this review

Difficulties exist with the different methods of prediction and synchronisation of ovulation. The usefulness of urinary LH monitoring is hampered by the possibility of false-negative results, which may occur in up to 23% to 35% of ovulatory cycles. The LH peak values may be below the limit of detection for the urine ovulation prediction kit, or the duration of the LH surge is too short to be easily detected. This can cause inaccurate timing and significantly lower pregnancy rates. On the other hand, the ease of performing a test at home, the lower costs and the non-invasiveness are advantages of urinary LH monitoring (Lewis 2006). Timing by ultrasound combined with hCG administration is time consuming and limited by the possible occurrence of premature LH surges and the possibility of triggering ovulation in the presence of an immature egg (Cantineau 2007; Cohlen 1998; Martinez 1991a). The major advantage of this hCG method is the clinical predictability of the ovulation. A combination of LH surge and hCG administration may minimise the limitations mentioned above (Kosmas 2006).

This review investigates which approach for synchronisation of ovulation results in the highest pregnancy and live birth rates for subfertile couples undergoing IUI.

OBJECTIVES

To evaluate the effectiveness of different synchronisation methods in natural and stimulated cycles for IUI in subfertile couples.

METHODS

Criteria for considering studies for this review

Types of studies

We included both published and unpublished randomised controlled trials (RCTs). The method of randomisation was assessed to determine whether the studies were truly randomised. Cross-over trials will be included, but only data from the first phase will be included in the meta analysis. There were no restrictions based on trial duration.

Types of participants

Subfertile couples were eligible for inclusion. We included all types of subfertility where IUI is the first treatment option (for example unexplained subfertility, male subfertility, mild endometriosis, cervical hostility and cycle disturbances).

Routine fertility evaluation should have consisted of confirmed ovulatory status (by a biphasic basal body temperature chart, mid-luteal progesterone, or sonographic evidence of ovulation), tubal patency (by hysterosalpingography or laparoscopy, or both) and normal results in semen analysis. Subfertility was regarded as due to male factor when at least two separate semen samples did not meet the WHO criteria of normality. A normal quality semen sample was described as having a sperm concentration of 20 x 10^6 per mL, total motility 50%, normal morphology in 50%, and no sperm antibodies (WHO 1987). In 1992, the WHO changed its criteria for sperm morphology from 50% to 30% (WHO 1992) and for recent trials we used the 1992 definition of normality. Trials before 1992 should have used the WHO criteria of 1987. When strict criteria for morphology were used > 14% was considered normal (Kruger 1993). Since 2010 the reference values have been adapted and the

most important changes are: semen volume of 1.5 mL, a sperm concentration of 15 x 10^6 per mL, total motility 40% and normal morphology in 4% (Cooper 2010; WHO 2010). For future trials these criteria will be applied.

Mild endometriosis was defined as grade I or II at diagnostic laparoscopy. Cervical factor was defined as a negative result with well-timed postcoital testing. We reported in the review the differences between trials in defining the types of subfertility. Slight differences did not lead to exclusion.

Types of interventions

RCTs comparing any two of the following interventions in couples undergoing IUI were eligible for inclusion:

- LH detection in urine or blood, single test;
- hCG administration;
- a combination of LH detection and hCG administration;
- the use of basal body temperature charts;
- ultrasound detection of ovulation;
- GnRH agonist administration;
- other timing methods.

We included both natural cycles and stimulated cycles and considered them separately. We included all types of ovarian stimulation.
We excluded trials comparing synchronisation methods using insemination techniques other than IUI, such as timed intercourse, intracervical insemination, gamete intrafallopian transfer (GIFT) and fallopian tube sperm perfusion.

Types of outcome measures

Primary outcomes

- Live birth rate per couple

Secondary outcomes

- Clinical pregnancy rate per couple (pregnancy rate per couple)
- Ongoing pregnancy rate per couple
- Optimal time interval from the hCG injection to IUI
- Costs of each method of timing (per treatment cycle)

Adverse outcomes

- Multiple pregnancies (multiple pregnancy rate per couple and per pregnancy)
- Miscarriage rate (miscarriage rate per couple and per pregnancy)
- Ovarian hyperstimulation syndrome (OHSS) per couple
- Tubal pregnancy (tubal pregnancy rate per couple)
- Dropouts (dropout rate per couple)

Clinical pregnancy was established by a positive hCG test in blood or urine and confirmed by ultrasound at around seven weeks of gestation. Ongoing pregnancy was defined as a pregnancy that extended beyond 12 weeks of gestation, confirmed by ultrasound.

Multiple pregnancies were confirmed by ultrasound or delivery. We included pregnancies in which selective reduction was performed, mentioning the original number of fetuses.

We defined a dropout as a couple leaving the study protocol after randomisation.

Not all outcome measures needed to be available to include a study.

Search methods for identification of studies

Electronic searches

We searched for all publications which described (or might describe) RCTs of synchronisation of ovulation with IUI in natural and stimulated cycles. No language restrictions were made and the search was performed in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

- The Cochrane Menstrual Disorders and Subfertility Group Specialised Register of controlled trials (from inception to October 2014) (Appendix 1).
- The Cochrane Central Register of Controlled Trials (CENTRAL; October 2014) (Appendix 2).
- The electronic databases of MEDLINE (inception to October 2014) (Appendix 3).
- EMBASE (inception to October 2014) (Appendix 4).
- PsycINFO (inception to October 2014) (Appendix 5).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying RCTs, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0; Chapter 6, 6.4.11) (Higgins 2011). The EMBASE search was combined with the trial filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/mehodology/filters.html#random).

Other electronic sources of trials included the following.

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

We searched the databases using the medical subject headings (MsSH terms) and keywords in Appendix 6.

Searching other resources

- We checked the reference lists of all identified studies for relevant articles.
- We performed a handsearch of abstracts of the American Society for Reproductive Medicine (1999 to October 2014) and the European Society for Human Reproduction and Embryology (1997 to October 2014) meetings.

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

Data collection and analysis

Selection of studies

After screening the titles and abstracts retrieved by the search, full texts of all potentially eligible studies were obtained. MJ Janssen and AEP Cantineau independently selected the trials to be included according to the above mentioned criteria. We resolved disagreements by consensus or through arbitration by BJ Cohlen. We performed an analysis of agreement for inclusion between the two review authors using the crude percentage agreement. This analysis was performed on the primary comparison, the method of randomisation and concealment of allocation. If it was not clear whether a criterion was met, we tried to contact the authors.

Data extraction and management

The same two review authors independently used a data extraction form to extract the data from published reports. We resolved disagreement as described above. This data extraction form includes information on the type of study, quality of the selected studies, types of participants, types of interventions and the types of outcome measures. An analysis of agreement between the two review authors on assessment of the method of randomisation and study design resulted in 100% agreement.

Type of studies

Randomised controlled trials (RCTs) only.

Trial quality

1. Randomisation:

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

Studies which claimed to be randomised but the method of randomisation was not described or not described in detail were placed in the category 'stated without further description'. We included these studies in the 'waiting for assessment' group and contacted the authors for additional information.

2. Concealment of allocation:

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

Studies with an allocation low risk of bias or unclear risk of bias were included in the meta-analysis.

3. Study design:

- parallel design, cross-over design or not clear (we included only parallel group studies or data before cross over, we designated studies that were unclear as 'awaiting assessment');
- single centre or multi-centre;
- inclusion criteria, exclusion criteria;
- groups similar at baseline regarding the most important prognostic indicators, yes (included), no (excluded), not stated.

4. Blinding:

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

5. Analysis:

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

6. Dropouts:

- percentage of dropouts;
- reasons for and details on dropouts (selective dropout?).

7. Cancelled cycles:

- percentage of cancelled cycles < 10% (> 10% cancelled cycles then mentioned but excluded from meta-analysis);
- reasons for cancelled cycles.

8. Follow up:

- duration of follow up;
- losses to follow up.

Study participants

9. Prognostic factors:

- woman's age;
- type of subfertility;
- primary or secondary subfertility;
- duration of subfertility;
- semen quality;
- body mass index.

10. Basic fertility work up:

- regular menstrual cycles with biphasic body temperature charts or normal luteal progesterone;
- patent tubes on hysterosalpingography or laparoscopy, or both.

11. Previous fertility treatment:

- tubal surgery;
- controlled ovarian hyperstimulation without insemination;
- other.

Type of interventions

12. Stimulation protocols:

- type and dosage of drugs for mild ovarian hyperstimulation;
- days of ovarian stimulation;
- number of dominant follicles (> 10 mm);
- cancellation criteria, risk of multiple pregnancies or OHSS;

- use of luteal support;
- allowance of unprotected intercourse during treatment.

13. Semen sample preparation techniques:

- type of semen injected, e.g. cryopreserved donor, partner's fresh semen;
- amount of semen injected, number of motile spermatozoa;
- method of sperm preparation (washing and centrifugation technique, swim up technique, other).

14. Insemination characteristics:

- type of insemination catheter;
- use of single or double insemination;
- number of treatment cycles;
- actual timing of IUI (time from LH detection to IUI, time from hCG administration to IUI).

Type of outcome measures

15. Primary outcomes:

- the number of live births.

16. Secondary outcomes:

- the number of clinical (total and ongoing) pregnancies.

17. Adverse outcomes:

- incidence of miscarriage, multiple pregnancies, OHSS, tubal pregnancy.

18. Best time interval for insemination.

19. Costs of each method.

Assessment of risk of bias in included studies

Data for trial characteristics which have been recognised as potential sources of bias, such as the method used in generating the allocation sequence, how allocation was concealed, comparability of participants' baseline variables, and differences in dropout rates between study arms, were independently determined by MJ Janssen and AEP Cantineau as part of the data collection process. The criteria outlined in the*Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Higgins 2011) were used. Where there was uncertainty, authors were contacted to clarify aspects of study design. Differences in agreement between review authors were resolved as described above.

Two review authors independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool (www.cochrane-handbook.org) using the following domains:

- selection bias (random sequence generation and allocation concealment);
- performance bias (blinding of participants and personnel);
- detection bias (blinding of outcome assessment);
- attrition bias (incomplete outcome data);
- reporting bias (selective reporting);
- other bias.

These domains were assessed to have:

- high risk of bias;
- unclear risk of bias;
- low risk of bias.

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

We judged that blinding of the researcher, the personnel or the participants could not influence the outcomes live birth rate, clinical pregnancy rate, miscarriage rate or any of the other outcomes. All included trials were therefore assessed as low risk of bias for blinding.

According to the *Cochrane Handbook for Systematic Reviews of Interventions*, a trial with missing data was judged as low risk of bias if the missing data were addressed adequately, there was no imbalance between intervention groups and the missing data were not related to the outcome.

Measures of treatment effect

We performed statistical analyses in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Higgins 2011).

For dichotomous data, we expressed results for each included study as Mantel-Haenszel odds ratios (OR) with 95% confidence intervals (CI).

Unit of analysis issues

The primary analysis was per woman randomised. If an included study only reported per cycle data, the author was contacted for additional information. Studies that could not provide us with per woman data were included in the review but not in the meta-analysis, and were described separately. We included both parallel group and cross-over trials in the analysis. For cross-over trials we used only the first cycle(s) before 'crossing over' when the data required were available.

Furthermore, multiple live births were counted as one live birth event.

Dealing with missing data

For missing data, we attempted to contact the investigators. When we could not obtain the missing data from the investigators, we explained the assumptions we made in the extraction and analysis of the data.

Assessment of heterogeneity

We noted statistical heterogeneity between the results of different studies by visually inspecting the scatter in the data points on the graphs and the overlap in their CIs and using the I^2 statistic. According to the *Cochrane Handbook for Systematic Reviews of Interventions*, an I^2 value greater than 50% was judged to indicate substantial heterogeneity. In the case of statistical heterogeneity, we planned to use a random-effects model instead of the fixed-

effect model, and to explore the original trials for clinical and methodological heterogeneity.

Assessment of reporting biases

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

Data synthesis

If appropriate, we combined the data in a meta-analysis with RevMan software (RevMan 5), using a fixed-effect model.

We considered live birth rate and pregnancy outcomes as a positive consequence of treatment. Therefore, a higher proportion achieving these outcomes was considered a benefit. For adverse outcomes such as multiple pregnancy rate, miscarriage rate and OHSS rate, which are negative consequences, higher numbers were considered to be detrimental (increased odds signify relative harm). This needs to be taken into consideration when interpreting the meta-analyses.

Subgroup analysis and investigation of heterogeneity

A priori, we planned to perform separate subgroup analyses if there were more than two studies in each subgroup, for trials which differed in the following.

- Subfertility causes: male factor, unexplained, cervical hostility, mild endometriosis.
- Ovarian stimulation protocols: oral ovulation induction agents (anti-estrogens) versus gonadotropins (follicle-stimulating hormone (FSH), human menopausal gonadotropin (HMG)).
- LH monitoring: once or twice daily, serum LH versus urinary LH.

Sensitivity analysis

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

- Restriction to studies without high risk of bias.
- Use of a random-effects model.
- Use of relative risk rather than odds ratio.

Overall quality of the body of evidence: summary of findings table

We prepared a summary of findings table using GRADEPRO software. This table evaluated the overall quality of the body of evidence for the review outcomes using GRADE criteria (study limitations that is risk of bias, consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) were justified, documented and incorporated into reporting of results for each outcome.

RESULTS

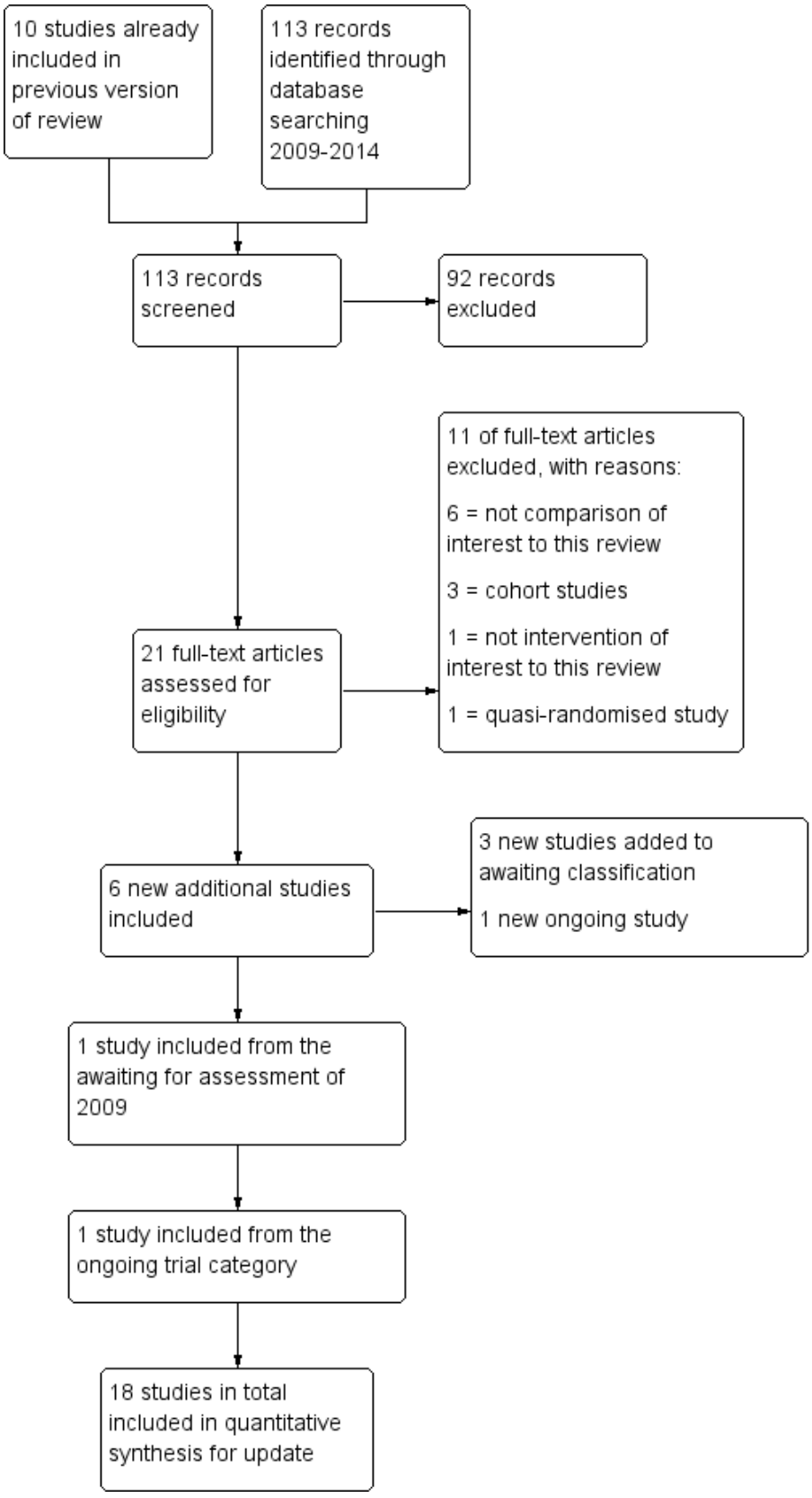
Description of studies

Results of the search

When this review was first published, we identified 95 articles relating to the subject. Of these, 39 were excluded as their title and abstract very clearly did not meet the basic inclusion criteria. The remaining 56 articles were analysed in detail, of which 10 studies were included, 2 studies were awaiting assessment and 1 study was defined as ongoing.

When updating the review in 2014 we performed the search again and 113 additional articles were found with the adapted search strategy; 21 studies were identified which potentially provided data comparing different timing modalities. Of these, 11 were excluded when analysed in detail by two review authors (AC and MJ) (Casadei 2006; Gerrits 2011; Ghanem 2011; Ghazizadeh 2009; Ghosh Dastidar 2009; Panchal 2009; Propst 2012; Ramon 2009; Ramon 2009a; Tonguc 2010). Further evaluation based on the inclusion criteria showed six new trials were eligible for inclusion in the review (AboulGheit 2010; da Silva 2012; Kyrou 2012; Nikbakht 2012; Rahman 2011; Sharma 2011). Furthermore, one study was included from the awaiting assessment category of 2009 (Schmidt-Sarosi 1995) and one study was included from the ongoing trial section (Weiss 2010). The remaining study in the awaiting assessment category (Propst 2007) was excluded. Four studies have been added to the awaiting assessment category (Aydin 2013; Blockeel 2014; Dehghani 2014; Mostafa 2014). One study is ongoing (OVO R&D 2012). Thus, eight studies were included in addition to the results of the first published version. Full agreement was obtained regarding all trials (see Figure 1).

Figure 1. Study flow diagram for 2009 to 2013 literature searches.



The study characteristics and inclusion and exclusion criteria for each study are described in the tables Characteristics of included studies and Characteristics of excluded studies.

Included studies

Eighteen studies were included in total (AboulGheit 2010; Andrés-Oros 2008; Claman 2004; da Silva 2012; Kyrou 2012; Lewis 2006; Lorusso 2008; Martinez 1991a; Martinez 1991b; Nikbakht 2012; Rahman 2011; Sakhel 2007; Scott 1994; Shalev 1995; Sharma 2011; Schmidt-Sarosi 1995; Weiss 2010; Zreik 1999) (see Characteristics of included studies). Twelve compared different synchronisation approaches, four compared the optimum time interval from the onset of hCG injection to IUI (AboulGheit 2010; Claman 2004; Rahman 2011; Weiss 2010), one study compared different dosages of hCG injection (Nikbakht 2012) and one study compared early hCG injection (dominant follicle of 16.0 to 16.9 mm) with late hCG injection (dominant follicle 18.0 to 18.9 mm) (da Silva 2012). The study of Lewis 2006, both studies of Martinez 1991a, and the study of Zreik 1999 were used in a meta-analysis to compare the methods of urinary LH surge versus hCG injection (264 women, 242 first cycle treatments). The study of Kyrou 2012 compared the methods of serum LH detection versus hCG injection in natural cycles. All other studies used some form of ovarian stimulation. Two studies (Lorusso 2008; Sakhel 2007) compared the use of recombinant hCG versus urinary hCG (409 women, 441 cycles) and five studies (Andrés-Oros 2008; Schmidt-Sarosi 1995; Scott 1994; Shalev 1995; Sharma 2011) compared the use of hCG versus a GnRH agonist for timing IUI (4 studies, 206 women, 486 cycles). The abstract of Sharma 2011 reported 450 included women but the number of cycles was unclear and the pregnancy rates were expressed in percentages only. Therefore the study was not included in the meta-analysis. The study of Claman 2004 was not used in a meta-analysis because only per cycle data were available (75 women, 189 cycles). The study of Kyrou 2012 was not used in the meta-analysis since more than half of the women underwent insemination for other reasons than subfertility, and there were no data available for the group with subfertility alone (Kyrou 2012). Finally, the study of Weiss 2010 was not included in the meta-analysis since data per cycle were available with couples who dropped out after randomisation excluded from the analysis (see Characteristics of included studies).

Participants

The age of the participants was stated in all but one trial (Sharma 2011) as either a mean with the standard deviation (SD) for each treatment group or overall. The mean age ranged from 26 to 34 years. There were no statistical differences recorded between the various treatment groups based on age.

All studies included different types of subfertility: unexplained subfertility, mild endometriosis, male factor, cervical factor and tubal or pelvic factor. The study population of Kyrou 2012 contained 58% of women without subfertility (lesbian, single mother) as stated above. Seven studies (Claman 2004; Nikbakht 2012; Sakhel 2007; Schmidt-Sarosi 1995; Shalev 1995; Weiss 2010; Zreik 1999) also included women with ovulatory disorders. In the studies of Claman 2004 and Zreik 1999 the women with ovulatory disorders comprised less than 15% of all women. In the studies of Sakhel 2007 and Schmidt-Sarosi 1995 these women comprised around 25% of the total group. In the study of Shalev 1995 69% of the total group of participants had cycle disorders. In all five studies they were equally distributed between the two treatment arms. In the studies of Nikbakht 2012 and Weiss 2010 the number and distribution of these women were not described. Finally, the study of da Silva 2012 included a category 'female factor' (23.4%) without describing details of this group.

The duration of subfertility was given in 10 trials (AboulGheit 2010; da Silva 2012; Lorusso 2008; Martinez 1991a; Martinez 1991b; Nikbakht 2012; Rahman 2011; Sakhel 2007; Weiss 2010; Zreik 1999). In two studies (AboulGheit 2010; Sakhel 2007) the duration was significantly different between the treatment groups. AboulGheit 2010 reported a mean duration of subfertility of 5.6 years in the 24 hours after hCG group compared to a mean of 3.1 and 3.5 years in the 34 hours and 48 hours after hCG groups. Although the pregnancy rates in the first group were lower compared to the other groups, this was not significant. Sakhel 2007 reported a longer duration of subfertility in the group treated with urinary hCG. This difference still remained a factor after analysing the data using logistic regression analysis with clinical pregnancy rate as the dependent variable and controlling for duration of infertility. They did not state if the difference was of any clinical relevance. In the studies of Martinez and co-workers the mean duration of subfertility was 5.6 and 6.3 years, which was quite long and could have negatively influenced their outcome parameters.

Four studies (da Silva 2012; Nikbakht 2012; Sakhel 2007; Weiss 2010) mentioned the number of couples with primary versus secondary subfertility. Their populations contained between 36% and 68.5% with primary subfertility.

Eight studies (da Silva 2012; Kyrou 2012; Lewis 2006; Martinez 1991a; Schmidt-Sarosi 1995; Shalev 1995; Sharma 2011; Zreik 1999) stated that they had included women who had undergone previous fertility treatment. Most of the women in the studies of Lewis 2006, Schmidt-Sarosi 1995 and Zreik 1999 had been treated with clomiphene citrate without IUI. Three studies (da Silva 2012; Martinez 1991a; Sharma 2011) included women who previously had undergone IUI treatment cycles. Kyrou 2012 and Shalev 1995 did not mention the type of previous fertility treatment.

Interventions

Three (Lewis 2006; Martinez 1991b; Zreik 1999) of the four studies comparing urinary LH versus hCG injection used clomiphene citrate as a method of ovarian stimulation. Clomiphene citrate was used either from cycle days three to seven or cycle days five to nine. The fourth study used HMG (Martinez 1991a). One study compared serum LH versus hCG injection in a natural cycle (Kyrou 2012). The studies Lorusso 2008 and Sakhel 2007 comparing recombinant hCG (r-hCG) with urinary hCG (u-hCG) both used recombinant FSH (r-FSH) for ovarian stimulation. However, Sakhel 2007 also added hMG and when the E2 level exceeded 300 pg/mL, or a leading follicle of more than 14 mm diameter was present, a gonadotropin-releasing hormone antagonist was applied. The studies comparing hCG with a GnRH agonist (Andrés-Oros 2008; Schmidt-Sarosi 1995; Scott 1994; Shalev 1995; Sharma 2011) used different ovarian stimulation protocols including clomiphene citrate (Schmidt-Sarosi 1995; Scott 1994; Sharma 2011), FSH (Andrés-Oros 2008) and hMG (Shalev 1995). Different stimulation protocols were also used in the studies trying to define the optimal timing of IUI. Rahman 2011 used clomiphene citrate as a method of ovarian stimulation, Claman 2004 and Weiss 2010 used hMG or r-FSH. Only AboulGheit 2010 compared the optimal timing of IUI after hCG in natural cycles. The

study of da Silva 2012 compared early hCG with late hCG depending on the size of the dominant follicle, stimulated with highly purified HMG. Finally, the study of Nikbakht 2012 comparing two doses of r-hCG achieved ovarian hyperstimulation with clomiphene citrate or letrozole and HMG

Urinary LH versus hCG injection

The use of the technique for timing IUI was one of the comparisons of interest in this review. Lewis 2006 included one group of women which used a home ovulation predictor kit once a day: in the afternoon, starting on day 12. Insemination was scheduled the morning after the first positive test. The women in the hCG group started ultrasound monitoring on day 12 and 10,000 IU hCG was given when there was at least one follicle with a mean diameter of 20 mm and the endometrial thickness was at least 8 mm. A single IUI was scheduled 33 to 42 hours later. Any woman who did not satisfy criteria for hCG administration was instructed to perform home monitoring for an LH surge until their next ultrasound, and to schedule an insemination if her predictor kit gave a positive result. There were no details on how often LH surges were detected in the ultrasound group before a follicle reached the size of 20 mm.

Martinez 1991a started daily ultrasound scanning when total urinary estradiol excretion exceeded 200 mmol/24 hours. When the largest follicle reached a diameter between 18 and 20 mm on ultrasound and the total estradiol excretion was between 300 and 1200 nmol/24 hours women received 10,000 IU hCG. LH detection in the urine was done twice daily from the moment the dominant follicle reached the size of 15 mm. A single IUI was performed 36 to 40 hours after hCG administration or 16 to 28 hours after urinary LH surge detection.

Martinez 1991b started urinary LH monitoring twice a day when the dominant follicle had reached 15 mm in diameter. Women were inseminated 21 hours after an evening positive urine or 24 hours after a morning positive urine. The other treatment group received 10,000 IU hCG when the dominant follicle reached a diameter size between 18 and 22 mm, measured daily by ultrasound when a dominant follicle had reached the size of 15 mm. From 37 to 40 hours after hCG a single IUI was performed.

Zreik 1999 started urinary LH monitoring in the morning on day 10 of the cycle. Ultrasound monitoring in the hCG group started on day 10 and 10,000 IU hCG was given when a leading follicle with diameter 18 mm diameter was noted. In both groups IUI was performed daily for the next two days.

Serum LH versus hCG injection

Kyrou 2012 was the only study using serum LH testing instead of urinary LH testing. The daily monitoring of serum LH levels could start from day 6 of the cycle until the LH rise. When LH started to rise, a second assessment was performed the next day to confirm the LH rise. Criteria for detection were an LH rise of 180% above the latest serum value. In the hCG group women received 5000 IU of hCG as soon as a follicle reached a diameter of ≥ 17 mm. A single IUI was performed 36 h after initiation of the LH rise or 36 h after the hCG injection. In the case where the serum LH suggested an imminent ovulation (LH rise and rise in progesterone) the insemination was performed after 24 h.

Recombinant hCG (r-hCG) versus urinary hCG (u-hCG)

Lorusso 2008 monitored ovarian response by ultrasound only. Urinary or recombinant hCG was given when one follicle with a mean diameter of 18 mm or more was present or no more than three follicles had a mean diameter of 16 mm. Double IUI was carried out 24 and 48 hours after administration, except when ovulation had occurred after 24 hours.

Sakhel 2007 monitored ovarian response by ultrasound and serum PGE2. When two or more follicles were 16 mm, with 200 pg/mL E2 per follicle, 10,000 IU u-hCG or 250 mg r-hCG was used to induce ovulation. A single IUI was performed 42 hours after the injection but this could be delayed by four hours when there was no collapse of the leading follicle observed on ultrasound. Luteal support was added with progesterone.

hCG versus GnRH agonist (GnRH-a)

Andrés-Oros 2008 administered a single injection of triptorelin (0.2 mg) or a single injection of r-hCG (250 µg) when at least one follicle, and not more than three, reached the size 18 mm or more. A single IUI was performed 36 hours after the injection. Luteal support with progesterone was applied.

Schmidt-Sarosi 1995 began ultrasound monitoring from cycle day 11. When the largest follicle was > 20 mm, 400 µg nafarelin intranasally (IN) was given on this and the following day, IUI was performed 48h after the first dose. The hCG group received an intramuscular injection of 5000 IU when the largest follicle reached > 20 mm and IUI was performed after 36 h. Luteal support in the GnRH-a group was given as seven doses of 400 µg nafarelin every 16 hours started 6 days after the first dose. Women in the hCG group received one injection of 2500 IU hCG six days after the primary injection.

Scott 1994 started daily pelvic ultrasound on cycle day 12. When the dominant follicle reached a diameter of 20 to 21 mm the women received GnRH-a (2 mg leuprolide acetate) subcutaneously or 10,000 IU hCG intramuscularly. Approximately 40 hours after injection, these women underwent a single IUI after a pelvic ultrasound was performed.

Shalev 1995 administered a single injection of triptorelin (0.1 mg) or single injection hCG (10,000 IU) when at least one follicle attained a diameter of 16 mm. Double IUI was performed 24 and 48 hours after the injection.

Sharma 2011 started follicle monitoring from cycle day 10. Urinary hCG (5000 IU) or GnRH-a (leuprolide 1 mg) was given when a follicular diameter was between 18 and 20 mm with endometrial thickness ≥ 7 mm. A single IUI was performed only after confirmation of ovulation with ultrasound. Luteal support was given with 300 mg vaginal micronized progesterone daily for 15 days.

Optimal time interval

Four studies compared the optimum time interval from ovulation induction to IUI. AboulGheit 2010 triggered ovulation with highly purified hCG (Choriomon, 10,000 IU) intramuscular injection when the leading follicle reached ≥ 18 mm and when at least two follicles reached ≥ 16 mm. Timing of IUI was 24 hours, 34 hours and 48 hours after hCG.

In the study of Claman 2004 the women received 5000 IU hCG intramuscularly or 10,000 IU hCG subcutaneously when two to five follicles were seen on ultrasound with a mean diameter of 17 to 21 mm. Timing of IUI was between 32 and 34 hours or 38 and 40 hours after hCG.

Rahman 2011 started ultrasound monitoring from cycle day 11 or earlier depending on the women's cycles. An ovulation trigger was given with injection of 5000 IU hCG when at least one follicle reached 18 mm or more and endometrial thickness was at least 7 mm. Single insemination was performed 24 or 36 hours after hCG injection.

Weiss 2010 administered hCG after a cycle with mild ovarian stimulation using gonadotropins and GnRH antagonist. The time and amount of hCG administered was not mentioned, but if five or more follicles over 15 mm were developed, or if ovulation took place before administration of the GnRH antagonist, the couple was excluded. Insemination took place 36 h, 42 h or 48 h after hCG administration. Luteal support was given with endometrin 100 mg twice a day from insemination until eight weeks of gestation.

Size of follicle at hCG injection

da Silva 2012 administered HMG from cycle day 4. Dose adjustments were made according to ovarian response until the criteria for hCG administration were met; 5000 IU of hCG was injected when the dominant follicle was between 16.0 and 16.9 mm diameter and 18.0 and 18.9 mm, respectively, and approximately 36 hours later IUI was performed. Luteal support was obtained with natural micronized progesterone 600 mg/day vaginally.

Two doses of recombinant hCG

In Nikbakht 2012 clomiphene or letrozole and HMG (Pergonal) were administered. When two or more follicles were 16 mm, r-hCG 250 or 500 ug was used to induce ovulation. A single IUI was performed 42 hours after r-hCG injection.

The studies used partners' semen, although this was not noted explicitly in all studies. Three studies noted donor cycles (Kyrou 2012; Lewis 2006; Weiss 2010). Semen preparation techniques, the amount of semen fluid injected, the number of motile semen injected and the type of insemination catheter were poorly described or not described at all (see table Characteristics of included studies).

Outcomes

Seven trials (Martinez 1991a; Rahman 2011; Sakhel 2007; Schmidt-Sarosi 1995; Scott 1994; Shalev 1995; Weiss 2010) reported live birth rates. All but one trial (Claman 2004) assessed pregnancy rate per couple. In one study (Weiss 2010) the couples who dropped out after inclusion were not included in the calculation of the live birth rate and pregnancy rate per couple. Therefore, the latter study was excluded from the meta-analysis.

Multiple pregnancy rates and miscarriage rates were reported in 11 studies (Andrés-Oros 2008; da Silva 2012; Lewis 2006; Lorusso 2008; Martinez 1991a; Martinez 1991b; Sakhel 2007; Schmidt-Sarosi 1995; Scott 1994; Shalev 1995; Weiss 2010). AboulGheit 2010 reported chemical pregnancies and clinical pregnancies separately. The OHSS rate was stated in five studies (Lorusso 2008; Martinez 1991a; Sakhel 2007; Schmidt-Sarosi 1995; Shalev 1995) and the ectopic pregnancy rate was stated in two publications (Sakhel 2007; Weiss 2010).

One of the studies assessed the costs of the treatment (Lewis 2006). The cost per pregnancy in the LH group was estimated to be USD 3695 and the cost per pregnancy in the hCG group was USD 4830.

Four studies (AboulGheit 2010; Lewis 2006; Nikbakht 2012; Sakhel 2007) diagnosed pregnancy by a rising concentration of hCG. In two studies (Lewis 2006; Rahman 2011) the pregnancy was called viable when a fetal pole with cardiac activity was noted on ultrasound. Five studies (AboulGheit 2010; da Silva 2012; Martinez 1991a; Martinez 1991b; Nikbakht 2012) stated that an ultrasound detection of fetal heart rate activity was performed four weeks after conception and in the study of Kyrou and co-workers ultrasound detection of fetal heart rate activity was performed 10 weeks after conception. Five studies (Andrés-Oros 2008; Lorusso 2008; Shalev 1995; Sharma 2011; Weiss 2010) defined clinical pregnancy by the presence of a gestational sac in the uterus, determined by transvaginal ultrasound. Three studies (Schmidt-Sarosi 1995; Scott 1994; Zreik 1999) did not mention the method of confirming pregnancy.

Studies awaiting assessment

All studies previously awaiting assessment were included (noting that the risk of bias was high, see table Characteristics of included studies).

Attempts have been made to contact authors to get further information about the methods of randomisation, to retrieve unpublished data and for details about published data. Eight replies have been received, resulting in exclusion of four trials (Diaz 2003a; Diaz 2003b; Lewis 2003; Pierson 2002) and inclusion of three trials (Scott 1994; Shalev 1995; Weiss 2010).

Four new studies (Aydin 2013; Blockeel 2014; Dehghani 2014; Mostafa 2014) that were identified will be assessed when this review is next updated.

Ongoing trials

One trial with the comparison of interest is registered on the ClinicalTrials.gov database and is still recruiting couples (OVO R&D 2012) (see Characteristics of ongoing studies). One of the ongoing trials of the 2009 review has been included (Weiss 2010).

Excluded studies

Fifty-five studies were excluded (see table Characteristics of excluded studies). Reasons for exclusion were: failure to use a truly randomised design (n = 19) (Agarwal 1995; Cedrin-Durnerin 1993; Check 1994; Costa Franco 2006; Diaz 2003a; Diaz 2008; Fondop 2005; Gerris 1995; Ghanem 2011; Khattab 2005; Kossoy 1989; Martinez 1994; Meherji 2004; Panchal 2009; Romeu 1997a; Romeu 1997b; Shanis 1995; Tavaniotou 2003; Tonguc 2010), not performing the comparison of interest (n = 18) (Arici 1994; Baroni 2001; Casadei 2006; Federman 1990; Fischer 1993; Gerrits 2011; Ghazizadeh 2009; Ghosh Dastidar 2009; Kotecki 2005; Nulsen 1993; Papageorgiou 1995; Pierson 2002; Pirard 2005; Ragni 1999; Ramon 2009; Robinson 1992; Silverberg 1991; Wang 2006), not performing IUI (n = 5) (Barratt 1989; Claraz 1989; George 2007; Odem 1991; Scarpellini 1991), did not meet the inclusion criteria for types of participants (n = 2) (Egbase 2003; Int rhCG study group 2001), or duplicate publications of abstracts or full text articles (n = 8) (Claman 2000;

Claman 2004a; Diaz 2003b; Lewis 2002; Lewis 2003; Ramon 2009a; Sakhel 2004; Wang 2001). Finally, one study was excluded from the awaiting assessment category since we did not receive the information we needed about the randomisation method (n = 1) (Propst 2007). The same authors published an abstract in 2012 on the same subject. The research population described seems to be the same group as published before. Additional information was lacking, thus this abstract was excluded as well (Propst 2012).

Risk of bias in included studies

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

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

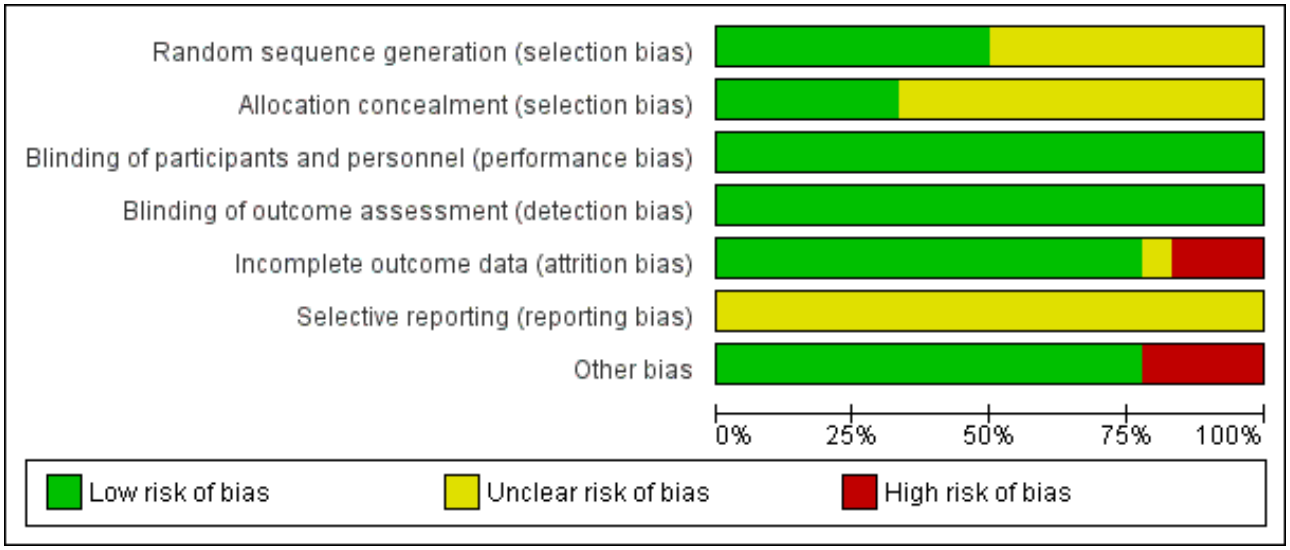
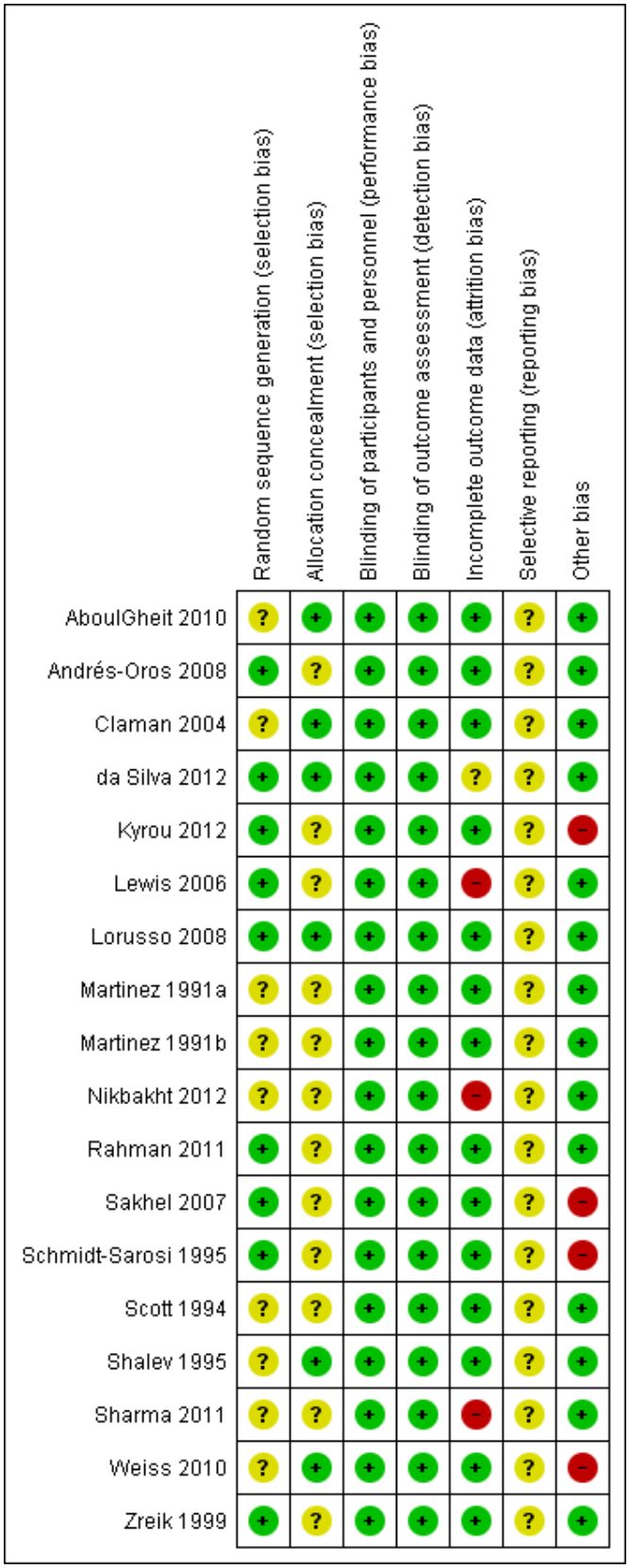


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Study design

Four studies (Martinez 1991a; Martinez 1991b; Scott 1994; Zreik 1999) used a cross-over design, with pre-cross over data available. For the meta-analysis we only included the first cycle data from these cross-over studies. The trial design was parallel group in the other included studies.

Allocation

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

Random sequence generation

Nine studies mentioned the use of a computer generated program for randomisation (Andrés-Oros 2008; da Silva 2012; Kyrou 2012; Lewis 2006; Lorusso 2008; Rahman 2011; Sakhel 2007; Shalev 1995; Weiss 2010; Zreik 1999). Five studies (Claman 2004; Martinez 1991a; Martinez 1991b; Schmidt-Sarosi 1995; Scott 1994) used a random number table, not further specified. Two studies (Nikbakht 2012; Sharma 2011) reported a random assignment without further specification.

Allocation concealment

Concealment of allocation was stated explicitly in six studies (AboulGheit 2010; da Silva 2012; Lewis 2006; Lorusso 2008; Weiss 2010; Zreik 1999). After additional information about allocation had been received, seven other trials (Andrés-Oros 2008; Claman 2004; Martinez 1991a; Martinez 1991b; Sakhel 2007; Scott 1994; Shalev 1995) could be deemed at low risk of bias in this domain. Concealment of allocation was done by the use of sealed opaque envelopes or a third party (Figure 2; Figure 3). Two studies (Nikbakht 2012; Sharma 2011) were deemed at high risk of this bias. Concealment of allocation was done with sealed envelopes in the latter study.

Blinding

In two studies (Scott 1994; Shalev 1995) blinding was performed. Scott and co-workers used blinding of the sonographer to minimise the risk of observer bias in determining if ovulation had taken place after injection of hCG or GnRH-a. None of the trials had details on blinded analysis of the results. All studies were rated at low risk of bias with respect to blinding as we determined that it was unlikely to influence our review outcomes.

Incomplete outcome data

Nine studies reported information on dropouts (Claman 2004; da Silva 2012; Kyrou 2012; Lewis 2006; Martinez 1991a; Martinez 1991b; Weiss 2010; Zreik 1999). The number of dropouts varied from 0% to 31%. Additional information on dropouts was received from four studies (Andrés-Oros 2008; Sakhel 2007; Shalev 1995; Weiss 2010). The first study (Andrés-Oros 2008) reported the dropping out of 18 couples who did not meet the criteria to induce ovulation (too many follicles, or no follicles). The main reason for dropout in the study of Weiss and co-workers was a transfer to in vitro fertilisation (IVF) because of overstimulation. The other five studies reported no dropouts.

Claman and co-workers stated that the most important reasons for dropping out were a spontaneous LH surge or an inadequate follicular response. Lewis and co-workers noted failure to detect an LH surge in 23% of the participants in the LH group. In the hCG group 5.3% of the participants dropped out due to personal reasons, especially because of time commitment. An ITT analysis was performed resulting in no significant difference between the treatment groups. In the study of Zreik and co-workers only one couple out of 54 was excluded, due to failure in compliance. None of the included women in the studies by Martinez 1991b and Kyrou 2012 dropped out. The other study of Martinez (Martinez 1991a) reported that five women decided to stop after the second cycle, and five did not complete the third cycle. Finally, the study of da Silva 2012 reported major protocol deviations in 117/635 couples, no hCG due to insufficient follicular growth in 61/635 couples, and serum estradiol (E2) > 1500 pg/ml or premature LH peak (LH > 10 mIU/ml). No explanation for protocol deviation was reported.

Selective reporting

A total of 44% of the included studies reported live birth rates. The remaining studies defined clinical pregnancy rates (see table Characteristics of included studies).

Other potential sources of bias

Sakhel and co-workers reported that the included women in the u-hCG group had a greater mean duration of infertility than the r-hCG group, which may have been a source of bias in this study. The same applies to the study of AboulGheit 2010 where the couples in the IUI 24 hours after hCG group had a longer mean duration of infertility. Weiss and co-workers reported significantly more miscarriages in the group with a time interval of 36 hours, and the study of Kyrou and co-workers included a high percentage of non-subfertile women. da Silva 2012 did not report the exact size of the dominant follicles per group, which might have introduced bias. Finally, Sharma 2011 excluded 20 couples before randomisation for unclear reasons.

Effects of interventions

See: **Summary of findings for the main comparison** hCG compared to LH surge for intrauterine insemination in subfertile couples; **Summary of findings 2** u-hCG compared to r-hCG for intrauterine insemination in subfertile couples; **Summary of findings 3** Short interval compared to long interval for intrauterine insemination in subfertile couples; **Summary of findings 4** hCG compared to GnRH-a for intrauterine insemination in subfertile couples; **Summary of findings 5** Early hCG compared to late hCG for intrauterine insemination in subfertile couples; **Summary of findings 6** Differing dosages of hCG for intrauterine insemination in subfertile couples

Overall 18 studies with a total of 2279 couples were included in the review.

1. hCG versus LH surge

Four studies compared hCG with LH surge for timing IUI (Lewis 2006; Martinez 1991a; Martinez 1991b; Zreik 1999).

1.1 Live birth rate

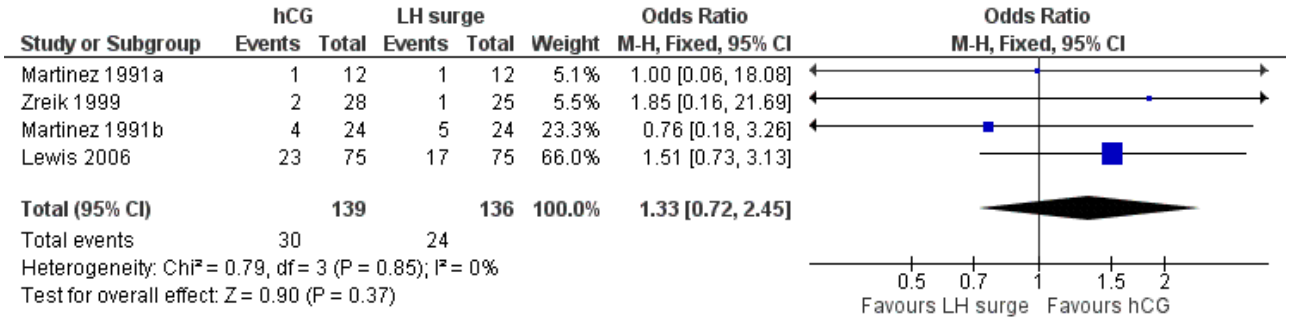
One study (Martinez 1991a) reported live birth rate. There was no evidence of a difference between hCG and LH surge (odds ratio (OR)

1.0, 95% confidence interval (CI) 0.06 to 18.08; 1 trial, 24 women, very low quality evidence) (Analysis 1.1).

1.2 Pregnancy rate

All trials included for this comparison reported pregnancy rate per couple. The result revealed no evidence of a difference in pregnancy rate per couple (OR 1.33, 95% CI 0.72 to 2.45; 4 trials, 275 women, I^2 = 0%, low quality evidence) (Analysis 1.2, Figure 4).

Figure 4. Forest plot of comparison: 1 hCG versus LH surge, outcome: 1.2 pregnancy rate per couple.



1.3 Multiple pregnancy rate

The meta-analysis of two studies (Lewis 2006; Martinez 1991a) revealed no evidence of a difference in multiple pregnancy rates (OR 1.12, 95% CI 0.17 to 7.6; 2 trials, 42 pregnancies, very low quality evidence) (Analysis 1.3).

2. u-hCG versus r-hCG

Two studies (Lorusso 2008; Sakhel 2007) compared u-hCG with r-hCG for timing IUI.

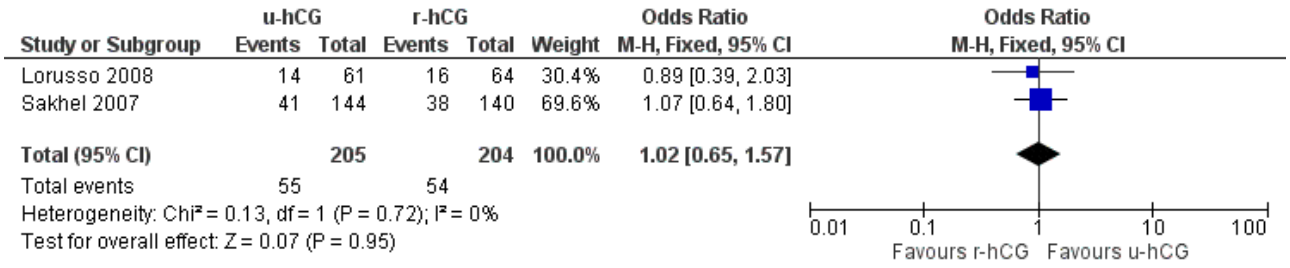
2.1 Live birth rate

One study (Sakhel 2007) reported live birth rate, which showed no evidence of a difference between u-hCG and r-hCG (OR 1.17, 95% CI 0.68 to 2.03; 1 trial, 284 women, low quality evidence) (Analysis 2.1).

2.2 Pregnancy rate

All trials included in this comparison reported pregnancy rate per couple. The result revealed no evidence of a difference in pregnancy rate per couple (OR 1.02, 95% CI 0.65 to 1.57; 2 trials, 409 women, I^2 = 0%, low quality evidence) (Analysis 2.2, Figure 5).

Figure 5. Forest plot of comparison: 2 u-hCG versus r-hCG, outcome: 2.2 pregnancy rate per couple.



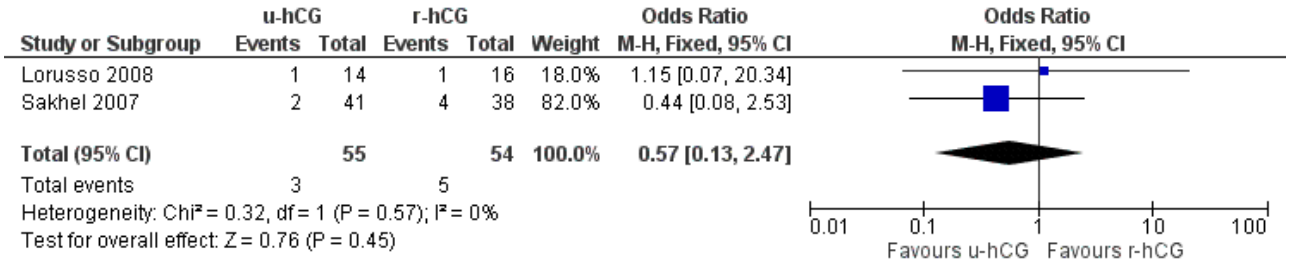
2.3 Multiple pregnancy rate

No evidence of a difference in multiple pregnancy rates was reported (OR 0.99, 95% CI 0.4 to 2.47; 2 trials, 109 pregnancies, low quality evidence) (Analysis 2.3).

2.4 Miscarriage rate

Miscarriages per treatment group showed no evidence of a difference between groups (OR 0.57, 95% CI 0.13 to 2.47; 2 trials, 109 pregnancies, I^2 = 0%, very low quality evidence) (Analysis 2.4, Figure 6).

Figure 6. Forest plot of comparison: 2 u-hCG versus r-hCG, outcome: 2.4 miscarriage rate per pregnancy.



2.5 OHSS rate

Both studies reported no cases of (severe) OHSS in a total of 468 cycles (moderate quality evidence) (Analysis 2.5).

3. Short versus long interval

Two studies (AboulGheit 2010; Rahman 2011) compared a short interval (24 hours) with a long interval (34 to 36 hours) after hCG. AboulGheit 2010 included a third group (IUI 48 hours after hCG).

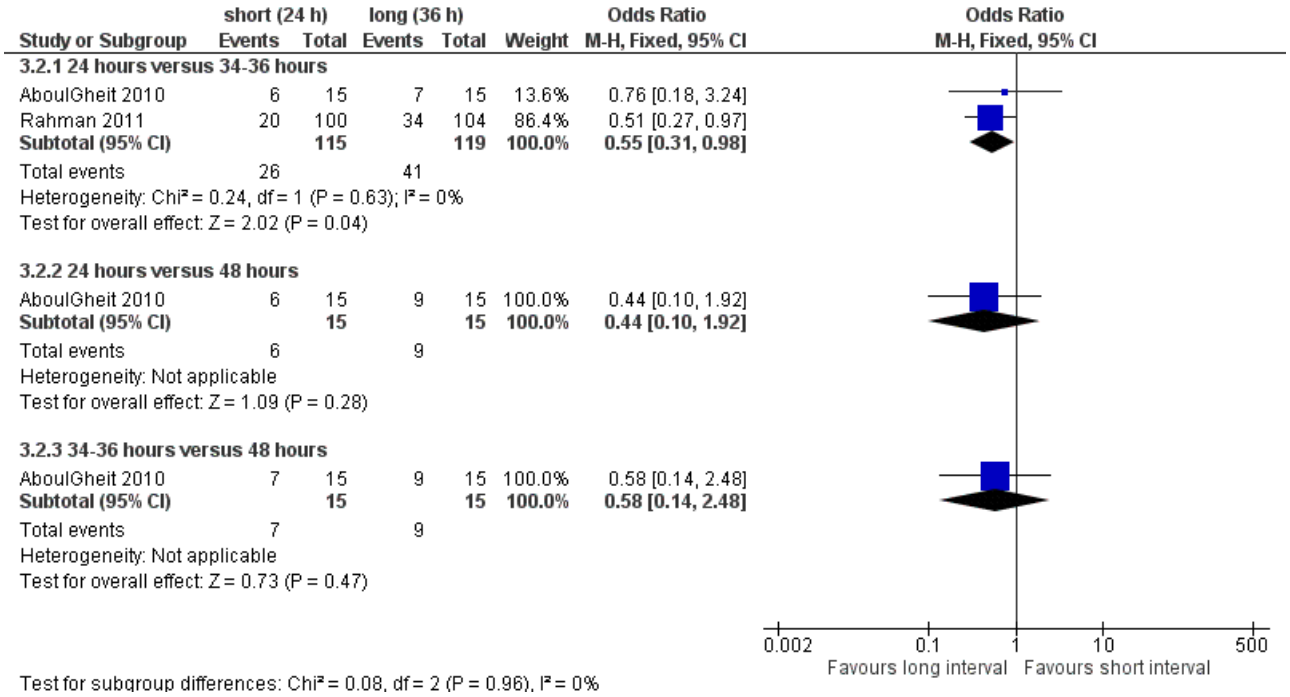
3.1 Live birth rate

One study (Rahman 2011) reported live birth rate, which showed no evidence of a difference between IUI after 24 hours and 34 hours (OR 0.52, 95% CI 0.27 to 1.00; 1 trial, 204 couples, low quality evidence) (Analysis 3.1).

3.2 Pregnancy rate

Both studies reported pregnancy rate per couple. The meta-analysis revealed a lower pregnancy rate in the 24 hour group, when IUI was after 24 hours compared with IUI after 34 to 36 hours (OR 0.55, 95% CI 0.31 to 0.98; 2 trials, 234 women, I^2 = 0%, low quality evidence) (Analysis 3.2). AboulGheit 2010 also compared IUI after 24 hours with IUI after 48 hours and found no evidence of a difference between the groups (OR 0.44, 95% CI 0.10 to 1.92; 1 trial, 30 women, low quality evidence) (Analysis 3.2). Nor was there a diffference between IUI after 34 to 36 hours and IUI after 48 hours (OR 0.58, 95% CI 0.14 to 2.48; 1 trial, 30 women, low quality evidence) (Analysis 3.2, Figure 7).

Figure 7. Forest plot of comparison: 3 short versus long interval, outcome: 3.2 pregnancy rate per couple.

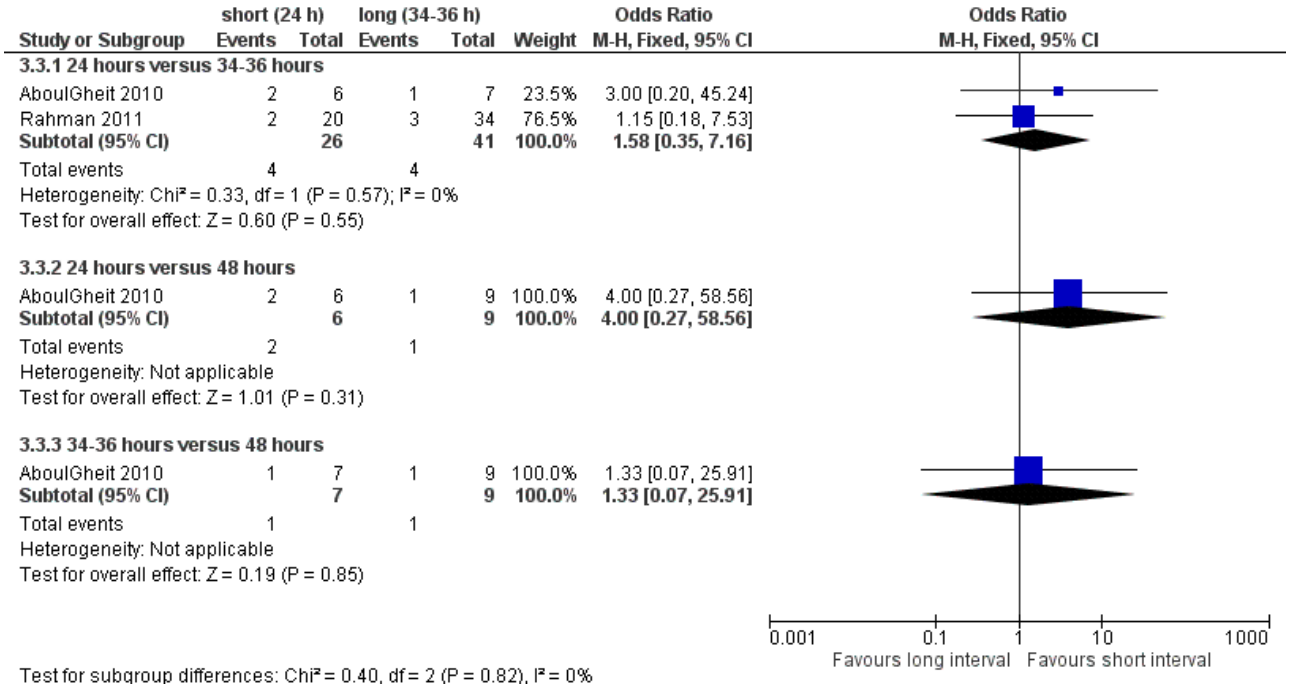


3.3 Miscarriage rate

Both studies reported miscarriage rates, with no evidence of a difference between the groups of 24 hours versus 34 to 36 hours (OR 1.58, 95% CI 0.35 to 7.16; 2 trials, 67 pregnancies, I^2 = 0%, very low quality evidence); 24 hours versus 48 hours (OR 4.0, 95% CI 0.27 to 58.56; 1 trial, 15 women, very low quality evidence); 34 to 36 hours versus 48 hours (OR 1.33, 95% CI 0.07 to 25.91; 1 trial, 16 women, very low quality evidence) (Analysis 3.3) respectively. Two studies (Claman 2004; Weiss 2010) were excluded from the meta-analysis since they reported results as pregnancy rates per cycle only. The former did not report a difference between 32 to 34 hours and 38 to

40 hours after hCG, and the latter study was stopped prematurely because of an unusual number of multi-fetal pregnancies; the study reported a higher pregnancy rate for 42 hours after hCG compared to 36 hours or 48 hours (see table 'Characteristics of included studies' for details, Figure 8).

Figure 8. Forest plot of comparison: 3 short versus long interval, outcome: 3.3 miscarriage rate per pregnancy.



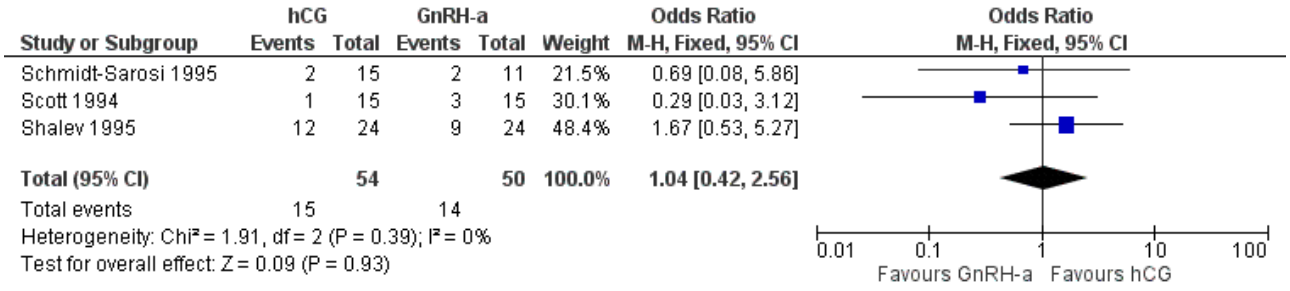
4. hCG versus GnRH-a

Four studies (Andrés-Oros 2008; Schmidt-Sarosi 1995; Scott 1994; Shalev 1995) compared hCG versus GnRH-a.

4.1 Live birth rate

The results for live birth rate per couple revealed no evidence of a difference between the groups (OR 1.04, 95% CI 0.42 to 2.56; 3 trials, 104 women, I^2 = 0%, low quality evidence) (Analysis 4.1, Figure 9).

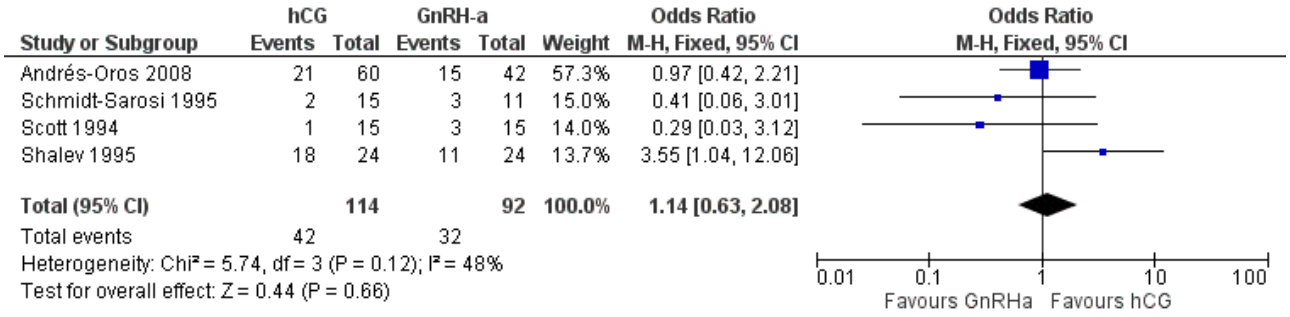
Figure 9. Forest plot of comparison: 4 hCG versus GnRH-a, outcome: 4.1 live birth rate per couple.



4.2 Pregnancy rate

All trials reported the pregnancy rate per couple revealing no evidence of a difference between groups (OR 1.14, 95% CI 0.63 to 2.08; 4 trials, 206 women, I^2 = 48%, low quality evidence) (Analysis 4.2, Figure 10).

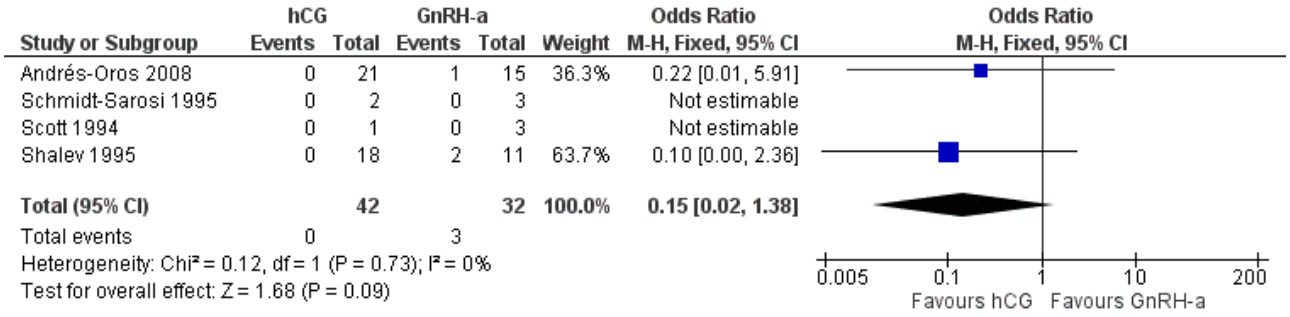
Figure 10. Forest plot of comparison: 4 hCG versus GnRH-a, outcome: 4.2 pregnancy rate per couple.



4.3 Multiple pregnancy rate

The studies reported three twin pregnancies in the GnRH-a group and none in the hCG group. There was no evidence of a difference in multiple pregnancy rates between hCG and GnRH-a (OR 0.15, 95% CI 0.02 to 1.38; 4 trials, 74 pregnancies, I^2 = 0%, very low quality evidence) (Analysis 4.3, Figure 11).

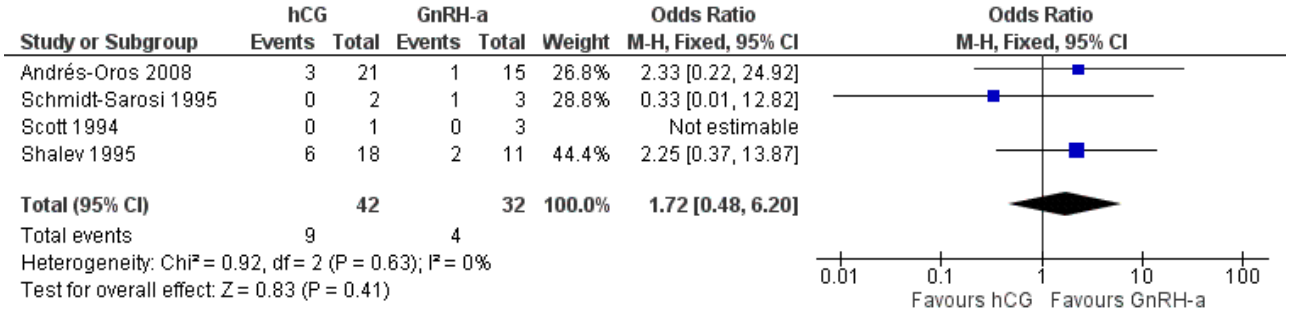
Figure 11. Forest plot of comparison: 4 hCG versus GnRH-a, outcome: 4.3 multiple pregnancy rate per pregnancy.



4.4 Miscarriage rate

There was no evidence of a difference in the miscarriage rate between the GnRH-a and hCG group (OR 1.72, 95% CI 0.48 to 6.2; 4 trials, 74 pregnancies, I^2 = 0%, very low quality evidence) (Analysis 4.4, Figure 12).

Figure 12. Forest plot of comparison: 4 hCG versus GnRH-a, outcome: 4.4 miscarriage rate per pregnancy.



4.5 OHSS rate

OHSS rates were compared and there was no evidence of a difference between groups (OR 2.27, 95% CI 0.65 to 7.91; 3 trials, 456 women, low quality evidence) (Analysis 4.5). Shalev 1995 reported four treatment cycles with grade three to grade four OHSS in the GnRH-a group, and eight treatment cycles with OHSS in the hCG group; the other two studies in this meta-analysis reported none in either group.

5. Early versus late hCG

One study (da Silva 2012) compared early hCG versus late hCG.

5.1 Pregnancy rate

No evidence of a difference was reported between both treatment groups in the pregnancy rate per couple (OR 1.32, 95% CI 0.77 to 2.25; 1 trial, 612 women, low quality evidence) (Analysis 5.1).

5.2 Miscarriage rate

No evidence of a difference between miscarriages rates was reported (OR 0.51, 95% CI 0.08 to 3.28; 1 trial, 65 pregnancies, very low quality evidence) (Analysis 5.2).

The authors reported two multiple pregnancies in the early hCG group and none in the late hCG group.

6. Different dosages of hCG

One trial (Nikbakht 2012) compared 250 ug r-hCG with 500 ug r-hCG.

6.1 Pregnancy rate

No evidence of a difference in pregnancy rate per couple was reported (OR 1.38, 95% CI 0.28 to 6.71; 1 trial, 66 women, very low quality evidence) (Analysis 6.1).

DISCUSSION

Summary of main results

The aim of this review was to investigate the optimal synchronisation of ovulation with intrauterine insemination (IUI) in subfertile couples undergoing natural and stimulated cycles with regard to live birth rates. The trials in this review revealed that not one of the available methods is superior to another. However, the available evidence is scarce due to small sample sizes and lack of data concerning the primary outcome.

hCG injection versus LH surge detection

Although the dropout rate in the LH surge group was much higher than in the hCG group (due to no detection of a LH surge in 23% of the cycles) there was no evidence of a difference in live birth or pregnancy rates between these treatment groups (OR 1.5, 95% CI 0.73 to 3.1) (Lewis 2006).

The cause of dropouts in the LH surge group could be the absence of detection of LH surges in urine samples. This has been reported in other studies as well, due to a short LH surge or incorrect use of the intervention by the woman (Miller 1996). When counselling couples, the advantages of home ovulation predictor tests (no difference in pregnancy outcomes compared to hCG injection, convenience and low costs) and disadvantages (high number of false-negative results) should be considered in relationship to the advantages (low number of false-negative results) and disadvantages (expensive and time consuming) of ultrasound detection combined with hCG injection. No data on the occurrences of premature LH surges in the hCG group have been reported in the pooled studies. This might negatively influence the treatment outcome in the hCG group, resulting in lower pregnancy rates and no perceptible difference between timing using LH surge detection and hCG injection (Cantineau 2007).

The general quality of the evidence was estimated to be low or very low, meaning that further research is likely or very likely to have an important impact on our confidence in the estimate of effect and is likely to change this estimate (Summary of findings for the main comparison).

Urinary hCG (u-hCG) versus recombinant hCG (r-hCG)

No evidence of a difference in pregnancy rates was found between u-hCG and r-hCG. Other reasons such as costs, injection site reactions and possible batch-to-batch inconsistencies should be considered in deciding which to use.

The general quality of the evidence was estimated to be low or very low (Summary of findings 2).

Short (24 hours) versus long interval (36 hours)

The evidence provided by prospective studies (AboulGheit 2010; Rahman 2011) comparing different hCG to IUI intervals after ovarian stimulation revealed more live births when an interval of 34 to 36 hours was used. However, this difference was not statistically significant. A higher number of pregnancies was reported when IUI was performed 34 to 36 hours after hCG compared to IUI 24 hours after hCG injection. This might be in part due to a significant difference in the duration of subfertility (significantly longer in the 24 hours group in the study of AboulGheit 2010). This study and other studies that only reported pregnancy rate per cycle suggest a more flexible approach in timing IUI after hCG, which allows women to inject hCG in the early evening when pharmacies are still open, in case of problems (Claman 2004).

The general quality of the evidence was estimated to be low or very low (Summary of findings 3).

hCG versus GnRH agonist (GnRH-a)

No evidence of a difference was found, when analysing live birth rates and pregnancy rates, between the timing methods using hCG and GnRH-a. More evidence is needed to determine the place of GnRH-a as a timing method for IUI, also considering costs and secondary outcomes such as the OHSS rate.

The general quality of the evidence was estimated to be low or very low (Summary of findings 4).

Early hCG versus late hCG depending on the size of the dominant follicle

As well as the ITT analysis, the per protocol analysis reported no advantage of hCG injection with a dominant follicle between 16.0 and 16.9 mm compared to a dominant follicle between 18.0 and 18.9 mm (da Silva 2012). Significantly more dominant follicles and significantly higher estradiol levels were seen in the late group without significantly increased numbers of premature LH surges or clinical pregnancies. No information was reported on the exact sizes of the dominant follicles. For example, when a dominant follicle was 17 mm in the early group it was unclear whether it was stated as a major protocol deviation. Since the day of hCG administration and the total dose of HMG did not differ, it is questionable how different the groups really were.

The general quality of the evidence was estimated to be low or very low (Summary of findings 5).

Different dosages of hCG

No evidence of a difference was found between 250 µg r-hCG and 500 µg r-hCG. Significantly more dominant follicles were seen in the 250 µg r-hCG group, which might be a confounding factor.

The quality of the evidence overall was estimated to be low or very low (Summary of findings 6).

Overall completeness and applicability of evidence

Definite answers could not be given for most comparisons. When performing IUI, small numbers show a positive effect of insemination around 34 to 36 hours compared to 24 hours after hCG injection.

Quality of the evidence

The quality of the evidence for most comparisons was low or very low. The main limitations in the evidence were failure to describe study methods, serious imprecision and attrition bias.

Potential biases in the review process

Our searches aimed to identify all potentially eligible studies.

Agreements and disagreements with other studies or reviews

No other reviews were available concerning the difference between hCG injection and the LH detection test for timing IUI. Other retrospective studies revealed conflicting results.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine whether different methods of synchronization of ovulation and insemination differ in safety and effectiveness. More research is needed.

There is no evidence to advise one of the treatment options over another (ultrasound combined with hCG injection versus urinary LH surge detection, medication to time the insemination, dose of medication, time interval between medication and insemination) since live births and pregnancy rates do not differ significantly. The choice should be based on hospital facilities, convenience for the couple, medical staff, costs and dropout levels.

The choice of urinary hCG or recombinant hCG should be based on costs and couples' preferences since pregnancy rates are not significantly different.

Since the evidence suggested an advantage of insemination 34 to 36 hours after hCG, this could be advised until more reliable evidence is available from well-powered RCTs.

The results suggest that no advice could be given on the timing of hCG injection in relationship to the size of the dominant follicles nor on the dosages of recombinant hCG.

Implications for research

Large prospective multi-centre trials with adequate concealment of allocation comparing ultrasound monitoring combined with hCG injection and LH surge detection in urinary samples should be performed with special attention to costs and the convenience of the treatments.

Large prospective multi-centre trials with adequate concealment of allocation and comparing different time intervals between hCG and IUI should be performed, with special attention to convenience for the patient. Data should be adequately reported as the live birth rate per couple or at least as the ongoing pregnancy rate per couple. Adverse effects should also be reported.

ACKNOWLEDGEMENTS

We would like to thank Dr R Bernardus as co-author of the publications with Dr Martinez for the additional information. The same applies to Dr Abuzeid for the additional information provided about the article of Sakhel and co-workers, and to Dr Lewis, Dr Andrés Oros, Dr Claman, Dr Scott, Dr Shalev, Dr Weiss, Dr García-Velasco and Dr Pierson for information on their publications.

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CHARACTERISTICS OF STUDIES

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

AboulGheit 2010

Methods	Single centre, parallel prospective randomised trial. Concealment of allocation: third party Blinding not stated. Follow up not stated. Duration study: January 2008 to July 2009 Power calculation not stated.
Participants	45 couples, 125 cycles, duration of subfertility not stated Exclusion criteria: couples with bilateral tubal block and women with endocrinological disorders Mean age of women, 24 h after hCG: 28.7 yrs ± 6.1, 34 h after hCG: 26.4 ± 4.5 and 48 h after hCG: 26.8 yrs ± 4.3 Type of subfertility: unexplained
Interventions	IUI 24 hours, 34 hours or 48 hours after hCG Stimulation method: was not stated except 10.000 IU hCG when the leading follicle reached ≥ 18 mm and at least two follicles reached ≥ 16 mm Type of semen: partner semen. Semen prepared with a swim up technique Insemination procedure: IUI catheter, one insemination per cycle
Outcomes	Clinical pregnancy rate per couple: 24 h group 6/15 (40%), 34 h group 7/15 (46%), 48 h group 9/15 (60%) Clinical pregnancy defined as gestational sac and later evidence of fetal heart activity on transvaginal ultrasound
Notes	Method of randomisation unclear. Signifcantly different in mean of subfertility between treatment groups Duration of subfertility was significantly longer in the group where IUI was performed after 24 hours The author did not have an explanation for this difference Setting: Obstetric and Gynaecology Department Cairo University, Egypt Funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation
Allocation concealment (selection bias)	Low risk	Couples were randomised into three groups by a third party (nurse)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding stated, but outcome is not likely to be influenced
Blinding of outcome assessment (detection bias)	Low risk	No blinding stated, but outcome is not likely to be influenced

AboulGheit 2010 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Andrés-Oros 2008

Methods	Single centre, parallel prospective randomised trial. Computer generated list of random numbers. Concealment of allocation: third party Blinding not stated. Follow up not stated. Duration study not stated Power calculation not stated
Participants	120 couples, 290 cycles, at least 2 years of subfertility Exclusion criteria: women with PCOS or other cycle disturbances, semen analysis < 5 million after work up Mean age of women: r-hCG group: 32.2 yrs ± 2.5 and GnRH-a group: 32.3 yrs ± 2.5 Type of subfertility: unexplained, endometriosis stage 1 or 2, male factor (WHO 1992), unilateral tubal factor
Interventions	GnRH-a versus r-hCG for triggering ovulation in IUI Stimulation method: 75 IU FSH, 250 ug r-hCG sc or 0.2 mg GnRH-a sc (triptorelin 0.2 mg) IUI 36 hours after injection of hCG or GnRH-a Type of semen not explicitly stated. Semen prepared with a swim up technique Insemination procedure: Gynetics catheter, one insemination per cycle
Outcomes	Clinical pregnancy rate per couple: r-hCG group 21/60 (35%), GnRH-a group 15/42 (35.7%) Number of miscarriages: r-hCG group 3/21 (14%), GnRH-a group 1/15 (6.7%) Multiple pregnancy rates: r-hCG group 0/21 (0%), GnRH-a group 1/15 (6.7%) Pregnancy diagnosed: transvaginal ultrasound demonstrating heart activity
Notes	60 couples received r-hCG and only 42 couples received GnRH-a. The other 18 couples did not reach the point to induce ovulation due to too many, or no follicles. The author did not have an explanation for this difference Setting: Assisted Reproduction Service. Miguel Servet University Hospital, Zaragoza, Spain No funding

Risk of bias

Bias	Authors' judgement	Support for judgement

Andrés-Oros 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computer generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding stated, outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding stated, outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Claman 2004

Methods	Single centre, parallel design with random number table. Concealment of allocation: third party No blinding used. Duration of the study and follow up not stated Power calculation: sample size of 190 with a power of 0.8 to detect an increase in pregnancy rate from 15% to 30% between groups with an alpha of 0.05. ITT: no
Participants	75 women, 189 cycles, > 2 years subfertility Exclusion criteria: cycles with endogenous LH surge Mean age of women: short hCG-IUI interval: 34.4 yrs ± 3.6 and long hCG-IUI interval: 34.3 yrs ± 3.6 Type of subfertility: unexplained, endometriosis stage 1 or 2, male factor (WHO 1992), clomiphene resistant oligo-ovulation, or combination of factors
Interventions	Stimulation method: 100 to 225 IU FSH, 5000 IU hCG im or 10,000 IU hCG sc IUI either 32 to 34 hours or 38 to 40 hours after injection of hCG Type of semen not explicitly stated. Semen prepared with a two-layer density gradient separation technique, final sample suspended in 0.35 ml of culture medium Insemination procedure: Tomcat catheter high up in the uterine fundus, one insemination per cycle
Outcomes	Pregnancy rate per cycle: short interval 20/96 (20%), long interval group 14/93 (15%) Secondary outcomes not stated Pregnancy diagnosed: transvaginal ultrasound demonstrating heart activity
Notes	Inclusion of couples with oligo-ovulation

Claman 2004 *(Continued)*

	Setting: Division of Reproductive Medicine, Department of Obstetrics and Gynecology, The Ottawa Hospital, Canada
	No funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	None stated; the author comment 'next random number in the table' does not state the random sequence generation
Allocation concealment (selection bias)	Low risk	Third party (a nurse) in the clinical care team picked the next random number in the table and crossed it
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed adequately
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

da Silva 2012

Methods	Multi-centre trial, parallel design with automatically generated randomisation. Concealment of allocation: third party (centralised telephonic system). Blinding was not stated. Duration of the study 3 years Power calculation: sample size of 260 in each group with a power of 0.8. ITT: stated, Per protocol group stated separately
Participants	635 women, cycles not stated, 2 to 5 years of subfertility Exclusion criteria: tubal obstruction, endometriosis grade III and IV, metrorrhagia of unknown origin, present or past malignant or metabolic or endocrine diseases, cervical infection, positive serology for hepatitis B, C, HIV or syphilis, anti-spermatozoa antibodies, positive sperm culture, ejaculation disorders, alcohol or drug addiction, participation in another clinical trial in the previous month. Occurence of a spontaneous LH surge during COS before the day of hCG administration Mean age of women: early hCG: 30.9 yrs ± 3.8 and late hCG: 31.0 yrs ± 3.8 Type of subfertility: unexplained, endometriosis stage 1 or 2, male factor, female factor or combination of factors
Interventions	Stimulation method: 75 IU FSH/day from day 4 (maximum dose 300 IU), 5000 IU hCG im IUI 36 hours after injection of hCG. hCG when DF 16.0 to 16.9 mm or within 18.0 to 18.9 mm

da Silva 2012 *(Continued)*

	Type of semen: husband. Semen prepared with double centrifugation technique using standardized protocols Insemination procedure: not stated. Luteal support with progesterone vaginally
Outcomes	Clinical pregnancy rate: early 36/309 (11.7%), late group 29/303 (9.6%) Secondary outcomes: ongoing intrauterine pregnancy rate (>10 weeks) and incidence of premature LH surge before hCG administration Pregnancy diagnosed: transvaginal ultrasound demonstrating heart activity
Notes	117 major protocol deviations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Groups of randomisation were automatically generated using a centralized telephonic system
Allocation concealment (selection bias)	Low risk	The use of a centralized telephonic system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only states 'treatment not initiated in 23 participants', does not state reason
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Kyrou 2012

Methods	Single centre, parallel design with randomisation on the basis of a computer generated list. Concealment of allocation: not stated No blinding used. Duration of the study: April 2009 until October 2010. Duration of follow up not stated Power calculation: sample size of 2943 couples in each group to achieve 80% power of at a 5% significance level to detect a difference of 3%. No ITT
Participants	300 women, 300 cycles Inclusion criteria: age ≤ 36 years, regular menstrual cycles, BMI between 18 and 29 kg/m^2, basal concentration of FSH (≤ 12 IU/L), estradiol (≤ 80 pg/ml) and progesterone (≤ 1.6 ng/ml) on cycle day 1 and normal hysterosalpingography. Husband semen with more than 5 million spermatozoa per ejaculation and morphology > 4% normal. Donor semen

Kyrou 2012 *(Continued)*

	Exclusion criteria: PCO and endometriosis Mean age of women: LH surge group: 31.5 ± 3.7 yrs, and hCG group: 31.4 ± 3.7 yrs Mean duration of subfertility not stated Type of subfertility: unexplained, male factor
Interventions	Stimulation method: natural cycle LH surge group: daily serum testing of LH from cycle day 6. hCG group: 10,000 IU hCG at follicle size of ≥ 17mm. IUI 24 to 36 hours later Husband semen and donor semen Insemination procedure: 0.3 ml of semen into the uterine cavity through a Friedman catheter, bed rest for 10 min. One insemination
Outcomes	Pregnancy rate per couple: LH surge group 34/150 (22.7%) and hCG group 16/150 (10.7%) Secondary outcome measures: not stated Costs: not stated Pregnancy diagnosed: ultrasound at 12 weeks gestation
Notes	Large group without subfertility (lesbian couples, single mother); LH group 58%, hCG group 58.7% Setting: Centre for Reproductive Medicine, University Hospital Brussels, Belgium No funding stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised on the basis of a computer generated list
Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Comment: high percentage of non-subfertile women included

Lewis 2006

Methods	Single centre, parallel design. Randomisation order was assigned by computer program Blinding until first ultrasound after informed consent. Duration of the study and follow up not stated Power calculation: a sample size of 75 women in each group was needed to detect differences in cumulative pregnancy rates of 22% versus 49% after 3 cycles. ITT was performed
Participants	150 women, 129 completed at least one cycle Inclusion criteria: > 1 year subfertility or three failed cycles of donor IUI. At least one patent tube and a functional ipsilateral ovary. Four million motile spermatozoa with normal morphology Exclusion criteria: elevated FSH levels on cycle day 3, severe endometriosis, recurrent pregnancy loss, previous use of superovulation and IUI Age of women: LH surge group: 33.5 ± 3.9 yrs and hCG group: 34.0 ± 3.9 yrs Type of subfertility: unexplained, mild endometriosis, male factor, cervical factor, tubal or pelvic factor
Interventions	Stimulation method: 100 mg clomiphene citrate from day 5 through day 9 LH surge group: home monitoring u-LH and IUI morning after positive test. hCG group: 10,000 IU hCG and IUI 33 to 42 hours later Husband semen and probably donor semen Insemination procedure: not stated. One insemination per cycle
Outcomes	Pregnancy rate per couple: LH surge group 25% and hCG group: 31% Multiple pregnancy rate per couple: LH surge group 11.1% and hCG group: 12.9%. Miscarriage rate per couple: LH surge group: 34% and hCG group: 18% Costs: stated in the abstract. Cost per pregnancy LH group USD 3695; cost per pregnancy hCG group USD 4830 Pregnancy diagnosed: rising concentration of hCG. Viable pregnancy is defined as a fetal pole with heart activity by ultrasound
Notes	The abstract used different pregnancy rates as did the full text article Setting: Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA Funding by product donation by Serono, Inc, Rockland, Massachusetts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation order was assigned by computer program
Allocation concealment (selection bias)	Unclear risk	Only states 'Treatment group assignment was not known', but method of concealment is not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced

Lewis 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason of missing data not stated; imbalance in numbers across intervention groups, possibly related to true outcome
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Lorusso 2008

Methods	Single centre, parallel design for three cycles. Randomisation order was assigned by computer generated table. Concealment of allocation: sealed opaque envelopes Blinding unclear. Follow up until pregnancy was beyond 12th week of gestation. Power calculation: at least 61 couples in each group would be required to achieve 80% power to detect an increase of 20% in progesterone levels in the r-hCG group. ITT was not stated Duration: IUI treatment between October 2005 and December 2007
Participants	125 women, 184 cycles were completed Inclusion criteria: endometriosis grade I or II according to the AFS, infertility due to sexual dysfunction, a normal uterine cavity and tubal patency assessed by HSG and/or laparoscopy, primary or secondary infertility lasting for at least 24 months, no infection of semen in last 6 months, normal semen analysis according to the WHO or at least 5 million motile spermatozoa after semen preparation, willingness to participate in the study and to comply with the procedure Exclusion criteria: maternal age > 40 years, severe male-factor infertility, endometriosis grade III or IV, previous IVF attempts, positive hepatitis B virus, hepatitis C virus or HIV serology, PCOS or recurrent miscarriage Age of women: r-hCG group: 33 ± 3.6 yrs and u-hCG group: 32.0 ± 4.4 yrs Duration of subfertility: r-hCG group: 4 ± 1.7 yrs and u-hCG group: 3 ± 2.4 yrs Type of subfertility: mild endometriosis, mild male factor, unexplained infertility
Interventions	Stimulation method: daily dose of 37.5 IU r-FSH starting from cycle day 2 to 3 for 5 days according to a low-dose, step up protocol 250 µg sc r-hCG or 5000 IU u-hCG IM when one follicle with mean diameter > 17 mm was present and no more than 3 follicles with a mean diameter > 15 mm IUI was carried out 24 hr and 48 hr after hCG administration Husband's semen Insemination procedure: not stated; two inseminations
Outcomes	Pregnancy rate per couple: r-hCG group 29.7% and u-hCG group: 24.6% Clinical pregnancy rate per couple: r-hCG group: 25% and u-hCG group: 22.9% Multiple pregnancy rate per couple: none. Miscarriage rate per pregnancy: r-hCG group: 6.3% and u-hCG group: 7.1%

Lorusso 2008 *(Continued)*

	Costs: not stated Pregnancy diagnosed: serum hCG testing 14 days after IUI. Clinical pregnancy was defined as fetal cardiac activity on transvaginal sonography
Notes	Primary endpoint was the ovulation rate Setting: Centre for Physiopathology of Human Reproduction and Gametes Cryopreservation, Gynaecology and Obstetrics, University of Bari, Italy No funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Couples were randomised by a computer generated table
Allocation concealment (selection bias)	Low risk	Concealment by use of sealed opaque envelopes, each containing a unique study number and prepared independently by a secretary
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Martinez 1991a

Methods	Single centre, cross-over. Random number table, sealed envelopes Blinding not stated. Follow up not stated. Power calculation not stated. ITT not stated Duration: trial was conducted between January and November 1990
Participants	12 women, 12 cycles (we only used pre-cross over first cycle data). Total study group: 48 women, 160 cycles Inclusion criteria: male subfertility or unexplained infertility Exclusion criteria: not stated Mean age for the total group of 48 women: 33 ± 2.9 yrs Mean duration of subfertility for the subfertility for the total group of 48 women: 6.3 ± 2.8 yrs

Martinez 1991a *(Continued)*

	Type of subfertility: male or idiopathic
Interventions	Stimulation method: 75 to 150 IU HMG IM LH surge group: u-LH detection kit two times a day, IUI 16 to 28 hours after a positive test. hCG group; 10,000 IU hCG, IUI after 36 to 40 hours Husband semen. Semen prepared with a two-layer Percoll gradient centrifugation, final sample suspended in 0.2 ml of culture media Insemination procedure: 0.5 cm from the uterine fundus with the use of a Makler's device, one insemination
Outcomes	Live birth rate: LH group 17%, hCG group 17% Clinical pregnancy rate: LH group: 17% , hCG group: 17% No secondary outcomes stated: no multiple pregnancies, no miscarriages, no costs Pregnancy diagnosed: hCG in urine 14 days after IUI
Notes	This study also compares IUI to timed intercourse. Because of the double comparison and the cross-over design, we only used the pre-cross over IUI data Setting: Department of Reproductive Endocrinology and Fertility, Free University Hospital, Amsterdam, the Netherlands Funding: supported by Organon International, Oss, the Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete data adequately addressed, no imbalance
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Martinez 1991b

Methods	Single centre, cross-over. Random number table, sealed opaque envelopes Blinding not stated. Follow up not stated. Power calculation not stated. No ITT Study duration not stated
Participants	48 women, 48 first cycles Inclusion criteria: idiopathic, male or cervical factor infertility Exclusion criteria: not stated. Mean age of women: 31.2 ± 3.8 yrs for the total group of women Mean duration of subfertility: 5.6 ± 2.6 yrs Type of subfertility: idiopathic, male or cervical factor infertility
Interventions	Stimulation method: 100 mg clomiphene citrate from day three through day seven LH group; home monitoring u-LH and IUI 21 to 24 hours after a positive test. hCG group: 10,000 IU hCG and IUI 37 to 40 hours later Husband semen. Semen prepared with a Percoll density gradient centrifugation, final sample suspended in 0,2 ml of culture media Insemination procedure: 0.5 cm from the uterine fundus with the use of a Makler's device, one insemination
Outcomes	Live birth rate: 21% LH group, 17% hCG group Pregnancy rate: 21% LH group, 17% hCG group Multiple pregnancy rate: not known in the LH group, 25% hCG group Costs: not stated Pregnancy diagnosed: hCG in urine 14 days after IUI
Notes	Only the first cycle pre-cross over data were used Setting: Department of Reproductive Endocrinology and Fertility, Free University Hospital, Amsterdam, the Netherlands Funding: Organon International, Oss, the Netherlands

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Author comment: 'sealed opaque envelopes', does not state numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced

Martinez 1991b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Nikbakht 2012

Methods	Single centre, randomised controlled clinical trial
	Randomisation method and concealment of allocation not stated
	Blinding not stated. Follow up until 6 weeks pregnancy. Power calculation: not stated
	Study duration June 2009 to April 2010
Participants	66 women, number of cycles not stated
	Inclusion criteria: healthy women age 22 to 44 years with > 1 year of non-tubal infertility
	Exclusion criteria: not stated
	Mean age of women: 28.5 ± 3 yrs (250 µg hCG) versus 31.9 ± 3 yrs (500 µg hCG)
	Mean duration of subfertility: 5.0 ± 4.6 yrs (250 µg hCG) versus 6.9 ± 6.8 yrs (500 µg hCG)
Interventions	Stimulation method: clomiphene citrate or letrozole and HMG
	Ovulation trigger: r-hCG 250 µg or 500 µg
	Type of semen not stated explicitly, with swim up method
	Insemination procedure: 0.3 ml inseminated, catheter type not stated. One insemination
	No luteal support was not stated
Outcomes	Pregnancy rate per cycle: 9.9% (250 µg) versus 12.1% (500 µg)
	Pregnancy diagnosed by vaginal ultrasound 4 weeks after IUI
Notes	Setting: Ahvaz, Iran
	In group with 250 µg hCG significantly more dominant follicles
	Funding: research grant from the Ahvaz Jundishapur University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

Nikbakht 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	States 66 women were randomly assigned to one of two groups at the start of the cycle and that 20 of the women refused to participate to the study; still there are data on 66 participants.
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Rahman 2011

Methods	Single centre, parallel design. Computer generated random tables Concealment of allocation not stated Blinding not stated. Follow up until delivery. Power calculation: 80 per group was proposed to provide 80% power for the primary comparison of pregnancy rates Study duration not stated
Participants	204 women, 461 first cycles Inclusion criteria: idiopathic, mild male factor infertility Exclusion criteria: severe male factor, women > 38 years, PCOS, endometriosis or tubal disease Mean age of women: 28.3 ± 3.2 yrs (36 h after hCG) versus 27.1 ± 2.3 yrs (24 h after hCG) Mean duration of subfertility: 4.5 ± 1.0 yrs (36 h after hCG) versus 4.3 ± 1.5 yrs (24 h after hCG) Type of subfertility: idiopathic, male or cervical factor infertility
Interventions	Stimulation method: 50 mg clomiphene citrate from day three through day seven Ovulation trigger: hCG 5000 IU, 24 hours or 36 hours later IUI Husband semen. Semen prepared with a density gradient centrifugation Insemination procedure: flexible intrauterine catheter, one insemination No luteal support
Outcomes	Live birth rate per couple: 31/104 (29.8%) 36 h after hCG, 18/100 (18%) 24 h after hCG Pregnancy rate per cycle: 34/231 (14.7%) 36 h after hCG, 20/230 (8.7%) 24 h after hCG Pregnancy rate per couple: 34/104 (32.7%) 36 h after hCG, 20/100 (20%) 24 h after hCG

Rahman 2011 *(Continued)*

	Pregnancy diagnosed: transvaginal ultrasound demonstrating heart activity
Notes	Setting: Department of Obstetrics and Gynaecology, All India Institute of Medical Science, New Dehli No funding used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The use of computer generated random tables
Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Sakhel 2007

Methods	Single centre, parallel. Randomly assigned by computer generated numbers, sealed envelopes Blinding not stated. Follow up: not clearly stated. Power calculation: performed afterwards, a power of 63% was achieved. ITT was not performed since no dropouts or cycle cancellations were reported Duration: April 2003 to March 2004
Participants	284 women, 284 cycles Inclusion criteria: healthy women between 22 and 44 years with non-tubal infertility. One fallopian tube should be patent, unexplained subfertility, ovulatory disorder, mild to moderate male factor, early stages of endometriosis and advanced stages of endometriosis after conservative operative laparoscopy Exclusion criteria: tubal blockage and severe male factor Mean age of women: r-hCG group: 31.9 ± 4.1 yrs and u-hCG group: 32.7 ± 4.8 yrs Duration of subfertility: r-hCG group: 2.3 ± 1.5 yrs and u-hCG group: 3.0 ± 2.3 yrs Type of subfertility: ovulatory disorders, early stage endometriosis, mild male factor, idiopathic infertility. Primary infertility in 55.8% of couples

Sakhel 2007 *(Continued)*

Interventions	Stimulation method: 75 to 150 IU FSH and HMG, GnRH antagonist IUI 42 hours after injection of 10,000 IU u-hCG or 250 µg r-hCG Type of semen injected: husband. Semen washed using the double-density gradient method. Insemination of 0.3 ml Insemination procedure: not stated, one insemination
Outcomes	Outcome live birth rate per couple: 22.1% r-hCG, 25% u-hCG Pregnancy rate per couple: 27.1% r-HCG, 28.5% u-hCG Multiple pregnancy rate per cycle: 36.8% r-hCG, 36.6% u-hCG Miscarriage rate per cycle: 10.5% r-hCG, 4.9% u-hCG OHSS rate: no cases of severe OHSS Ectopic pregnancy rate per cycle: 7.9% r-hCG, 7.3% u-hCG Costs: not stated Pregnancy diagnosed: serum hCG level two weeks after the insemination
Notes	Aggressive stimulation with a mean number of ovulated follicles of 2.3 ± 1.4 r-hCG group and 3.0 ± 2.0 u-hCG group, resulting in a high pregnancy and multiple pregnancy rate Setting: IVF Michigan PC, Rochester Hills, MI, USA Funding: supported in part by Serono, Rockland, Massachusetts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by computer generated numbers
Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Comment: the included women in the u-hCG group had a greater mean duration of infertility than the r-hCG group

Schmidt-Sarosi 1995

Methods	Single centre, parallel design. Random number table, concealment of allocation not stated Blinding not stated. Follow up until birth characteristics were available Power calculation performed: when assuming a 20% pregnancy rate and defining a clinically important pregnancy rate of at least 10%, 6600 cycles were needed in each treatment group to achieve a power of 80% No ITT
Participants	26 women, 26 cycles Inclusion criteria: at least unilateral tubal patency, laboratory values euthyroid and normoprolactinemic and > 5 million motile sperm cells after swim up Exclusion criteria: previously undergone clomiphene citrate/hCG stimulation Mean age of women: hCG group: 30.2 yrs and GnRH-a group: 34.5 yrs Duration of subfertility: not stated Type of subfertility: anovulation, luteal phase defect or unexplained
Interventions	Stimulation method: 50 mg clomiphene citrate from cycle day 5 to 9 Intervention: two doses of 400 µg nafarelin intranasal (IN) versus 5000 IU hCG IM injection. IUI 48h after the first dose of nafarelin or 36 h after hCG injection Luteal support was given with nafarelin or hCG in each group Type of semen injected: not stated Insemination procedure: not stated, single insemination
Outcomes	Live birth rate per couple: GnRH-a group: 2/11 (18.2%). hCG group: 2/15 (13.3%) Pregnancy rate per couple: GnRH-a group: 3/11 (27.3%). hCG group: 2/15 (13.3%) Miscarriage rate: GnRH-a group: 1/3 (33.3%). hCG group: 0/2 (0%) No multiple pregnancies and no OHSS Costs: not stated Pregnancy diagnosed: no definition of pregnancy was stated
Notes	Concealment of allocation not stated Small groups using different forms of luteal support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via a random numbers table
Allocation concealment (selection bias)	Unclear risk	None stated

Schmidt-Sarosi 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data addressed adequately
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Comment: the use of different forms of luteal support in both groups

Scott 1994

Methods	Single centre, cross-over. Randomisation through random number table. Concealment of allocation: sealed envelopes Blinding was used: the sonographer was blinded to which treatment the woman had received Study duration and follow up not stated. Power calculation: only stated for the incidence of unruptured follicle syndrome. ITT not stated
Participants	30 women, 30 first cycles Inclusion criteria: women with subfertility of at least one year and ovulatory cycles Exclusion criteria: not stated Mean age of women: 32.2 ± 1.0 SD Duration of subfertility: at least one year, not further stated Type of subfertility: unexplained (n = 26), male factor (n = 4)
Interventions	Stimulation method: clomiphene citrate 100 mg orally each day, from cycle day 5 to 9 Intervention: 2 mg of leuprolide acetate or 10.000 IU hCG. IUI after 40 hours Type of semen: not stated. Insemination procedure: not stated. One insemination
Outcomes	Pregnancy rate per couple: 20% GnRH-a group, 6.7% hCG group Live birth rate per couple: 20% GnRH-a group, 6.7% hCG group Secondary outcome measures: not stated Costs: not stated Pregnancy diagnosed: not stated
Notes	Primary outcome measure was not pregnancy rate, but the endocrine dynamics during the periovular interval, the incidence of luteinised unruptured follicle syndrome and the characteristics of the adequate luteal phase

Scott 1994 *(Continued)*

	Setting: Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Wilford Hall Medical Center, Lackland Air Force Base, Texas
	No funding stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	None stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The sonologists were blinded to which treatment the couples had received to minimize the risk of observer bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete data adequately addressed
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Shalev 1995

Methods	Trial design: parallel. Randomisation by self made computer program. Concealment of allocation by third party
	Blinding was used. Follow up: until birth characteristics were available. Power calculation for reduction in rate of OHSS was performed, but not further mentioned. ITT was not performed
	Study duration not stated
Participants	48 women, 140 cycles
	Inclusion criteria: anovulation, oligo-ovulation or unexplained infertility
	Exclusion criteria: women at high risk of developing severe OHSS (> 20 mature pre-ovulatory follicles and estradiol concentrations > 4000 pg/ml)
	Mean age of women: hCG group: 30.4 yrs and GnRH-a group: 29.2 yrs
	Duration of subfertility: not stated per group, but at least one year
	Type of subfertility: anovulation, oligo-ovulation or unexplained infertility
Interventions	Stimulation method: individualized regime of HMG starting on cycle day five
	Intervention: 0.1 mg triptorelin or 10.000 IU hCG, IUI 24 and 48 hours after injection

Shalev 1995 *(Continued)*

	Type of semen injected: husband. Semen prepared by discontinuous Percoll gradient and washed twice. A volume of 0.3 to 0.5 ml of sperm suspension containing an average of 19 x 106 per ml of motile spermatozoa Insemination procedure: Tefcat catheter high in uterine cavity Number of inseminations: two
Outcomes	Outcome live birth rate per cycle: 17.6% hCG group, 12.5% GnRH-a group Pregnancy rate per cycle: 26.5% hCG group, 15.3% GnRH-a group Pregnancy rate per couple: 45.8% hCG group, 66.7% GnRH-a group Multiple pregnancy rate: 0% hCG group, 18% GnRH-a group Miscarriage rate: 33.3% hCG group, 18% GnRH-a group OHSS rate: 11.8% hCG group, 5.6% GnRH-a group Ectopic pregnancy rate: not stated Costs: not stated Pregnancy diagnosed: rising concentration of hCG. Clinical pregnancy was diagnosed by fetal heart beat
Notes	Very high pregnancy rate per couple Setting: Fertility Unit, Department of Obstetrics and Gynaecology, Central Emek Hospital, Afula, Israel No funding stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Author comment: randomisation was performed using a self made computer program. Adequate sequence generation not stated
Allocation concealment (selection bias)	Low risk	Author comment: third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding stated, but outcome not likely to be influenced either way
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding stated, but outcome not likely to be influenced either way
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete data adequately addressed
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Sharma 2011

Methods	Single centre, prospective randomised study. Concealment of allocation with sealed envelopes No blinding was stated. Follow up until clinical pregnancy. No power calculation was stated. No ITT analysis was stated Study duration: January to October 2010
Participants	505 women were eligible, 450 women included Inclusion criteria: unexplained subfertility with two previous failed clomiphene citrate/IUI cycles, with follicular endometrial dys-synchrony (follicle ≥ 18 mm, endometrial thickness < 7 mm) Exclusion criteria: women with persistent endometrial thickness < 7 mm. IUI was cancelled when a luteinised unruptured follicle was present or semen collection failed Mean age of women: not state Mean duration of subfertility: not stated Type of subfertility: unexplained infertility
Interventions	Stimulation method: clomiphene citrate 100 mg Intervention: 1 mg GnRH-a versus 5000 IU uhCG im injection IUI after confirmation of ovulation (time frame not stated) Type of semen injected:not stated Insemination procedure: not stated, one insemination. Luteal support was given: 300 mg progesterone vaginally
Outcomes	Ongoing pregnancy rate per couple: 9.8% (GnRH-a) versus 4.4% (hCG) Clinical pregnancy rate per couple: 10.2% (GnRH-a) versus 4.9% (hCG) Miscarriage rate: 10% (GnRH-a) versus 8.7% (hCG) Clinical pregnancy defined as the presence of gestational sac with cardiac activity on ultrasound
Notes	Unclear why 20 couples were excluded who met the criteria for ovulation triggering Setting: Institute of reproductive medicine, Kolkata, India Results could not be included in the meta-analysis since it was not clear whether the results were given for the total group of included couples or only those couples who underwent an IUI procedure Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Only states ‘sealed envelopes’, not opaque or numbered

Sharma 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear why 20 couples were excluded before randomisation
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias

Weiss 2010

Methods	Single centre, parallel. Random number generator, sealed opaque envelopes No blinding used. Follow up until after delivery. No power calculation performed: the study was stopped before reaching significant power following an unusual number of multi-fetal pregnancies. No ITT analysis: couples were withdrawn from the study if they were transferred to IVF or IUI was cancelled Study duration: from July 2008 to not stated
Participants	92 completed cycles Inclusion criteria: ovulatory disorders, male factor, partial mechanical factor, endometriosis, unexplained infertility Exclusion criteria: known allergy to the utilized drugs, No patent tubes, sperm count < 1 million total motile sperm of normal morphology, women who are candidates for mono-ovulation, failure to receive consent and women with baseline functional cysts (> 12 mm) Mean age of women: 31.6 ± 5.8 yrs (36 h after hCG) versus 31.8 ± 6.5 yrs (42 h after hCG) versus 29.4 ± 5.7 yrs (48 h after hCG) Mean duration of subfertility: 2.2 ± 1.5 yrs (36 h after hCG) versus 2.1 ± 1.4 yrs (42 h after hCG versus 2.1 ± 1.3 yrs (48 h after hCG) Type of subfertility: mild to moderate male infertility, anovulation, unilateral mechanical factor, endometriosis and unexplained infertility
Interventions	Stimulation method: gonadotropins either recombinant or urinary. Dosing was flexible and based on womens' age Interventions: IUI either 36 hours, 42 hours or 48 hours after hCG (dosage not stated) Type of semen injected: husband or donor Insemination procedure: not stated, one insemination
Outcomes	Live birth rate per cycle: 5/35 (14%) 36 h after hCG, 9/24 (38%) 42 h after hCG, 7/33 (21%) 48 h after hCG Pregnancy rate per cycle: 10/35 (29%) 36 h after hCG, 9/24 (38%) 42 h after hCG, 8/33 (24%) 48 h after hCG

Weiss 2010 *(Continued)*

	Number of miscarriage: 5/10 (50%) 36 h after hCG, 0/9 (0%) 42 h after hCG, 1/8 (11%) 48 h after hCG
	Multiple pregnancy rate: 3/10 (30%) 36 h after hCG, 4/9 (44%) 42 h after hCG, 3/8 (38%) 48 h after hCG
	Tubal pregnancy rate: 0/35 (0%) 36 h after hCG, 0/24 (0%) 42 h after hCG, 1/33 (3%) 48 h after hCG
	Pregnancy diagnosed: transvaginal ultrasound demonstrating a gestational sac
Notes	Inclusion of women with ovulatory disorders
	Number of women included not stated
	Study stopped prematurely because of an unusual number of multi-fetal pregnancies
	Setting: HaEmek Medical Center. Afula, Israel
	Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Author comment: The numbers were placed in consecutively ordered sealed opaque envelopes. At the time of enrolment, the envelope was opened and group assignment was made
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data adequately addressed (9 women were withdrawn for hyperstimulation, premature ovulation or for lack of response to gonadotropins)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Comment: there were significantly more miscarriages in the 36 h group

Zreik 1999

Methods	Single centre, cross-over. Randomisation was performed with the use of a computer generated random number table
	Blinding until informed consent was obtained. Follow up not clearly stated. ITT was performed
	Duration: from September 1994 to July 1996
Participants	54 women, 53 first cycles

Zreik 1999 *(Continued)*

	Inclusion criteria: normal hysterosalpingography, a normal endometrium biopsy, history of clomiphene citrate use of < six months' duration Exclusion criteria: not stated Mean age of women: hCG group: 32 range 24 to 41 LH surge group: 33 range 25 to 41 years Duration of subfertility: 2.8 years, range 1 to 8 hCG group, 3.2 years, range 1 to 10 LH group Type of subfertility: unexplained, male factor, anovulation
Interventions	50-100 clomiphene citrate from cycle day three to seven LH group: home monitoring u-LH, IUI daily after positive test for the next two days. hCG group: 10,000 IU hCG, IUI daily for the next two days type of semen injected not stated Insemination procedure: not stated, double insemination
Outcomes	Outcome pregnancy rate per couple: 4% LH group, 7.1% hCG group Secondary outcome measures: not stated Costs: not stated Pregnancy diagnosed: no definition of pregnancy was stated
Notes	Cross-over study design. Only the first cycle pre-cross over data were used. Inclusion of 15 women with anovulation. Pregnancy rate very low Setting: Yale Reproductive Medicine Center, New Haven, Conneticut, USA No funding stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The use of a computer generated random number table
Allocation concealment (selection bias)	Unclear risk	States that the assignment was not known to the treating physician or the couple until consent was obtained, but does not state method of concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcome not likely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data adequately addressed
Selective reporting (reporting bias)	Unclear risk	No protocol available

Zreik 1999 *(Continued)*

Other bias	Low risk	No other bias

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

Study	Reason for exclusion
Agarwal 1995	Retrospective study
Arici 1994	Compared stimulated with non-stimulated cycles. Double and single insemination used
Baroni 2001	Compared different timing methods at different follicle sizes at different times to IUI
Barratt 1989	Endo-cervical and peri-cervical insemination
Casadei 2006	Comparing single IUI versus double IUI versus TI with IUI
Cedrin-Durnerin 1993	Quasi-randomised trial
Check 1994	Prospective non-randomised study
Claman 2000	Abstract of an included study
Claman 2004a	Abstract of an included study
Claraz 1989	Intracervical insemination
Costa Franco 2006	Retrospective study design
Diaz 2003a	Inadequate randomisation; random numbers in an open list
Diaz 2003b	Abstract of an excluded study
Diaz 2008	Inadequate randomisation; random numbers in an open list. Same study as Diaz 2003a
Egbase 2003	Inclusion of PCOS women only
Federman 1990	Comparing single versus double insemination. Cross-over study
Fischer 1993	Investigates the time interval from hCG administration to follicular wall rupture
Fondop 2005	Cohort study
George 2007	Timed intercourse
Gerris 1995	Prospective non-randomised study
Gerrits 2011	Trial to determine the safety of orally administered LH agonists
Ghanem 2011	Cohort study
Ghazizadeh 2009	Comparing the usefulness of GnRH antagonist administration in preventing premature LH surge
Ghosh Dastidar 2009	Comparing the supplementation of LH in the stimulation protocol

Study	Reason for exclusion
Int rhCG study group 2001	Included anovulatory patients only. Used both IUI and timed intercourse
Khattab 2005	Retrospective study design
Kossoy 1989	Cohort study
Kotecki 2005	Comparison of five different ovarian stimulation protocols
Lewis 2002	Abstract of an included study
Lewis 2003	Abstract of an included study
Martinez 1994	Retrospective study
Meherji 2004	Commentary report
Nulsen 1993	Cross-over study. Comparing stimulated with non-stimulated cycles. Comparing double versus single insemination
Odem 1991	Quasi-randomised trial. Insemination through cervical cap
Panchal 2009	Cohort study
Papageorgiou 1995	Comparing stimulated with non-stimulated cycles
Pierson 2002	Dose finding study
Pirard 2005	Investigated the luteal support between hCG triggered cycles and GnRHa administered cycles
Propst 2007	Cohort study. Not the comparison of interest
Propst 2012	Not comparison of interest
Ragni 1999	Compared a single peri-ovulatory IUI with two double IUI regimes
Ramon 2009	Ultrasound guided IUI versus blind IUI
Ramon 2009a	Abstract of an excluded study
Robinson 1992	Inclusion of donor insemination only
Romeu 1997a	Prospective non-randomised trial
Romeu 1997b	Failure to use a truly randomised design
Sakhel 2004	Abstract of an included study
Scarpellini 1991	Also comparing IUI with timed intercourse
Shanis 1995	Not truly randomised
Silverberg 1991	Comparing single versus double insemination
Tavaniotou 2003	Cohort study

Study	Reason for exclusion
Tonguc 2010	Inadequate randomisation; sequentially enrolled into three groups according to their entry
Wang 2001	Abstract of an excluded study
Wang 2006	Ovulation induction at different follicle sizes

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

Aydin 2013

Methods	Single centre, parallel. Randomisation was performed with the use of a computer generated random numbers, upon enrolment an opaque envelope was opened Follow up until clinical pregnancy. ITT was performed Duration: from September 2011 to January 2013
Participants	220 women, 220 first cycles Inclusion criteria: normal hysterosalpingography, normal hormone essay, semen analysis total progressive motile sperm count > 5 million/ml with > 4% morphology after sperm preparation Exclusion criteria: women with endocrinologic disorders, women with any history of surgery on the reproductive system, women < 20 years and > 35 years, women with expected to be poor responders due to day 3 baseline ultrasonography and or FSH > 10 mIU/ml, estradiol > 40 pg/ml and an antral follicle count (AFC < 6), women who had previously smoked, with advanced male factor infertility (referred for IVF) Mean age of women: 34 to 36 hrs after hCG group: 30.6 ± 3.4 IUI with hCG: 30.7 ± 3.3 Duration of subfertility: 4.9 ± 4.9 years 34 to 36 hrs after hCG group, 5.2 ± 4.7 years, IUI with hCG group Type of subfertility: unexplained, male factor
Interventions	75 to 112.5 IU r-FSH from cycle day 3, with low dose step up. Ovulation triggering 250 µg r-hCG Type of semen: partner Insemination procedure: two-layer density gradient separation technique, single IUI
Outcomes	Outcome pregnancy rate per couple: 10/106 (9.4%) 34 to 36 hrs after hCG, 12/98 (12.2%) IUI with hCG group Secondary outcome measures: not stated Costs: not stated Pregnancy diagnosed: presence of an embryo with cardiac activity on ultrasound
Notes	Setting: Eskisehir Osmangazi University, Center for Reproductive Health, Eskisehir, Turkey Long duration of subfertility No funding stated

Blockeel 2014

Methods	Single centre, parallel designed randomised trial with computer generated list. Concealment of allocation: third party Single blinding used (investigator). Follow up until 12 weeks pregnancy
Participants	Women who are candidates for intrauterine insemination in a natural cycle Inclusion criteria: Age between 18 and 39 yrs. Donor semen. Cycle with less then 3 follicles reaching 15 mm or more, basal hormonal values of progesterone Exclusion criteria: after more than 6 intrauterine inseminations, tubal infertility
Interventions	IUI 24 or 48 hours after spontaneous LH peak
Outcomes	Primary outcome measure: Clinical pregnancy rate per couple. Secondary outcome measure: live birth rate
Notes	Inclusion of donor semen

Dehghani 2014

Methods	Single centre, parallel designed randomised trial with computer generated list. Concealment of allocation: third party Single blinding used (investigator). Follow up until 12 weeks pregnancy
Participants	100 infertile couples were divided into two groups Inclusion criteria: 18 to 35 years; open fallopian tubes confirmed by hysterosalpingography Exclusion criteria: tubal factor, severe endometriosis, hypothalamic amenorrhea, or severe oligospermia (sperm count lower than 5 million per ml based on WHO 2012 classification) (Table 1) in their husbands
Interventions	HCG injection before IUI and HCG injection after IUI
Outcomes	The main outcome measure was the result of an hCG test that was done two weeks after the IUI; if it was positive, transvaginal sonography would be performed in the seventh week for clinical confirmation of pregnancy
Notes	

Mostafa 2014

Methods	Single centre, parallel designed randomised trial with random computer generated table. Concealment of allocation: not stated Blinding: not stated. Follow up: till pregnancy test
Participants	One hundred infertile couples with a diagnosis of unexplained infertility who had been scheduled for intrauterine insemination (IUI) by husband semen Inclusion criteria: age of female partner less than 37 years; a normal basal hormonal profile (FSH, LH, TSH, E2 and prolactin); a satisfactory basal (day 2) transvaginal ultrasound examination Cases with failed previous 3 IUI trials were excluded

Mostafa 2014 *(Continued)*

Interventions	Study group: 50 women in whom hCG (10,000 IU) was injected 3 to 5 min after IUI Control group: 50 women in whom hCG (10,000 IU) was injected 24 to 32 h before IUI
Outcomes	Pregnancy rate
Notes	All patients gave informed consent and the study was approved by local ethics committee for scientific research

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

OVO R&D 2012

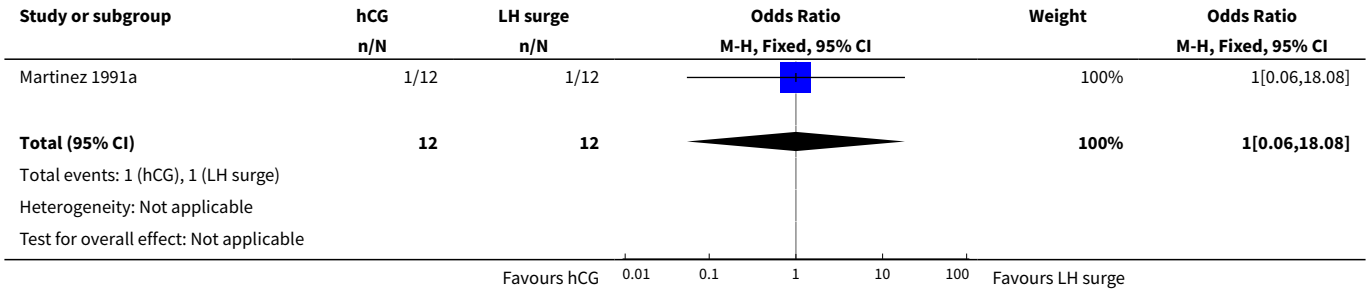
Trial name or title	Combining Urinary Luteinizing hormone Testing with ultrasound monitoring in intrauterine insemination cycles
Methods	Parallel designed randomised trial
Participants	Women who undergo IUI treatment for unexplained infertility, mild male factor or donor insemination Inclusion criteria: women between 18 and 39 years. natural and stimulated cycles with clomiphene citrate or letrozole. At least one patent tube and an antral follicular count ≥ 10 and FSH ≤ 10
Interventions	Ultrasound monitoring with hCG administration at a leading follicle of 18 mm versus ultrasound monitoring with LH testing in urine
Outcomes	Primary outcome measure: pregnancy rate. Secondary outcome measure: rate of positive LH testing
Starting date	January 2011
Contact information	Harnois M, Levesque C, Ovo fertilite, Montreal, Canada
Notes	Inclusion of donor semen. Sponsored study

DATA AND ANALYSES

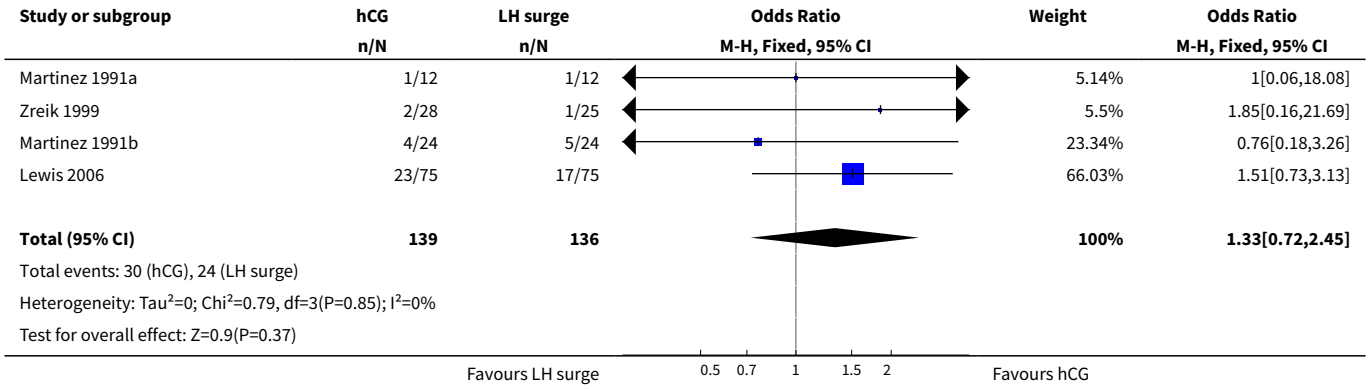
Comparison 1. hCG versus LH surge

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	1	24	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 18.08]
2 pregnancy rate per couple	4	275	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.72, 2.45]
3 multiple pregnancy rate per pregnancy	2	42	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.17, 7.60]

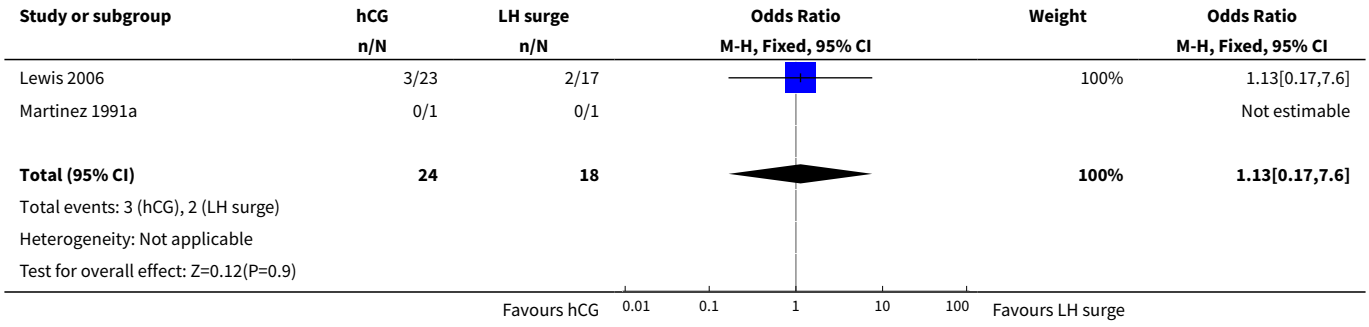
Analysis 1.1. Comparison 1 hCG versus LH surge, Outcome 1 live birth rate per couple.



Analysis 1.2. Comparison 1 hCG versus LH surge, Outcome 2 pregnancy rate per couple.



Analysis 1.3. Comparison 1 hCG versus LH surge, Outcome 3 multiple pregnancy rate per pregnancy.

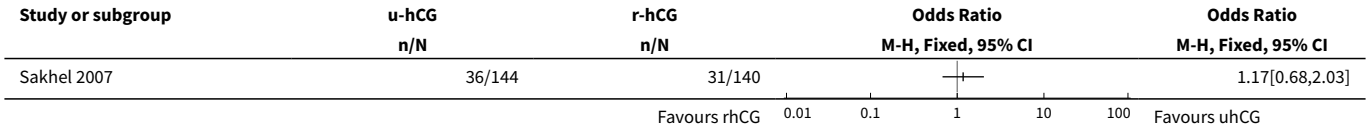


Comparison 2. u-hCG versus r-hCG

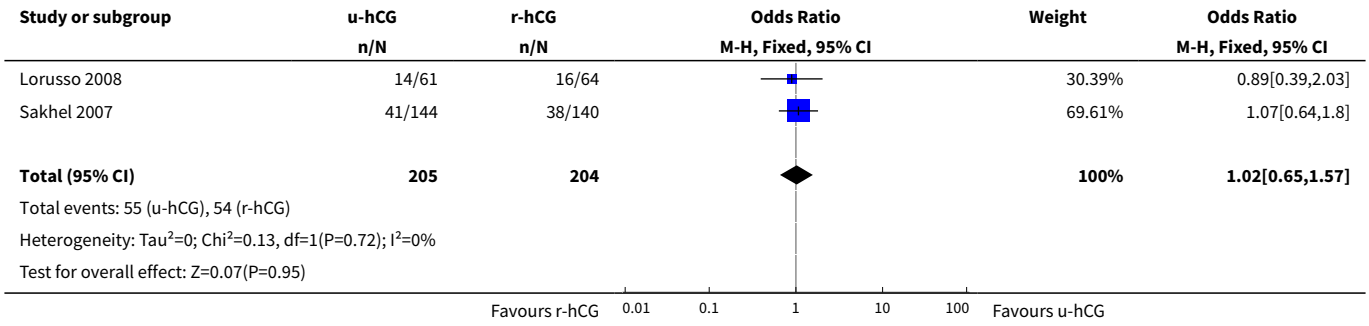
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 pregnancy rate per couple	2	409	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.65, 1.57]
3 multiple pregnancy rate per pregnancy	2	109	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.40, 2.47]
4 miscarriage rate per pregnancy	2	109	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.13, 2.47]
5 OHSS rate per cycle	2	468	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

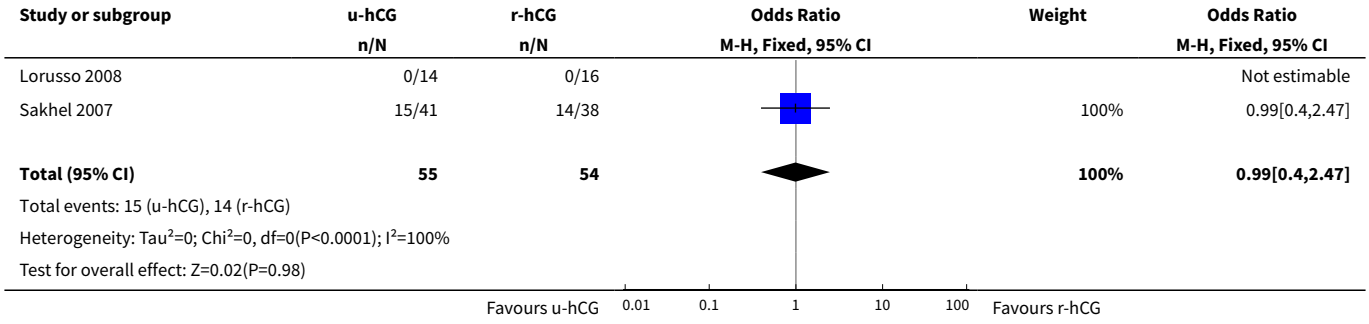
Analysis 2.1. Comparison 2 u-hCG versus r-hCG, Outcome 1 live birth rate per couple.



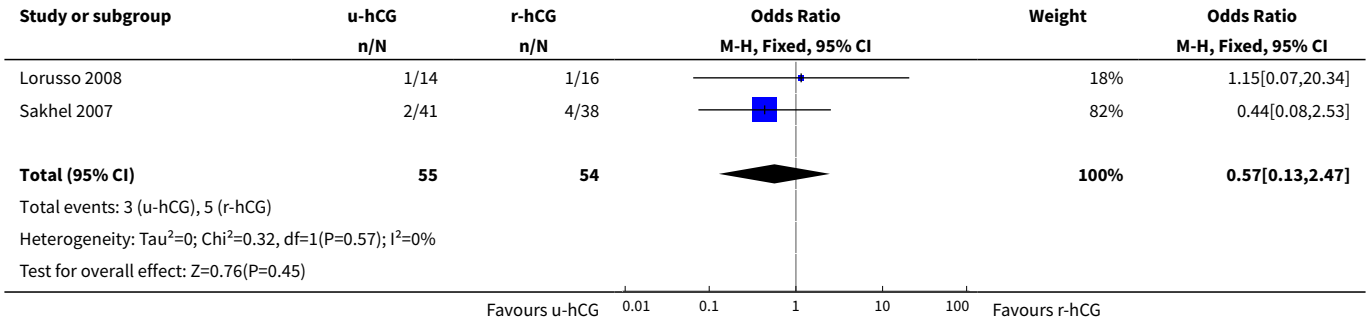
Analysis 2.2. Comparison 2 u-hCG versus r-hCG, Outcome 2 pregnancy rate per couple.



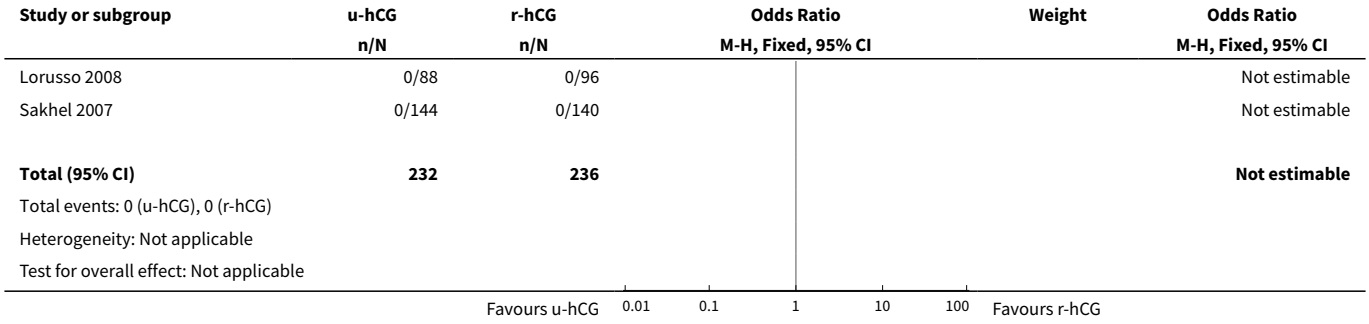
Analysis 2.3. Comparison 2 u-hCG versus r-hCG, Outcome 3 multiple pregnancy rate per pregnancy.



Analysis 2.4. Comparison 2 u-hCG versus r-hCG, Outcome 4 miscarriage rate per pregnancy.



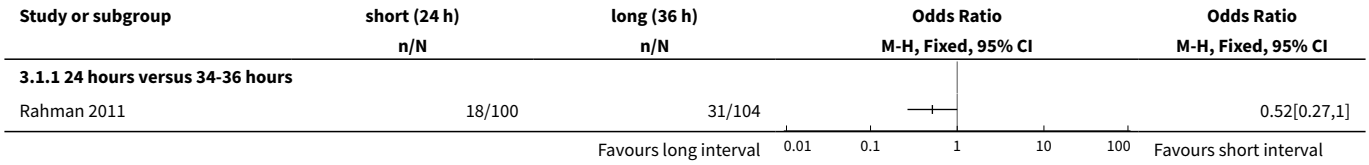
Analysis 2.5. Comparison 2 u-hCG versus r-hCG, Outcome 5 OHSS rate per cycle.



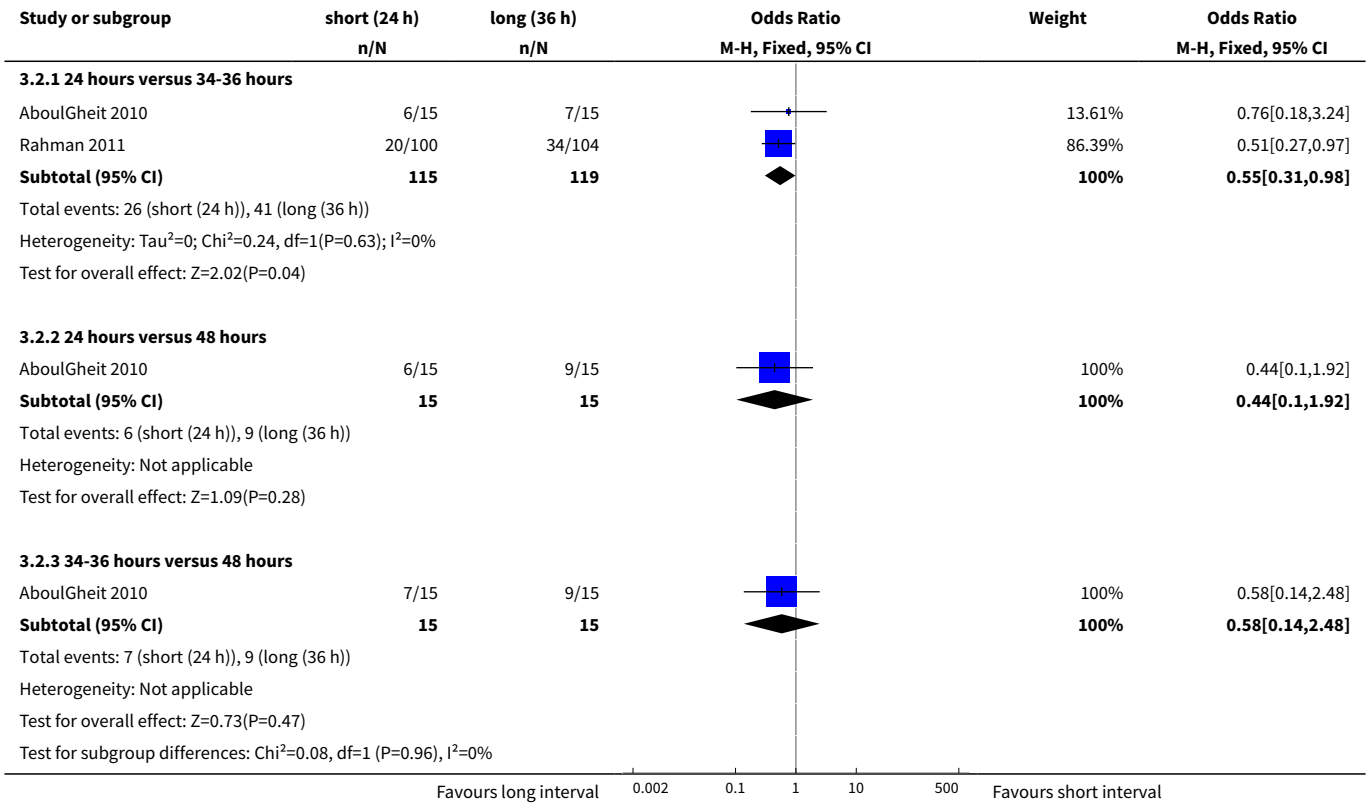
Comparison 3. Short versus long interval

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 24 hours versus 34-36 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 pregnancy rate per couple	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 hours versus 34-36 hours	2	234	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.31, 0.98]
2.2 24 hours versus 48 hours	1	30	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.10, 1.92]
2.3 34-36 hours versus 48 hours	1	30	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.48]
3 miscarriage rate per pregnancy	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 hours versus 34-36 hours	2	67	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.35, 7.16]
3.2 24 hours versus 48 hours	1	15	Odds Ratio (M-H, Fixed, 95% CI)	4.0 [0.27, 58.56]
3.3 34-36 hours versus 48 hours	1	16	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.07, 25.91]

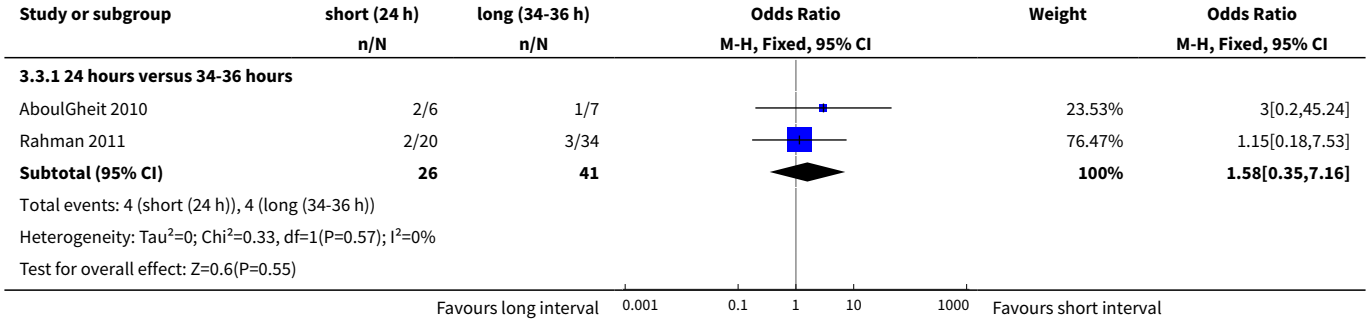
Analysis 3.1. Comparison 3 Short versus long interval, Outcome 1 live birth rate per couple.

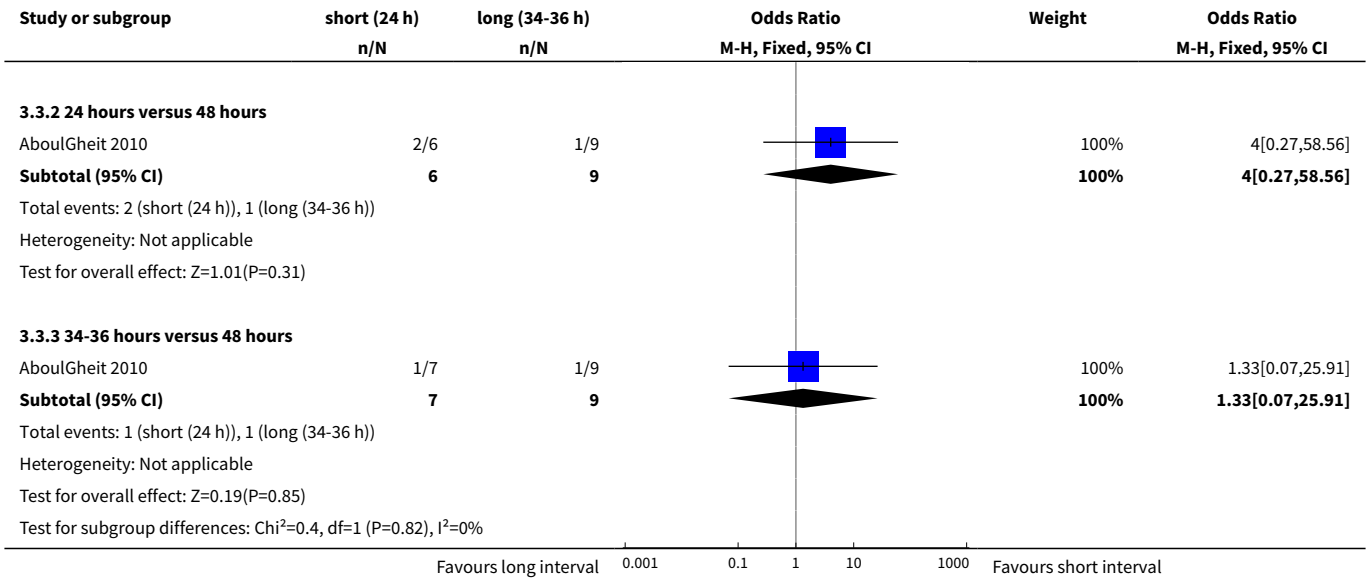


Analysis 3.2. Comparison 3 Short versus long interval, Outcome 2 pregnancy rate per couple.



Analysis 3.3. Comparison 3 Short versus long interval, Outcome 3 miscarriage rate per pregnancy.

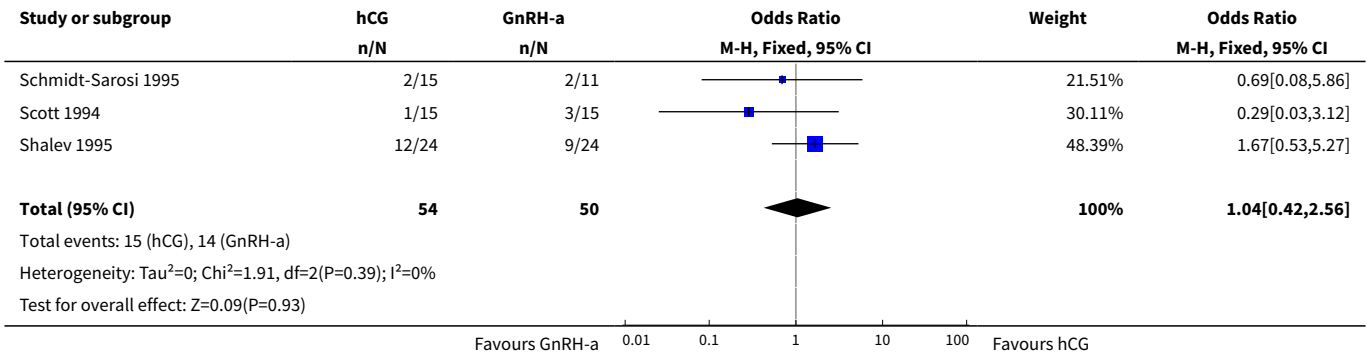




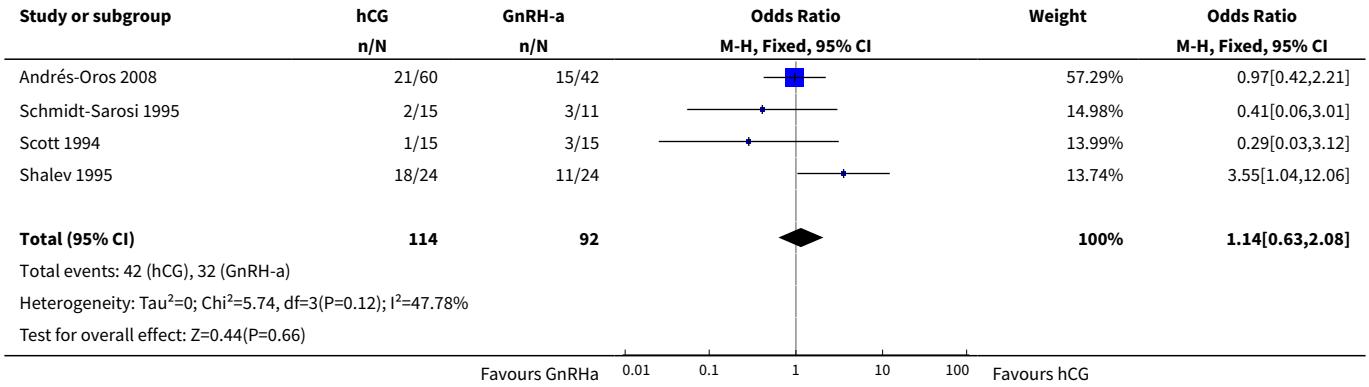
Comparison 4. hCG versus GnRH-a

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	3	104	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.42, 2.56]
2 pregnancy rate per couple	4	206	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.63, 2.08]
3 multiple pregnancy rate per pregnancy	4	74	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.38]
4 miscarriage rate per pregnancy	4	74	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.48, 6.20]
5 OHSS per cycle	3	456	Odds Ratio (M-H, Fixed, 95% CI)	2.27 [0.65, 7.91]

Analysis 4.1. Comparison 4 hCG versus GnRH-a, Outcome 1 live birth rate per couple.

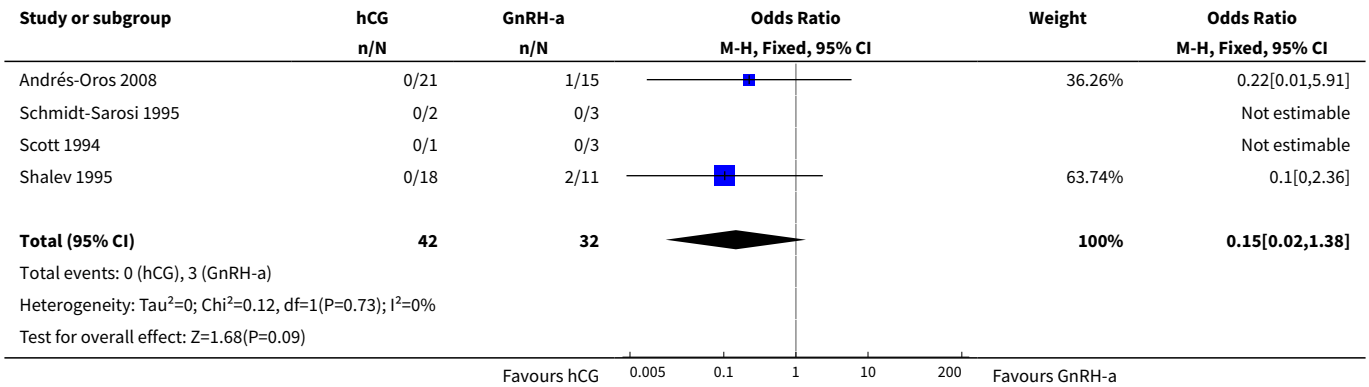


Analysis 4.2. Comparison 4 hCG versus GnRH-a, Outcome 2 pregnancy rate per couple.



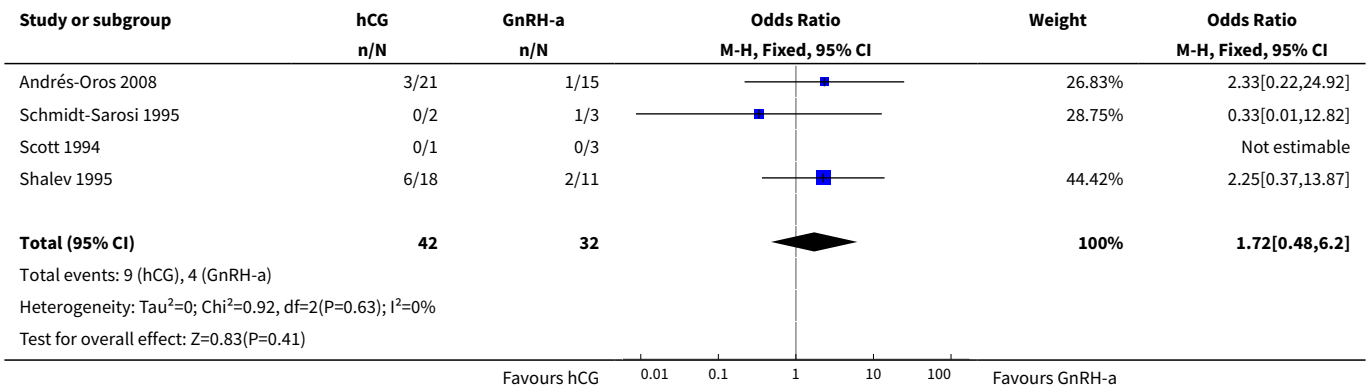
Study or subgroup	hCG n/N	GnRH-a n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Andrés-Oros 2008	21/60	15/42		57.29%	0.97[0.42,2.21]
Schmidt-Sarosi 1995	2/15	3/11		14.98%	0.41[0.06,3.01]
Scott 1994	1/15	3/15		13.99%	0.29[0.03,3.12]
Shalev 1995	18/24	11/24		13.74%	3.55[1.04,12.06]
Total (95% CI)	**114**	**92**		**100%**	**1.14[0.63,2.08]**
Total events: 42 (hCG), 32 (GnRH-a)					
Heterogeneity: Tau²=0; Chi²=5.74, df=3(P=0.12); I²=47.78%					
Test for overall effect: Z=0.44(P=0.66)					

Analysis 4.3. Comparison 4 hCG versus GnRH-a, Outcome 3 multiple pregnancy rate per pregnancy.



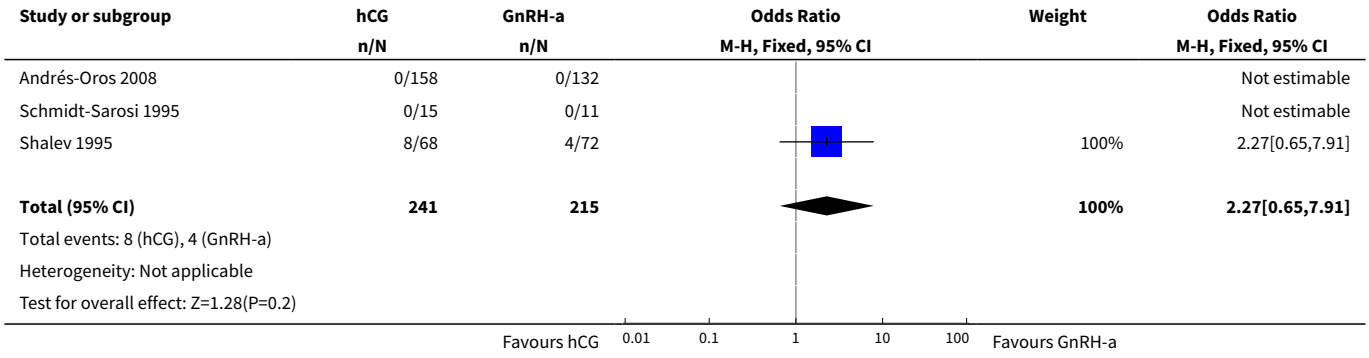
Study or subgroup	hCG n/N	GnRH-a n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Andrés-Oros 2008	0/21	1/15		36.26%	0.22[0.01,5.91]
Schmidt-Sarosi 1995	0/2	0/3			Not estimable
Scott 1994	0/1	0/3			Not estimable
Shalev 1995	0/18	2/11		63.74%	0.1[0,2.36]
Total (95% CI)	**42**	**32**		**100%**	**0.15[0.02,1.38]**
Total events: 0 (hCG), 3 (GnRH-a)					
Heterogeneity: Tau²=0; Chi²=0.12, df=1(P=0.73); I²=0%					
Test for overall effect: Z=1.68(P=0.09)					

Analysis 4.4. Comparison 4 hCG versus GnRH-a, Outcome 4 miscarriage rate per pregnancy.



Study or subgroup	hCG n/N	GnRH-a n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Andrés-Oros 2008	3/21	1/15		26.83%	2.33[0.22,24.92]
Schmidt-Sarosi 1995	0/2	1/3		28.75%	0.33[0.01,12.82]
Scott 1994	0/1	0/3			Not estimable
Shalev 1995	6/18	2/11		44.42%	2.25[0.37,13.87]
Total (95% CI)	**42**	**32**		**100%**	**1.72[0.48,6.2]**
Total events: 9 (hCG), 4 (GnRH-a)					
Heterogeneity: Tau²=0; Chi²=0.92, df=2(P=0.63); I²=0%					
Test for overall effect: Z=0.83(P=0.41)					

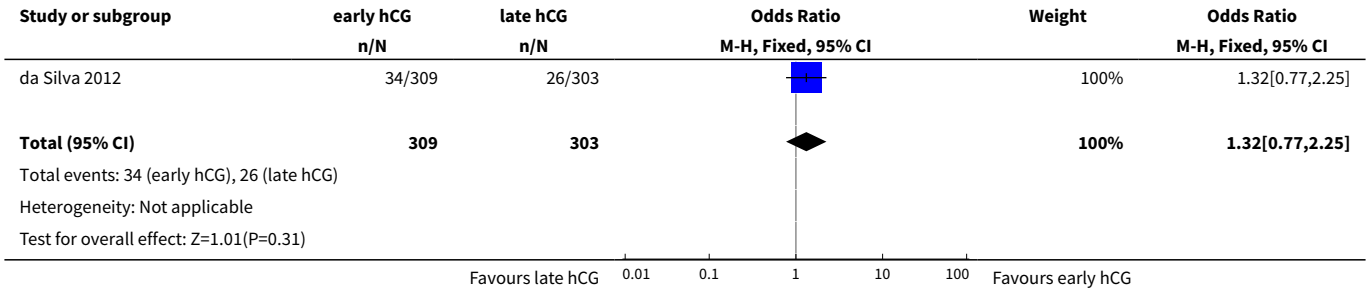
Analysis 4.5. Comparison 4 hCG versus GnRH-a, Outcome 5 OHSS per cycle.



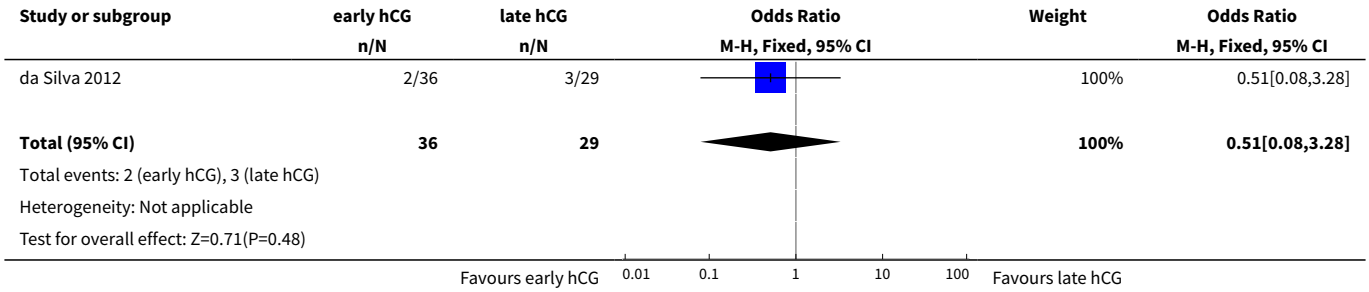
Comparison 5. Early hCG versus late hCG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 pregnancy rate per couple	1	612	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.77, 2.25]
2 miscarriage rate	1	65	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.08, 3.28]

Analysis 5.1. Comparison 5 Early hCG versus late hCG, Outcome 1 pregnancy rate per couple.



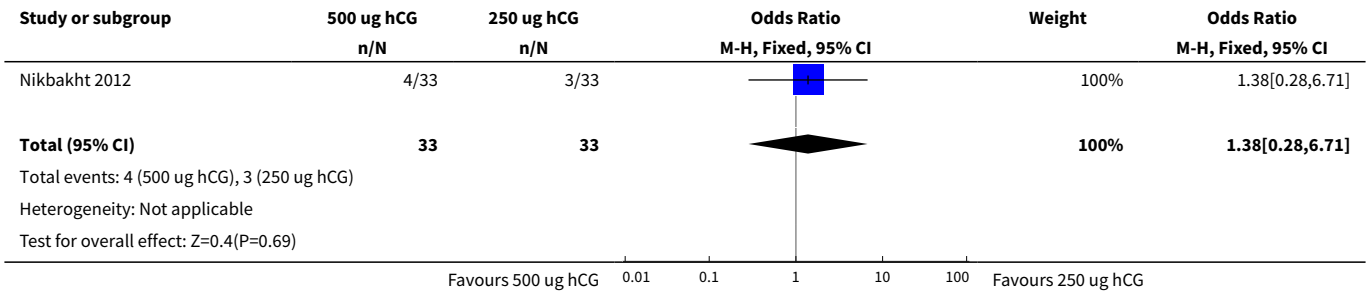
Analysis 5.2. Comparison 5 Early hCG versus late hCG, Outcome 2 miscarriage rate.



Comparison 6. Different dosages of hCG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 pregnancy rate per couple	1	66	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.28, 6.71]

Analysis 6.1. Comparison 6 Different dosages of hCG, Outcome 1 pregnancy rate per couple.



APPENDICES

Appendix 1. MDSG search strategy

Keywords CONTAINS "artificial insemination" or "IUI" or "IUI timing" or "Intrauterine Insemination" or Title CONTAINS "artificial insemination" or "IUI" or "IUI timing" or "Intrauterine Insemination"

AND

Keywords CONTAINS "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "human menopausal gonadotrophin" or "HCG" or "chorionic gonadotrophins" or "GnRH agonist" or "GnRH agonists" or "GnRH analog" or "GnRH analogue" or "GnRH analogues" or "GnRHa" or "GnRHa-gonadotropin" or "Luteinising hormone releasing hormone" or "luteinizing hormone" or "Lutenising hormone releasing hormone" or "luteinizing hormone supplementation" or "lh" or "basal body temp" or "hMG" or "Profasi" or "BBT" or "ultrasonography" or "ultrasound" or "timing LH surge" or "timing of insemination" or "timing ovulation" or "timing of administration" or "timed intercourse" or "time of insemination"

Appendix 2. CENTRAL search strategy

Central Register of Controlled Trials <1st Quarter 2009>

1 human chorionic gonadotropin.tw. (311)
2 hCG.tw. (829)
3 choriogon$.tw. (5)
4 (pregnyl or chorulon or gonabion).tw. (2)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1775)
6 (LH or ICSH).tw. (1829)
7 exp Chorionic Gonadotropin/ (524)
8 body temperature$.tw. (1125)
9 GnRH agonist.tw. (503)
10 GnRH analogue.tw. (110)
11 gonadotropin releasing hormone agonist.tw. (245)
12 GnRHa.tw. (169)
13 HMG.tw. (1026)
14 human menopausal gonadotropin.tw. (169)
15 (profasi or ovitrelle).tw. (9)

16 gonadotrophin releasing hormone agonist.tw. (111)
17 BBT.tw. (26)
18 ultrasound$.tw. (4652)
19 ultrasonograph$.tw. (2199)
20 time$.tw. (99572)
21 timing.tw. (2259)
22 or/1-21 (110066)
23 Artificial Insemination.tw. (51)
24 intrauter$ inseminat$.tw. (329)
25 (intra-uter$ adj2 inseminat$).tw. (25)
26 iui.tw. (227)
27 AIH.tw. (23)
28 exp artificial insemination/ or exp ovulation induction/ (858)
29 or/23-28 (1085)
30 22 and 29 (711)
31 (ivf or icsi).tw. (1833)
32 (in vitro fertilization or intracytoplasmic sperm injection).tw. (1271)
33 or/31-32 (2318)
34 30 not 33 (392)
35 from 34 keep 1-392 (392)

Cochrane Central Register of Controlled Trials <April 2012>

1 human chorionic gonadotropin.tw. (371)

2 hCG.tw. (981)

3 choriogon$.tw. (5)

4 (pregnyl or chorulon or gonabion).tw. (2)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1964)

6 (LH or ICSH).tw. (2030)

7 exp Chorionic Gonadotropin/ (587)

8 body temperature$.tw. (1279)

9 GnRH agonist.tw. (579)

10 GnRH analogue.tw. (123)

11 gonadotropin releasing hormone agonist.tw. (270)

12 GnRHa.tw. (190)

13 HMG.tw. (1112)

14 human menopausal gonadotropin.tw. (182)

15 (profasi or ovitrelle).tw. (10)

16 gonadotrophin releasing hormone agonist.tw. (117)

17 BBT.tw. (30)

18 ultrasound$.tw. (5976)

19 ultrasonograph$.tw. (2664)

20 time$.tw. (120256)

21 timing.tw. (2821)

22 or/1-21 (132789)

23 exp Insemination, Artificial/ (269)

24 Artificial Insemination.tw. (53)

25 intrauter$ inseminat$.tw. (386)

26 (intra-uter$ adj2 inseminat$).tw. (27)

27 iui.tw. (284)

28 AIH.tw. (26)

29 or/23-28 (558)

30 22 and 29 (264)

31 limit 30 to yr="2009 -Current" (38)

Central register of controlled trials < dec 2012>

1 human chorionic gonadotropin.tw. (374)
2 hCG.tw. (995)
3 choriogon$.tw. (5)
4 (pregnyl or chorulon or gonabion).tw. (2)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1965)
6 (LH or ICSH).tw. (2040)
7 exp Chorionic Gonadotropin/ (588)
8 body temperature$.tw. (1285)
9 GnRH agonist.tw. (589)
10 GnRH analogue.tw. (124)
11 gonadotropin releasing hormone agonist.tw. (271)
12 GnRHa.tw. (190)
13 HMG.tw. (1116)
14 human menopausal gonadotropin.tw. (182)
15 (profasi or ovitrelle).tw. (10)
16 gonadotrophin releasing hormone agonist.tw. (118)
17 BBT.tw. (30)
18 ultrasound$.tw. (6038)
19 ultrasonograph$.tw. (2674)
20 time$.tw. (121198)
21 timing.tw. (2855)
22 or/1-21 (133854)
23 exp Insemination, Artificial/ (270)
24 Artificial Insemination.tw. (54)
25 intrauter$ inseminat$.tw. (399)
26 (intra-uter$ adj2 inseminat$).tw. (28)
27 iui.tw. (293)
28 AIH.tw. (26)
29 or/23-28 (580)
30 22 and 29 (269)
31 limit 30 to yr="2012 -Current" (3)

Appendix 3. MEDLINE search strategy

MEDLINE (1966 to March 2009)

1 human chorionic gonadotropin.tw. (9408)

2 hCG.tw. (17711)

3 choriogon$.tw. (806)

4 (pregnyl or chorulon or gonabion).tw. (49)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (48292)

6 (LH or ICSH).tw. (39220)

7 exp Chorionic Gonadotropin/ (26357)

8 body temperature$.tw. (17493)

9 GnRH agonist.tw. (2074)

10 GnRH analogue.tw. (610)

11 gonadotropin releasing hormone agonist.tw. (1062)

12 GnRHa.tw. (819)

13 HMG.tw. (10035)

14 human menopausal gonadotropin.tw. (1057)

15 (profasi or ovitrelle).tw. (27)

16 gonadotrophin releasing hormone agonist.tw. (302)

17 BBT.tw. (291)

18 ultrasound$.tw. (99121)

19 ultrasonograph$.tw. (55953)

20 time$.tw. (1545099)

21 timing.tw. (50623)

22 or/1-21 (1789257)

23 exp Insemination, Artificial/ (8561)

24 Artificial Insemination.tw. (3649)

25 intrauter$ inseminat$.tw. (1295)

26 (intra-uter$ adj2 inseminat$).tw. (140)

27 iui.tw. (808)

28 AIH.tw. (902)

29 or/23-28 (10983)

30 22 and 29 (2844)

31 randomised controlled trial.pt. (266031)

32 controlled clinical trial.pt. (78661)

33 (randomised or randomised).ab. (210367)

34 placebo.ab. (110319)

35 drug therapy.fs. (1291549)

36 randomly.ab. (128228)

37 trial.ab. (183721)

38 groups.ab. (888340)

39 or/31-38 (2358832)

40 (animals not (humans and animals)).sh. (3251132)

41 39 not 40 (1999305)

42 30 and 41 (469)

43 (ivf or icsi or intracytoplasmic sperm injection$).tw. (13661)

44 42 not 43 (394)

45 from 44 keep 1-394 (394)

MEDLINE (January 2009 to 07 May 2012)

1 human chorionic gonadotropin.tw. (10613)

2 hCG.tw. (19802)

3 choriogon$.tw. (862)

4 (pregnyl or chorulon or gonabion).tw. (65)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (51259)

6 (LH or ICSH).tw. (43606)

7 exp Chorionic Gonadotropin/ (28013)

8 body temperature$.tw. (20554)

9 GnRH agonist.tw. (2496)

10 GnRH analogue.tw. (726)

11 gonadotropin releasing hormone agonist.tw. (1204)

12 GnRHa.tw. (984)

13 HMG.tw. (11574)

14 human menopausal gonadotropin.tw. (1093)

15 (profasi or ovitrelle).tw. (30)

16 gonadotrophin releasing hormone agonist.tw. (341)

17 BBT.tw. (347)

18 ultrasound$.tw. (131852)

19 ultrasonograph$.tw. (68456)

20 time$.tw. (2066122)

21 timing.tw. (69281)

22 or/1-21 (2365234)

23 exp Insemination, Artificial/ (9448)

24 Artificial Insemination.tw. (4477)

25 intrauter$ inseminat$.tw. (1616)

26 (intra-uter$ adj2 inseminat$).tw. (165)

27 iui.tw. (1036)

28 AIH.tw. (1276)

29 or/23-28 (12947)

30 22 and 29 (3554)

31 randomized controlled trial.pt. (327017)

32 controlled clinical trial.pt. (84075)

33 randomized.ab. (242418)

34 placebo.tw. (139743)

35 clinical trials as topic.sh. (159870)

36 randomly.ab. (178062)

37 trial.ti. (104315)

38 (crossover or cross-over or cross over).tw. (53309)

39 or/31-38 (801493)

40 exp animals/ not humans.sh. (3712811)

41 39 not 40 (739736)

42 30 and 41 (294)

43 (2009$ or 2010$ or 2011$ or 2012$).ed. (3080766)

44 42 and 43 (56

MEDLINE (May 2012 to 04 Feb 2013)
1 human chorionic gonadotropin.tw. (10853)
2 hCG.tw. (20241)
3 choriogon$.tw. (869)
4 (pregnyl or chorulon or gonabion).tw. (71)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (51761)
6 (LH or ICSH).tw. (44399)
7 exp Chorionic Gonadotropin/ (28368)
8 body temperature$.tw. (21082)
9 GnRH agonist.tw. (2630)
10 GnRH analogue.tw. (754)
11 gonadotropin releasing hormone agonist.tw. (1260)
12 GnRHa.tw. (1028)
13 HMG.tw. (11735)
14 human menopausal gonadotropin.tw. (1131)
15 (profasi or ovitrelle).tw. (31)
16 gonadotrophin releasing hormone agonist.tw. (353)
17 BBT.tw. (359)
18 ultrasound$.tw. (138745)
19 ultrasonograph$.tw. (71151)
20 time$.tw. (2158722)
21 timing.tw. (72720)
22 or/1-21 (2468620)
23 exp Insemination, Artificial/ (9640)
24 Artificial Insemination.tw. (4650)
25 intrauter$ inseminat$.tw. (1692)
26 (intra-uter$ adj2 inseminat$).tw. (173)
27 iui.tw. (1092)
28 AIH.tw. (1347)
29 or/23-28 (13345)
30 22 and 29 (3735)
31 randomized controlled trial.pt. (339054)
32 controlled clinical trial.pt. (85098)
33 randomized.ab. (256457)
34 placebo.tw. (144132)

35 clinical trials as topic.sh. (162088)
36 randomly.ab. (187749)
37 trial.ti. (109412)
38 (crossover or cross-over or cross over).tw. (55285)
39 or/31-38 (833381)
40 exp animals/ not humans.sh. (3754079)
41 39 not 40 (768269)
42 30 and 41 (306)
43 (2012$ or 2013$).ed. (1118579)
44 42 and 43 (17)

Appendix 4. EMBASE search strategy

EMBASE (1974 to March 2009)

1 human chorionic gonadotropin.tw. (7671)

2 hCG.tw. (14541)

3 choriogon$.tw. (657)

4 (pregnyl or chorulon or gonabion).tw. (1250)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (35470)

6 (LH or ICSH).tw. (30151)

7 exp Chorionic Gonadotropin/ (21583)

8 body temperature$.tw. (13145)

9 GnRH agonist.tw. (2019)

10 GnRH analogue.tw. (547)

11 gonadotropin releasing hormone agonist.tw. (1044)

12 GnRHa.tw. (810)

13 HMG.tw. (9668)

14 human menopausal gonadotropin.tw. (970)

15 (profasi or ovitrelle).tw. (1323)

16 gonadotrophin releasing hormone agonist.tw. (303)

17 BBT.tw. (216)

18 ultrasound$.tw. (92192)

19 ultrasonograph$.tw. (49842)

20 time$.tw. (1321475)

21 timing.tw. (42682)

22 or/1-21 (1529635)

23 Artificial Insemination.tw. (1376)

24 intrauter$ inseminat$.tw. (1274)

25 (intra-uter$ adj2 inseminat$).tw. (144)

26 iui.tw. (845)

27 AIH.tw. (970)

28 exp artificial insemination/ or exp ovulation induction/ (10395)

29 or/23-28 (12514)

30 22 and 29 (6018)

31 Clinical Trial/ (534452)

32 Randomized Controlled Trial/ (166828)

33 exp randomisation/ (26635)

34 Single Blind Procedure/ (8034)

35 Double Blind Procedure/ (71767)

36 Crossover Procedure/ (21100)

37 Placebo/ (124638)

38 Randomi?ed controlled trial$.tw. (32668)

39 Rct.tw. (2683)

40 random allocation.tw. (637)

41 randomly allocated.tw. (10170)

42 allocated randomly.tw. (1350)

43 (allocated adj2 random).tw. (560)

44 Single blind$.tw. (7444)

45 Double blind$.tw. (84622)

46 ((treble or triple) adj blind$).tw. (140)

47 placebo$.tw. (109819)

48 prospective study/ (80677)

49 or/31-48 (702424)

50 case study/ (5962)

51 case report.tw. (118966)

52 abstract report/ or letter/ (493672)

53 or/50-52 (616305)

54 49 not 53 (677956)

55 30 and 54 (1225)

56 limit 55 to yr="2008 - 2009" (88)

57 from 56 keep 1-88 (88)

Ovid EMBASE (January 2010 to 07 May 2012)

EMBASE is only searched two years back as the UKCC has hand searched EMBASE to this point and these trials are already in CENTRAL.

1 human chorionic gonadotropin.tw. (10712)

2 hCG.tw. (22067)

3 choriogon$.tw. (881)

4 (pregnyl or chorulon or gonabion).tw. (1485)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (54337)

6 (LH or ICSH).tw. (45662)

7 exp Chorionic Gonadotropin/ (34988)

8 body temperature$.tw. (22592)

9 GnRH agonist.tw. (3159)

10 GnRH analogue.tw. (881)

11 gonadotropin releasing hormone agonist.tw. (1335)

12 GnRHa.tw. (1226)

13 HMG.tw. (13943)

14 human menopausal gonadotropin.tw. (1157)

15 (profasi or ovitrelle).tw. (1503)

16 gonadotrophin releasing hormone agonist.tw. (372)

17 BBT.tw. (364)

18 ultrasound$.tw. (171377)

19 ultrasonograph$.tw. (86331)

20 time$.tw. (2414703)

21 timing.tw. (79935)

22 or/1-21 (2776077)

23 Artificial Insemination.tw. (4325)

24 intrauter$ inseminat$.tw. (2100)

25 (intra-uter$ adj2 inseminat$).tw. (267)

26 iui.tw. (1532)

27 AIH.tw. (1935)

28 exp artificial insemination/ or exp ovulation induction/ (20846)

29 or/23-28 (25228)

30 22 and 29 (10464)

31 Clinical Trial/ (864714)

32 Randomized Controlled Trial/ (320860)

33 exp randomization/ (57970)

34 Single Blind Procedure/ (15808)

35 Double Blind Procedure/ (108521)

36 Crossover Procedure/ (33692)

37 Placebo/ (197302)

38 Randomi?ed controlled trial$.tw. (73975)

39 Rct.tw. (9062)

40 random allocation.tw. (1134)

41 randomly allocated.tw. (16989)

42 allocated randomly.tw. (1796)

43 (allocated adj2 random).tw. (705)

44 Single blind$.tw. (12061)

45 Double blind$.tw. (126812)

46 ((treble or triple) adj blind$).tw. (265)

47 placebo$.tw. (173231)

48 prospective study/ (202252)

49 or/31-48 (1240932)

50 case study/ (15388)

51 case report.tw. (223558)

52 abstract report/ or letter/ (829909)

53 or/50-52 (1064356)

54 49 not 53 (1206183)

55 30 and 54 (2195)

56 (2010$ or 2011$ or 2012$).em. (2405704)

57 55 and 56 (386)

Ovid Embase (May 2012 to 04 Feb 2013)

1 human chorionic gonadotropin.tw. (11139)
2 hCG.tw. (23106)
3 choriogon$.tw. (896)
4 (pregnyl or chorulon or gonabion).tw. (1535)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (55784)
6 (LH or ICSH).tw. (47444)
7 exp Chorionic Gonadotropin/ (36305)
8 body temperature$.tw. (23776)
9 GnRH agonist.tw. (3359)
10 GnRH analogue.tw. (934)
11 gonadotropin releasing hormone agonist.tw. (1394)
12 GnRHa.tw. (1315)
13 HMG.tw. (14461)
14 human menopausal gonadotropin.tw. (1174)
15 (profasi or ovitrelle).tw. (1555)
16 gonadotrophin releasing hormone agonist.tw. (386)
17 BBT.tw. (391)
18 ultrasound$.tw. (187297)
19 ultrasonograph$.tw. (91634)
20 time$.tw. (2601310)
21 timing.tw. (86897)
22 or/1-21 (2985880)
23 Artificial Insemination.tw. (4492)
24 intrauter$ inseminat$.tw. (2229)
25 (intra-uter$ adj2 inseminat$).tw. (277)
26 iui.tw. (1647)

27 AIH.tw. (2159)
28 exp artificial insemination/ or exp ovulation induction/ (21522)
29 or/23-28 (26288)
30 22 and 29 (10961)
31 Clinical Trial/ (876466)
32 Randomized Controlled Trial/ (336673)
33 exp randomization/ (60661)
34 Single Blind Procedure/ (16967)
35 Double Blind Procedure/ (112989)
36 Crossover Procedure/ (36118)
37 Placebo/ (212667)
38 Randomi?ed controlled trial$.tw. (83349)
39 Rct.tw. (10867)
40 random allocation.tw. (1206)
41 randomly allocated.tw. (18256)
42 allocated randomly.tw. (1863)
43 (allocated adj2 random).tw. (716)
44 Single blind$.tw. (13000)
45 Double blind$.tw. (133772)
46 ((treble or triple) adj blind$).tw. (300)
47 placebo$.tw. (184418)
48 prospective study/ (224710)
49 or/31-48 (1305860)
50 case study/ (18516)
51 case report.tw. (238003)
52 abstract report/ or letter/ (857366)
53 or/50-52 (1108963)
54 49 not 53 (1269963)
55 30 and 54 (2283)
56 (2012$ or 2013$).em. (1409980)
57 55 and 56 (146)

Appendix 5. PsycINFO search strategy

PsycINFO <1806 to March Week 3 2009>

1 human chorionic gonadotropin.tw. (44)
2 hCG.tw. (42)
3 choriogon$.tw. (0)
4 (pregnyl or chorulon or gonabion).tw. (0)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (968)
6 (LH or ICSH).tw. (1789)
7 exp Chorionic Gonadotropin/ (0)
8 body temperature$.tw. (2652)
9 GnRH agonist.tw. (22)
10 GnRH analogue.tw. (3)
11 gonadotropin releasing hormone agonist.tw. (25)
12 GnRHa.tw. (9)
13 HMG.tw. (70)
14 human menopausal gonadotropin.tw. (3)
15 (profasi or ovitrelle).tw. (0)
16 gonadotrophin releasing hormone agonist.tw. (1)
17 BBT.tw. (23)
18 ultrasound$.tw. (1090)
19 ultrasonograph$.tw. (271)
20 time$.tw. (310399)
21 timing.tw. (13204)
22 or/1-21 (323545)
23 Artificial Insemination.tw. (198)
24 intrauter$ inseminat$.tw. (4)
25 (intra-uter$ adj2 inseminat$).tw. (0)
26 iui.tw. (10)

27 AIH.tw. (8)
28 exp artificial insemination/ or exp ovulation induction/ (861)
29 or/23-28 (970)
30 22 and 29 (121)
31 from 30 keep 1-121 (121)

Database: PsycINFO <1806 to May Week 1 2012>

1 human chorionic gonadotropin.tw. (65)

2 hCG.tw. (64)

3 (pregnyl or chorulon or gonabion).tw. (1)

4 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1161)

5 (LH or ICSH).tw. (2202)

6 body temperature$.tw. (3106)

7 GnRH agonist.tw. (33)

8 GnRH analogue.tw. (7)

9 gonadotropin releasing hormone agonist.tw. (28)

10 GnRHa.tw. (19)

11 HMG.tw. (126)

12 human menopausal gonadotropin.tw. (3)

13 (profasi or ovitrelle).tw. (0)

14 gonadotrophin releasing hormone agonist.tw. (1)

15 BBT.tw. (35)

16 ultrasound$.tw. (1801)

17 ultrasonograph$.tw. (514)

18 time$.tw. (410417)

19 timing.tw. (18060)

20 or/1-19 (427843)

21 Artificial Insemination.tw. (211)

22 intrauter$ inseminat$.tw. (13)

23 iui.tw. (19)

24 AIH.tw. (20)

25 or/21-24 (253)

26 20 and 25 (38)

27 random.tw. (35121)

28 control.tw. (273455)

29 double-blind.tw. (15930)

30 clinical trials/ (6006)

31 placebo/ (3203)

32 exp Treatment/ (514585)

33 or/27-32 (779748)

34 26 and 33 (10)

35 limit 34 to yr="2009 -Current" (4)

PsycINFO <1806 to January Week 5 2013>

1 human chorionic gonadotropin.tw. (66)
2 hCG.tw. (65)
3 (pregnyl or chorulon or gonabion).tw. (1)
4 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1200)
5 (LH or ICSH).tw. (2299)
6 body temperature$.tw. (3205)
7 GnRH agonist.tw. (37)
8 GnRH analogue.tw. (7)
9 gonadotropin releasing hormone agonist.tw. (30)
10 GnRHa.tw. (19)
11 HMG.tw. (143)
12 human menopausal gonadotropin.tw. (3)
13 (profasi or ovitrelle).tw. (0)
14 gonadotrophin releasing hormone agonist.tw. (2)
15 BBT.tw. (37)
16 ultrasound$.tw. (1970)
17 ultrasonograph$.tw. (580)
18 time$.tw. (435066)
19 timing.tw. (19256)
20 or/1-19 (453493)
21 Artificial Insemination.tw. (215)
22 intrauter$ inseminat$.tw. (13)
23 iui.tw. (19)
24 AIH.tw. (22)
25 or/21-24 (259)
26 20 and 25 (39)
27 random.tw. (37054)
28 control.tw. (287829)
29 double-blind.tw. (16599)
30 clinical trials/ (6539)
31 placebo/ (3372)
32 exp Treatment/ (536873)
33 or/27-32 (816147)
34 26 and 33 (11)
35 limit 34 to yr="2012 - 2013" (1)

Appendix 6. Other electronic sources search strategy (PubMed)

intrauterine; intra uterine; intra-uterine; insemination; inseminate; IUI; artificial insemination; AI; Artificial insemination husband; AIH; timing; hCG; human chorionic gonadotropin; human chorionic gonadotrophin; gonadotrophins; Pregnyl; Ovitrelle; Profasi; GnRH agonist; GnRH agonists; GnRH analogue; GnRH analogue; GnRH analogues; GnRHa; GnRHa-gonadotropin; Luteinising hormone; Luteinising hormone releasing hormone; LH; LH surge; LH determination; LH rise; LH detection kit; urinary LH; basal body temp; BBT; hMG; ultrasonography; ultrasound; timing of insemination; timing ovulation; timing of administration; subfertile; subfertility; infertility; (randomised controlled trial [Publication Type], controlled clinical trial [Publication Type], randomised controlled trials, random allocation, double-blind method, single-blind method, clinical trial [Publication Type], clinical trials, (clinical AND trial*)).

Appendix 7. Search string

MEDLINE (1966 to March 2009)

1 human chorionic gonadotropin.tw. (9408)

2 hCG.tw. (17711)

3 choriogon$.tw. (806)

4 (pregnyl or chorulon or gonabion).tw. (49)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (48292)

6 (LH or ICSH).tw. (39220)

7 exp Chorionic Gonadotropin/ (26357)

8 body temperature$.tw. (17493)

9 GnRH agonist.tw. (2074)

10 GnRH analogue.tw. (610)

11 gonadotropin releasing hormone agonist.tw. (1062)

12 GnRHa.tw. (819)

13 HMG.tw. (10035)

14 human menopausal gonadotropin.tw. (1057)

15 (profasi or ovitrelle).tw. (27)

16 gonadotrophin releasing hormone agonist.tw. (302)

17 BBT.tw. (291)

18 ultrasound$.tw. (99121)

19 ultrasonograph$.tw. (55953)

20 time$.tw. (1545099)

21 timing.tw. (50623)

22 or/1-21 (1789257)

23 exp Insemination, Artificial/ (8561)

24 Artificial Insemination.tw. (3649)

25 intrauter$ inseminat$.tw. (1295)

26 (intra-uter$ adj2 inseminat$).tw. (140)

27 iui.tw. (808)

28 AIH.tw. (902)

29 or/23-28 (10983)

30 22 and 29 (2844)

31 randomised controlled trial.pt. (266031)

32 controlled clinical trial.pt. (78661)

33 (randomised or randomised).ab. (210367)

34 placebo.ab. (110319)

35 drug therapy.fs. (1291549)

36 randomly.ab. (128228)

37 trial.ab. (183721)

38 groups.ab. (888340)

39 or/31-38 (2358832)

40 (animals not (humans and animals)).sh. (3251132)

41 39 not 40 (1999305)

42 30 and 41 (469)

43 (ivf or icsi or intracytoplasmic sperm injection$).tw. (13661)

44 42 not 43 (394)

45 from 44 keep 1-394 (394)

MEDLINE (January 2009 to 07 May 2012)

1 human chorionic gonadotropin.tw. (10613)

2 hCG.tw. (19802)

3 choriogon$.tw. (862)

4 (pregnyl or chorulon or gonabion).tw. (65)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (51259)

6 (LH or ICSH).tw. (43606)

7 exp Chorionic Gonadotropin/ (28013)

8 body temperature$.tw. (20554)

9 GnRH agonist.tw. (2496)

10 GnRH analogue.tw. (726)

11 gonadotropin releasing hormone agonist.tw. (1204)

12 GnRHa.tw. (984)

13 HMG.tw. (11574)

14 human menopausal gonadotropin.tw. (1093)

15 (profasi or ovitrelle).tw. (30)

16 gonadotrophin releasing hormone agonist.tw. (341)

17 BBT.tw. (347)

18 ultrasound$.tw. (131852)

19 ultrasonograph$.tw. (68456)

20 time$.tw. (2066122)

21 timing.tw. (69281)

22 or/1-21 (2365234)

23 exp Insemination, Artificial/ (9448)

24 Artificial Insemination.tw. (4477)

25 intrauter$ inseminat$.tw. (1616)

26 (intra-uter$ adj2 inseminat$).tw. (165)

27 iui.tw. (1036)

28 AIH.tw. (1276)

29 or/23-28 (12947)

30 22 and 29 (3554)

31 randomized controlled trial.pt. (327017)

32 controlled clinical trial.pt. (84075)

33 randomized.ab. (242418)

34 placebo.tw. (139743)

35 clinical trials as topic.sh. (159870)

36 randomly.ab. (178062)

37 trial.ti. (104315)

38 (crossover or cross-over or cross over).tw. (53309)

39 or/31-38 (801493)

40 exp animals/ not humans.sh. (3712811)

41 39 not 40 (739736)

42 30 and 41 (294)

43 (2009$ or 2010$ or 2011$ or 2012$).ed. (3080766)

44 42 and 43 (56

MEDLINE (May 2012 to 04 Feb 2013)
1 human chorionic gonadotropin.tw. (10853)
2 hCG.tw. (20241)
3 choriogon$.tw. (869)
4 (pregnyl or chorulon or gonabion).tw. (71)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (51761)
6 (LH or ICSH).tw. (44399)
7 exp Chorionic Gonadotropin/ (28368)
8 body temperature$.tw. (21082)
9 GnRH agonist.tw. (2630)
10 GnRH analogue.tw. (754)
11 gonadotropin releasing hormone agonist.tw. (1260)
12 GnRHa.tw. (1028)
13 HMG.tw. (11735)
14 human menopausal gonadotropin.tw. (1131)
15 (profasi or ovitrelle).tw. (31)
16 gonadotrophin releasing hormone agonist.tw. (353)
17 BBT.tw. (359)
18 ultrasound$.tw. (138745)
19 ultrasonograph$.tw. (71151)
20 time$.tw. (2158722)
21 timing.tw. (72720)
22 or/1-21 (2468620)
23 exp Insemination, Artificial/ (9640)
24 Artificial Insemination.tw. (4650)
25 intrauter$ inseminat$.tw. (1692)
26 (intra-uter$ adj2 inseminat$).tw. (173)
27 iui.tw. (1092)
28 AIH.tw. (1347)
29 or/23-28 (13345)
30 22 and 29 (3735)

31 randomized controlled trial.pt. (339054)
32 controlled clinical trial.pt. (85098)
33 randomized.ab. (256457)
34 placebo.tw. (144132)
35 clinical trials as topic.sh. (162088)
36 randomly.ab. (187749)
37 trial.ti. (109412)
38 (crossover or cross-over or cross over).tw. (55285)
39 or/31-38 (833381)
40 exp animals/ not humans.sh. (3754079)
41 39 not 40 (768269)
42 30 and 41 (306)
43 (2012$ or 2013$).ed. (1118579)
44 42 and 43 (17)

EMBASE (1974 to March 2009)

1 human chorionic gonadotropin.tw. (7671)

2 hCG.tw. (14541)

3 choriogon$.tw. (657)

4 (pregnyl or chorulon or gonabion).tw. (1250)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (35470)

6 (LH or ICSH).tw. (30151)

7 exp Chorionic Gonadotropin/ (21583)

8 body temperature$.tw. (13145)

9 GnRH agonist.tw. (2019)

10 GnRH analogue.tw. (547)

11 gonadotropin releasing hormone agonist.tw. (1044)

12 GnRHa.tw. (810)

13 HMG.tw. (9668)

14 human menopausal gonadotropin.tw. (970)

15 (profasi or ovitrelle).tw. (1323)

16 gonadotrophin releasing hormone agonist.tw. (303)

17 BBT.tw. (216)

18 ultrasound$.tw. (92192)

19 ultrasonograph$.tw. (49842)

20 time$.tw. (1321475)

21 timing.tw. (42682)

22 or/1-21 (1529635)

23 Artificial Insemination.tw. (1376)

24 intrauter$ inseminat$.tw. (1274)

25 (intra-uter$ adj2 inseminat$).tw. (144)

26 iui.tw. (845)

27 AIH.tw. (970)

28 exp artificial insemination/ or exp ovulation induction/ (10395)

29 or/23-28 (12514)

30 22 and 29 (6018)

31 Clinical Trial/ (534452)

32 Randomized Controlled Trial/ (166828)

33 exp randomisation/ (26635)

34 Single Blind Procedure/ (8034)

35 Double Blind Procedure/ (71767)

36 Crossover Procedure/ (21100)

37 Placebo/ (124638)

38 Randomi?ed controlled trial$.tw. (32668)

39 Rct.tw. (2683)

40 random allocation.tw. (637)

41 randomly allocated.tw. (10170)

42 allocated randomly.tw. (1350)

43 (allocated adj2 random).tw. (560)

44 Single blind$.tw. (7444)

45 Double blind$.tw. (84622)

46 ((treble or triple) adj blind$).tw. (140)

47 placebo$.tw. (109819)

48 prospective study/ (80677)

49 or/31-48 (702424)

50 case study/ (5962)

51 case report.tw. (118966)

52 abstract report/ or letter/ (493672)

53 or/50-52 (616305)

54 49 not 53 (677956)

55 30 and 54 (1225)

56 limit 55 to yr="2008 - 2009" (88)

57 from 56 keep 1-88 (88)

Ovid EMBASE (January 2010 to 07 May 2012)

EMBASE is only searched two years back as the UKCC has hand searched EMBASE to this point and these trials are already in CENTRAL.

1 human chorionic gonadotropin.tw. (10712)

2 hCG.tw. (22067)

3 choriogon$.tw. (881)

4 (pregnyl or chorulon or gonabion).tw. (1485)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (54337)

6 (LH or ICSH).tw. (45662)

7 exp Chorionic Gonadotropin/ (34988)

8 body temperature$.tw. (22592)

9 GnRH agonist.tw. (3159)

10 GnRH analogue.tw. (881)

11 gonadotropin releasing hormone agonist.tw. (1335)

12 GnRHa.tw. (1226)

13 HMG.tw. (13943)

14 human menopausal gonadotropin.tw. (1157)

15 (profasi or ovitrelle).tw. (1503)

16 gonadotrophin releasing hormone agonist.tw. (372)

17 BBT.tw. (364)

18 ultrasound$.tw. (171377)

19 ultrasonograph$.tw. (86331)

20 time$.tw. (2414703)

21 timing.tw. (79935)

22 or/1-21 (2776077)

23 Artificial Insemination.tw. (4325)

24 intrauter$ inseminat$.tw. (2100)

25 (intra-uter$ adj2 inseminat$).tw. (267)

26 iui.tw. (1532)

27 AIH.tw. (1935)

28 exp artificial insemination/ or exp ovulation induction/ (20846)

29 or/23-28 (25228)

30 22 and 29 (10464)

31 Clinical Trial/ (864714)

32 Randomized Controlled Trial/ (320860)

33 exp randomization/ (57970)

34 Single Blind Procedure/ (15808)

35 Double Blind Procedure/ (108521)

36 Crossover Procedure/ (33692)

37 Placebo/ (197302)

38 Randomi?ed controlled trial$.tw. (73975)

39 Rct.tw. (9062)

40 random allocation.tw. (1134)

41 randomly allocated.tw. (16989)

42 allocated randomly.tw. (1796)

43 (allocated adj2 random).tw. (705)

44 Single blind$.tw. (12061)

45 Double blind$.tw. (126812)

46 ((treble or triple) adj blind$).tw. (265)

47 placebo$.tw. (173231)

48 prospective study/ (202252)

49 or/31-48 (1240932)

50 case study/ (15388)

51 case report.tw. (223558)

52 abstract report/ or letter/ (829909)

53 or/50-52 (1064356)

54 49 not 53 (1206183)

55 30 and 54 (2195)

56 (2010$ or 2011$ or 2012$).em. (2405704)

57 55 and 56 (386)

Ovid EMBASE (May 2012 to 04 Feb 2013)

1 human chorionic gonadotropin.tw. (11139)
2 hCG.tw. (23106)
3 choriogon$.tw. (896)
4 (pregnyl or chorulon or gonabion).tw. (1535)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (55784)
6 (LH or ICSH).tw. (47444)
7 exp Chorionic Gonadotropin/ (36305)
8 body temperature$.tw. (23776)
9 GnRH agonist.tw. (3359)
10 GnRH analogue.tw. (934)
11 gonadotropin releasing hormone agonist.tw. (1394)
12 GnRHa.tw. (1315)
13 HMG.tw. (14461)
14 human menopausal gonadotropin.tw. (1174)
15 (profasi or ovitrelle).tw. (1555)
16 gonadotrophin releasing hormone agonist.tw. (386)
17 BBT.tw. (391)
18 ultrasound$.tw. (187297)
19 ultrasonograph$.tw. (91634)
20 time$.tw. (2601310)
21 timing.tw. (86897)

22 or/1-21 (2985880)
23 Artificial Insemination.tw. (4492)
24 intrauter$ inseminat$.tw. (2229)
25 (intra-uter$ adj2 inseminat$).tw. (277)
26 iui.tw. (1647)
27 AIH.tw. (2159)
28 exp artificial insemination/ or exp ovulation induction/ (21522)
29 or/23-28 (26288)
30 22 and 29 (10961)
31 Clinical Trial/ (876466)
32 Randomized Controlled Trial/ (336673)
33 exp randomization/ (60661)
34 Single Blind Procedure/ (16967)
35 Double Blind Procedure/ (112989)
36 Crossover Procedure/ (36118)
37 Placebo/ (212667)
38 Randomi?ed controlled trial$.tw. (83349)
39 Rct.tw. (10867)
40 random allocation.tw. (1206)
41 randomly allocated.tw. (18256)
42 allocated randomly.tw. (1863)
43 (allocated adj2 random).tw. (716)
44 Single blind$.tw. (13000)
45 Double blind$.tw. (133772)
46 ((treble or triple) adj blind$).tw. (300)
47 placebo$.tw. (184418)
48 prospective study/ (224710)
49 or/31-48 (1305860)
50 case study/ (18516)
51 case report.tw. (238003)
52 abstract report/ or letter/ (857366)
53 or/50-52 (1108963)
54 49 not 53 (1269963)
55 30 and 54 (2283)
56 (2012$ or 2013$).em. (1409980)
57 55 and 56 (146)

Central Register of Controlled Trials <1st Quarter 2009>

1 human chorionic gonadotropin.tw. (311)
2 hCG.tw. (829)
3 choriogon$.tw. (5)
4 (pregnyl or chorulon or gonabion).tw. (2)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1775)
6 (LH or ICSH).tw. (1829)
7 exp Chorionic Gonadotropin/ (524)
8 body temperature$.tw. (1125)
9 GnRH agonist.tw. (503)
10 GnRH analogue.tw. (110)
11 gonadotropin releasing hormone agonist.tw. (245)
12 GnRHa.tw. (169)
13 HMG.tw. (1026)
14 human menopausal gonadotropin.tw. (169)
15 (profasi or ovitrelle).tw. (9)
16 gonadotrophin releasing hormone agonist.tw. (111)
17 BBT.tw. (26)
18 ultrasound$.tw. (4652)
19 ultrasonograph$.tw. (2199)
20 time$.tw. (99572)
21 timing.tw. (2259)
22 or/1-21 (110066)
23 Artificial Insemination.tw. (51)

24 intrauter$ inseminat$.tw. (329)
25 (intra-uter$ adj2 inseminat$).tw. (25)
26 iui.tw. (227)
27 AIH.tw. (23)
28 exp artificial insemination/ or exp ovulation induction/ (858)
29 or/23-28 (1085)
30 22 and 29 (711)
31 (ivf or icsi).tw. (1833)
32 (in vitro fertilization or intracytoplasmic sperm injection).tw. (1271)
33 or/31-32 (2318)
34 30 not 33 (392)
35 from 34 keep 1-392 (392)

Cochrane Central Register of Controlled Trials <April 2012>

1 human chorionic gonadotropin.tw. (371)

2 hCG.tw. (981)

3 choriogon$.tw. (5)

4 (pregnyl or chorulon or gonabion).tw. (2)

5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1964)

6 (LH or ICSH).tw. (2030)

7 exp Chorionic Gonadotropin/ (587)

8 body temperature$.tw. (1279)

9 GnRH agonist.tw. (579)

10 GnRH analogue.tw. (123)

11 gonadotropin releasing hormone agonist.tw. (270)

12 GnRHa.tw. (190)

13 HMG.tw. (1112)

14 human menopausal gonadotropin.tw. (182)

15 (profasi or ovitrelle).tw. (10)

16 gonadotrophin releasing hormone agonist.tw. (117)

17 BBT.tw. (30)

18 ultrasound$.tw. (5976)

19 ultrasonograph$.tw. (2664)

20 time$.tw. (120256)

21 timing.tw. (2821)

22 or/1-21 (132789)

23 exp Insemination, Artificial/ (269)

24 Artificial Insemination.tw. (53)

25 intrauter$ inseminat$.tw. (386)

26 (intra-uter$ adj2 inseminat$).tw. (27)

27 iui.tw. (284)

28 AIH.tw. (26)

29 or/23-28 (558)

30 22 and 29 (264)

31 limit 30 to yr="2009 -Current" (38)

Central register of controlled trials < dec 2012>

1 human chorionic gonadotropin.tw. (374)
2 hCG.tw. (995)
3 choriogon$.tw. (5)
4 (pregnyl or chorulon or gonabion).tw. (2)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1965)
6 (LH or ICSH).tw. (2040)
7 exp Chorionic Gonadotropin/ (588)
8 body temperature$.tw. (1285)
9 GnRH agonist.tw. (589)
10 GnRH analogue.tw. (124)
11 gonadotropin releasing hormone agonist.tw. (271)
12 GnRHa.tw. (190)
13 HMG.tw. (1116)
14 human menopausal gonadotropin.tw. (182)
15 (profasi or ovitrelle).tw. (10)
16 gonadotrophin releasing hormone agonist.tw. (118)
17 BBT.tw. (30)
18 ultrasound$.tw. (6038)
19 ultrasonograph$.tw. (2674)
20 time$.tw. (121198)
21 timing.tw. (2855)
22 or/1-21 (133854)
23 exp Insemination, Artificial/ (270)
24 Artificial Insemination.tw. (54)
25 intrauter$ inseminat$.tw. (399)
26 (intra-uter$ adj2 inseminat$).tw. (28)
27 iui.tw. (293)
28 AIH.tw. (26)
29 or/23-28 (580)
30 22 and 29 (269)
31 limit 30 to yr="2012 -Current" (3)

PsycINFO <1806 to March Week 3 2009>

1 human chorionic gonadotropin.tw. (44)
2 hCG.tw. (42)
3 choriogon$.tw. (0)
4 (pregnyl or chorulon or gonabion).tw. (0)
5 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (968)
6 (LH or ICSH).tw. (1789)
7 exp Chorionic Gonadotropin/ (0)
8 body temperature$.tw. (2652)
9 GnRH agonist.tw. (22)
10 GnRH analogue.tw. (3)
11 gonadotropin releasing hormone agonist.tw. (25)
12 GnRHa.tw. (9)
13 HMG.tw. (70)
14 human menopausal gonadotropin.tw. (3)
15 (profasi or ovitrelle).tw. (0)
16 gonadotrophin releasing hormone agonist.tw. (1)
17 BBT.tw. (23)
18 ultrasound$.tw. (1090)
19 ultrasonograph$.tw. (271)

20 time$.tw. (310399)
21 timing.tw. (13204)
22 or/1-21 (323545)
23 Artificial Insemination.tw. (198)
24 intrauter$ inseminat$.tw. (4)
25 (intra-uter$ adj2 inseminat$).tw. (0)
26 iui.tw. (10)
27 AIH.tw. (8)
28 exp artificial insemination/ or exp ovulation induction/ (861)
29 or/23-28 (970)
30 22 and 29 (121)
31 from 30 keep 1-121 (121)

Database: PsycINFO <1806 to May Week 1 2012>

1 human chorionic gonadotropin.tw. (65)

2 hCG.tw. (64)

3 (pregnyl or chorulon or gonabion).tw. (1)

4 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1161)

5 (LH or ICSH).tw. (2202)

6 body temperature$.tw. (3106)

7 GnRH agonist.tw. (33)

8 GnRH analogue.tw. (7)

9 gonadotropin releasing hormone agonist.tw. (28)

10 GnRHa.tw. (19)

11 HMG.tw. (126)

12 human menopausal gonadotropin.tw. (3)

13 (profasi or ovitrelle).tw. (0)

14 gonadotrophin releasing hormone agonist.tw. (1)

15 BBT.tw. (35)

16 ultrasound$.tw. (1801)

17 ultrasonograph$.tw. (514)

18 time$.tw. (410417)

19 timing.tw. (18060)

20 or/1-19 (427843)

21 Artificial Insemination.tw. (211)

22 intrauter$ inseminat$.tw. (13)

23 iui.tw. (19)

24 AIH.tw. (20)

25 or/21-24 (253)

26 20 and 25 (38)

27 random.tw. (35121)

28 control.tw. (273455)

29 double-blind.tw. (15930)

30 clinical trials/ (6006)

31 placebo/ (3203)

32 exp Treatment/ (514585)

33 or/27-32 (779748)

34 26 and 33 (10)

35 limit 34 to yr="2009 -Current" (4)

PsycINFO <1806 to January Week 5 2013>

1 human chorionic gonadotropin.tw. (66)
2 hCG.tw. (65)
3 (pregnyl or chorulon or gonabion).tw. (1)
4 (Luteinizing Hormone or interstitial cell stimulating hormone or lutropin or luteoz?man).ti,ab,sh. (1200)
5 (LH or ICSH).tw. (2299)
6 body temperature$.tw. (3205)
7 GnRH agonist.tw. (37)
8 GnRH analogue.tw. (7)
9 gonadotropin releasing hormone agonist.tw. (30)
10 GnRHa.tw. (19)
11 HMG.tw. (143)
12 human menopausal gonadotropin.tw. (3)
13 (profasi or ovitrelle).tw. (0)
14 gonadotrophin releasing hormone agonist.tw. (2)
15 BBT.tw. (37)
16 ultrasound$.tw. (1970)
17 ultrasonograph$.tw. (580)
18 time$.tw. (435066)
19 timing.tw. (19256)
20 or/1-19 (453493)
21 Artificial Insemination.tw. (215)
22 intrauter$ inseminat$.tw. (13)
23 iui.tw. (19)
24 AIH.tw. (22)
25 or/21-24 (259)
26 20 and 25 (39)
27 random.tw. (37054)
28 control.tw. (287829)
29 double-blind.tw. (16599)
30 clinical trials/ (6539)
31 placebo/ (3372)
32 exp Treatment/ (536873)
33 or/27-32 (816147)
34 26 and 33 (11)
35 limit 34 to yr="2012 - 2013" (1)

WHAT'S NEW

Date	Event	Description
15 October 2014	New search has been performed	Eight new trials were included in the review (AboulGheit 2010; da Silva 2012; Kyrou 2012; Nikbakht 2012; Rahman 2011; Shar-

Date	Event	Description
		ma 2011; Schmidt-Sarosi 1995; Weiss 2010). Four studies were placed in awaiting classification (Aydin 2013; Blockeel 2014; Dehghani 2014; Mostafa 2014).
15 October 2014	New citation required but conclusions have not changed	Based on the new meta-analysis the conclusions are not changed.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 4, 2010

Date	Event	Description
6 July 2009	Amended	The protocol stated that no couples with cycle disturbances should be included, however almost all studies, apart from in unexplained subfertility and male subfertility, also included a category of women with cycle disturbances. We accepted this when only a some of the included couples belonged to this category.
10 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Astrid Cantineau: title registration; substantial contribution to developing protocol; reviewing articles for inclusion in review and update; substantial contribution writing review.

Mirjam Janssen: writing the protocol; performing search, selection of articles; substantial contribution writing review and update.

Ben Cohlen: formulation of research question; critical view on protocol; arbitration with reviewing the articles; substantial contribution writing review and update.

Thomas Allersma: reviewing articles for inclusion in updated review; substantial contribution writing update.

DECLARATIONS OF INTEREST

None known for any of the review authors.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol stated that women with ovulatory disturbances should not be included. Since the available evidence was scarce we decided to include studies where a proportion of the included women suffered from ovulatory disturbances. In the updated version we were more liberal towards whether a study was truly randomised; when the trial design did not mention the allocation concealment certain studies were included, identifying it as at high risk on bias in the table of included studies.

The protocol stated that if more than 10% of the cycles were cancelled, these data would not be incorporated in the meta-analysis. Since only a few studies were available, higher dropout rates and cancelled cycles were accepted in the published version as well as in the updated version of the review.

The protocol stated that we would report miscarriage and multiple pregnancy results per woman randomised. For the full review and this update we reported miscarriage and multiple pregnancy results per pregnancy.

2014 update: methods sections updated to current Cochrane recommendations.

INDEX TERMS

Medical Subject Headings (MeSH)

Body Temperature; Chorionic Gonadotropin [administration & dosage]; Gonadotropin-Releasing Hormone [agonists]; Infertility [*therapy]; Insemination, Artificial [*methods]; Luteinizing Hormone [blood] [urine]; Ovulation Detection [methods]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Adult; Female; Humans; Male; Young Adult