Synchronised approach for intrauterine insemination in subfertile couples. (Review)

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**Abstract**

Background

Intrauterine insemination (IUI) should logically be performed around the moment of ovulation. Since spermatozoa and oocytes have only limited survival times correct timing 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) (*The Cochrane Library*), (1966 to March 2009), EMBASE (1974 to March 2009) and Science Direct (1966 to March 2009) electronic databases. Furthermore, we checked the reference lists of all obtained studies and performed a handsearch of conference abstracts.

Selection criteria

Only truly randomised controlled trials 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 to be included according to the above mentioned criteria. We performed statistical analyses in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration.

Main results

Ten studies were included comparing urinary LH surge versus hCG injection; recombinant hCG versus urinary hCG; and hCG versus a GnRH agonist. One study compared the optimum time interval from hCG injection to IUI. The results of these studies showed no significant differences between different timing methods for IUI expressed as live birth rates: hCG versus LH surge (odds ratio (OR) 1.0, 95% CI 0.06 to 18); urinary hCG versus recombinant hCG (OR 1.2, 95% CI 0.68 to 2.0); and hCG versus GnRH agonist (OR 1.1, 95% CI 0.42 to 3.1). All the secondary outcomes analysed showed no significant differences between treatment groups.
Authors’ conclusions

There is no evidence to advise one particular treatment option over another. The choice should be based on hospital facilities, convenience for the patient, medical staff, costs and drop-out levels. Since different time intervals between hCG and IUI did not result in different pregnancy rates, a more flexible approach might be allowed.

Plain Language Summary

What is the best timing technique for intrauterine insemination

It remains unclear which technique of timing for intrauterine insemination results in the best treatment outcome, a live birth. Intrauterine insemination (IUI) is an assisted reproduction procedure that places sperm directly into the uterus. Timing of IUI can be performed with hormone (luteinising hormone) detection in urine or blood, human chorionic gonadotropin (hCG) injection and other more infrequently used methods. Results of this review of randomised controlled trials indicate there is no difference in live birth rates between timing methods, but the amount of evidence is scarce. The optimal moment for the actual insemination in relation to either luteinising hormone (LH) surge or hCG administration is also unclear.

Background

Description of the condition

The usual definition of subfertility is couples who have tried to conceive for at least one year. This is approximately 10% of couples who try to conceive. Subfertility is considered to be unexplained when routine fertility evaluation does not show 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 1992). Couples with cervical hostility are 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. Finally, mild endometriosis is defined as grade I or II at diagnostic laparoscopy.

In the majority of cases, the first treatment for subfertile couples consists of intrauterine insemination (IUI), which can be combined with ovarian stimulation (Cohen 2005; Goverde 2000). 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 type of subfertility, semen quality, ovarian stimulation and, probably one of the most important factors, the timing of insemination (Mitwally 2004).

As spermatozoa and oocytes survive for only a limited period of time, correct timing is 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), recombinant LH and gonadotropin-releasing hormone (GnRH) agonist administration, and basal body temperatures (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 extensive because of the high costs (Diaz 2003; Egbase 2002). Less commonly used approaches are ultrasound timing alone, timing on the basis of BBT charts, and the use of recombinant human LH (Barratt 1989; Odem 1991; Pierson 2002).

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 (Arici 1992; Lewis 2006). 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 (Robinson 1992). Limitations of timing by ultrasound and hCG administration are the occurrence of premature LH surges or the possibility of triggering ovulation in the presence of an immature follicle (Cantineau 2007; Cohlen 1998; Martinez 1991). 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 (Fuh 1997; 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 only randomised controlled trials. The method of randomisation was assessed to determine whether the studies were truly randomised. There were no restrictions based on trial duration.

Types of participants

Subfertile couples, with subfertility defined as the inability of a couple to conceive after at least one year of unprotected intercourse. We included all types of subfertility where IUI is the first treatment option (for example unexplained subfertility, male subfertility, mild endometriosis and cervical hostility). In the protocol of this review we stated that women with cycle disturbances would be excluded. However, since the available evidence was scarce we decided to include studies where a proportion of the included women suffered from ovulatory disturbances as well.

Unexplained subfertility was defined as subfertility of at least one year’s duration in combination with an infertility work up that was unable to detect any abnormality. Routine fertility evaluation should have consisted of confirmed ovulatory status (by 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 $20 \times 10^6$/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).

Mild endometriosis was defined as grade I or II at diagnostic laparoscopy.

Cervical factor was defined as a negative result with well-timed post-coital 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

Randomised controlled trials comparing different synchronisation methods for ovulation in couples undergoing IUI, including the following interventions:

1) LH detection in urine or blood, single test;
2) hCG administration;
3) a combination of LH detection and hCG administration;
4) the use of basal body temperature charts;
5) ultrasound detection of ovulation;
6) GnRH agonist administration;
7) 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 (in euro or dollars per treatment cycle)

**Adverse outcomes**:

- Multiple pregnancies (multiple pregnancy rate per couple)
- Miscarriage rate (miscarriage rate per couple)
- Ovarian hyperstimulation syndrome (OHSS) per couple
- Tubal pregnancy (tubal pregnancy rate per couple)
- Drop outs (drop-out rate per couple)

Clinical pregnancy was established by a positive hCG test in blood or urine and confirmed by ultrasound 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 drop out 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) randomised controlled trials of synchronisation of ovulation with IUI in natural and stimulated cycles.

1) We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of controlled trials and the Cochrane Central Register of Controlled Trials (CENTRAL).
2) We searched the electronic databases MEDLINE (1966 to March 2009), EMBASE (1974 to March 2009) and Science Direct (1966 to March 2009) (see Appendix 1). The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.0.1; Chapter 6, 6.4.11).
3) We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of controlled trials and the Cochrane Central Register of Controlled Trials (CENTRAL).
4) We searched the electronic databases MEDLINE (1966 to March 2009), EMBASE (1974 to March 2009) and Science Direct (1966 to March 2009) (see Appendix 1).
5) We searched in prospective trial registers for upcoming relevant randomised controlled trials (ClinicalTrials.gov; controlled-trials.com).

**Searching other resources**

3) We checked the reference lists of all obtained studies for relevant articles.
5) We searched in prospective trial registers for upcoming relevant randomised controlled trials (ClinicalTrials.gov; controlled-trials.com).

When important information was lacking from the original publications we tried to contact the authors. We incorporated additional information in the review. There was no language restriction.

**Data collection and analysis**

**Selection of studies**

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 Cohen. We performed analysis of agreement for inclusion between the two review authors using 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 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.

**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;
   - quasi-randomised, e.g. alternating record numbers, dates of birth or odds and even numbers;
   - 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. We excluded studies with a quasi-randomised design.

2. Concealment of allocation:
   - adequate (score A), e.g. sealed opaque envelopes or third party randomisation;
   - inadequate (score C), e.g. open list of random numbers, open envelopes, tables, alternating numbers;
   - stated without further description or not stated (score B).

Studies with an allocation score of A or B were included in the meta-analysis. Score C will be excluded.

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 patient, the care provider and the outcome assessor blinded? Double blinded (included), single blinded (included), not blinded (included).

5. Analysis:
   - by intention to treat (ITT) yes (included), no (excluded), not stated;
   - power calculation (prospective power calculation, no power calculation or not stated).

6. Drop outs:
   - percentage of drop outs;
   - reasons and details on drop outs (selective drop out?).

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 ovarian hyperstimulation syndrome (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 drop-out 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 5.0.1) were used. Where there was uncertainty, authors were contacted to clarify aspects of study design. Differences in agreement were resolved as described above (see Figure 1; Figure 2).

Figure 1. Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

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Measures of treatment effect
We performed statistical analyses in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration. Enough studies should have been included (at least two) to make meta-analysis possible.
For dichotomous data, we expressed results for each included study as odds ratios (OR) with 95% confidence intervals (CI) and combined them in a meta-analysis with RevMan software (RevMan 5) using the Peto method, or the Mantel-Haenszel method when data were sparse. We combined continuous data in a meta-analysis using the weighted mean difference (WMD) with 95% CI using a fixed-effect model.

Unit of analysis issues
The primary analysis has been per women. 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 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 was 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 data.

Assessment of heterogeneity
We noted heterogeneity between the results of different studies by inspecting the scatter in the data points on the graphs and the overlap in their CIs.

Assessment of reporting biases
Besides statistical and clinical heterogeneity, publication bias might influence the interpretation of the pooled results. To detect publication bias we performed a funnel graph, plotting sample size versus effect size. This graph is only relevant when five or more studies are included. The graph is symmetrical when bias is absent.

Data synthesis
We considered the live birth rate and pregnancy rate 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 signifies 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.

The heterogeneity was checked by the results of the I² statistic for inconsistency. A value of greater than 50% was considered as substantial heterogeneity. In the case of statistical heterogeneity, we used the random-effects model instead of the fixed-effect model, and we re-assessed the original trials for clinical heterogeneity and methodological heterogeneity. When trials performed adequate randomisation and allocation, met the inclusion criteria and performed the same intervention we considered it appropriate to pool their results. But when the trials differed with respect to their participants and interventions we performed subgroup analysis, whenever possible.

Sensitivity analysis
It was planned to perform sensitivity analyses (if there were more than four trials included in a meta analysis) to examine stability regarding the direction of outcomes. A sensitivity analysis was not done since not more than four trials were included in each meta-analysis.

RESULTS

Description of studies

Synchronised approach for intrauterine insemination in subfertile couples. (Review)
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See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

Using the search strategies mentioned above, 95 articles were found relating to the subject. Of these, 39 were directly excluded as their title and abstract very clearly did not meet basic inclusion criteria. The remaining 56 articles were analysed in detail by two review authors (AC and MJ). Full agreement was obtained regarding all trials.

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

Included studies

Ten studies were included (Andrés-Oros 2008; Claman 2004; Lewis 2006; Lorusso 2008; Martinez 1991a; Martinez 1991b; Sakhel 2007; Scott 1994; Shalev 1995; Zreik 1999) (see table of Characteristics of included studies). Nine compared different synchronisation approaches and one compared the optimum time interval from the onset of hCG injection to IUI (Claman 2004). 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 urinary LH surge versus hCG injection (264 women, 242 first cycle treatments). Two studies (Lorusso 2008; Sakhel 2007) compared the use of recombinant hCG versus urinary hCG (409 women, 441 cycles) and three studies (Andrés-Oros 2008; Scott 1994; Shalev 1995) compared the use of hCG versus a GnRH agonist for timing IUI (180 women, 460 cycles). The study of Claman 2004 was not used in a meta-analysis because only per cycle data were available (75 women, 189 cycles) (Table 1).

Participants

The age of the participants was stated in all trials as either a mean with standard deviation or a range. The mean age ranged from 22 to 44 years and was similar in all trials. There were no statistical differences recorded between the various treatment groups. All studies included different types of subfertility: unexplained subfertility, mild endometriosis, male factor, cervical factor and tubal or pelvic factor. Four studies (Claman 2004; Sakhel 2007; Shalev 1995; Zreik 1999) also included patients with ovulatory disorders. In the studies of Claman 2004 and Zreik 1999 the patients with ovulatory disorders comprised less than 15% of all women. In the study of Sakhel 2007 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 four studies they were equally distributed between the two treatment arms.

The duration of subfertility was given in five trials (Lorusso 2008; Martinez 1991a; Martinez 1991b; Sakhel 2007; Zreik 1999). In one study (Sakhel 2007) the duration was significant different between the two treatment groups, with a longer duration of subfertility in the group treated with urinary hCG (u-hCG). The authors stated that this difference still remained a factor after analysing the data using logistic regression analysis with clinical pregnancy rate as the dependant variable and controlling for duration of infertility. They did not state if the difference was of any clinical relevance. In the studies of Martinez et al the mean duration of subfertility was 5.6 and 6.3 years, which is quite long and could have negatively influenced their outcome parameters.

One study only (Sakhel 2007) mentioned the number of patients with primary versus secondary subfertility. Their population contained 55.8% with primary subfertility.

Four studies (Lewis 2006; Martinez 1991a; Shalev 1995; Zreik 1999) stated that they had included women who had undergone previous fertility treatment. Most of the women in the studies of Lewis 2006 and Zreik 1999 had been treated with clomiphene citrate without IUI. Only Martinez 1991a included women who previously had undergone IUI treatment cycles. The number of cycles was 3.6 ± 1 SD (range 2 to 6). 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 (CC) 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). The studies comparing recombinant hCG (r-hCG) with urinary hCG (u-hCG) (Lorusso 2008; Sakhel 2007) both used recombinant FSH (r-FSH) for ovarian stimulation. However, Sakhel et al 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; Scott 1994; Shalev 1995) used different ovarian stimulation protocols. Scott 1994 used clomiphene citrate, Andrés-Oros 2008 et al used FSH, and Shalev 1995 used hMG for ovarian stimulation. Finally, Claman 2004 used hMG or r-FSH as a method of ovarian stimulation.

Urinary LH versus hCG injection

The use of the technique for timing IUI was the comparison of interest in this review. Lewis et al had 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. Zeik et al 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 of 18 mm diameter was noted. In both groups IUI was performed daily for the next two days. Martinez 1991a started daily ultrasound scanning when total urinary E2 excretion exceeded 200 nmol/24 hours. When the largest follicle reached a diameter of between 18 to 20 mm on ultrasound and the total E2 excretion was between 300 and 1200 nmol/24 hours women received 10,000 IU hCG. LH detection in 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.

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

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 with progesterone.

Lorusso et al monitored ovarian response by ultrasound only. Urinary or r-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 for when ovulation had occurred after 24 hours.

hCG versus GnRH agonist (GnRH-a)

Sakhel 2007 administered single injection 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.

Andrés-Oros et al 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.

Scott 1994 started daily pelvic ultrasound on cycle day 12. When the dominant follicle reached a diameter of 20 to 21 mm the woman 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.

Optimal time interval

Claman et al compared the optimum time interval from ovulation induction to IUI. 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 to 34 or 38 to 40 hours later. The studies used partners’ semen although this was not noted explicitly in all studies. Only Lewis noted donor cycles. Semen preparation techniques, the amount of semen 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

Four trials (Martinez 1991a; Sakhel 2007; Scott 1994; Shalév 1995) reported live birth rates. All but one trial (Claman 2004) assessed pregnancy rate per couple.

Multiple pregnancy rates and miscarriage rates were stated in eight publications (Andrés-Oros 2008; Lorusso 2008; Martinez 1991a; Martinez 1991b; Sakhel 2007; Scott 1994; Shalév 1995; Lewis 2006). The ovarian hyperstimulation syndrome (OHSS) rate was stated in four studies (Lorusso 2008; Martinez 1991a; Sakhel 2007; Shalév 1995) and ectopic pregnancy rate was stated in one publication (Sakhel 2007).

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.

Two studies (Lewis 2006; Sakhel 2007) diagnosed pregnancy by a rising concentration of hCG. In the study of Lewis et al the pregnancy was called viable when a fetal pole with cardiac activity was noted on ultrasound. Martinez et al stated that an ultrasound detection of fetal heart rate activity was performed four weeks after conception. Three studies (Andrés-Oros 2008; Lorusso 2008; Shalév 1995) defined clinical pregnancy by the presence of a gestational sac in the uterus, determined by transvaginal ultrasound. Two studies (Scott 1994; Zeik 1999) did not mention the method of confirming pregnancy.

Studies waiting for assessment

Two studies are awaiting assessment (see table Characteristics of studies awaiting classification). In these study reports randomisation was stated but it was questionable whether the studies were truly randomised (Propst 2007; Schmidt-Sarosi 1995). For one of these studies we had the abstract of a congress registration only, so more detailed data are needed. 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. Six replies have been received, resulting in exclusion of four trials (Diaz 2003a; Diaz 2003b; Lewis 2003; Pierson 2002) and inclusion of two trials (Scott 1994; Shalév 1995).
Ongoing trials
One trial with the comparison of interest is registered on the ClinicalTrials.gov database, but no patients had been included at the time of writing this review (Amir Weiss 2009) (see table Characteristics of ongoing studies).

Excluded studies
Forty-three studies were excluded (see table Characteristics of excluded studies). Reasons for exclusion were: failure to use a truly randomised design (n = 16) (Agarwal 1995; Cedrin-Durnerin 1993; Check 1994; Costa Franco 2006; Diaz 2003a; Diaz 2008; Fondop 2005; Garris 1995; Khattab 2005; Kossoy 1989; Martinez 1994; Meherji 2004; Romeu 1997a; Romeu 1997b; Shanis 1995; Tavaniotou 2003), not performing the comparison of interest (n = 13) (Arici 1994; Baroni 2001; Federman 1990; Fischer 1993; Kotecki 2005; Nilsen 1993; Papageorgiou 1995; Pierson 2002; Pirard 2005; Ragni 1999; Robinson 1992; Silverberg 1991; Wang 2006), not performing IUS (n = 5) (Barratt 1989; Claraz 1989; George 2007; Odem 1991; Scarpellini 1991), or different type of subfertility (anovulatory women only) (n = 2) (Egbasie 2003; Int rhCG study group 2001). Finally, seven publications were excluded since they were duplicate publications of the abstract and full text (Claman 2000; Claman 2004a; Diaz 2003b; Lewis 2002; Lewis 2003; Sakhel 2004; Wang 2001).

Risk of bias in included studies

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 six 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, after additional information about allocation was received, only high quality studies were included.

Six studies mentioned the use of a computer generated program for randomisation (Andrés-Oros 2008; Lewis 2006; Lorusso 2008; Sakhel 2007; Shalev 1995; Zreik 1999). Four studies (Claman 2004; Martinez 1991a; Martinez 1991b; Scott 1994) used a random number table, not further specified. Concealment of allocation was stated explicitly in three studies (Lorusso 2008; Lewis 2006; 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 included. Concealment of allocation was done by sealed opaque envelopes or a third party (Figure 1; Figure 2).

Blinding
In three studies (Lewis 2006; Scott 1994; Shalev 1995) blinding was performed. In the study of Lewis et al the treatment group assignment was not known to the patient or treating physician until after informed consent was obtained and the baseline ultrasound was performed. Scott et al used blinding of the sonographer to minimise the risk of observer bias in determining if ovulation had taking place after injection of hCG or GnRHα. None of the trials had details on blinded analysis of the results.

Incomplete outcome data
Five studies reported information on drop outs (Claman 2004; Lewis 2006; Martinez 1991a; Martinez 1991b; Shalev 1995). The number of drop outs varied from 0% to 31%. Additional information from three studies (Andrés-Oros 2008; Sakhel 2007; Shalev 1995) on drop outs was received. 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 other two studies reported no drop outs.

Claman et al stated that the most important reasons for dropping out were a spontaneous LH surge or an inadequate follicular response. Lewis et al 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 intention-to-treat analysis was performed resulting in no significant difference between both treatment groups. In the study of Zreik et al only one couple out of 54 was excluded, due to failure in compliance. None of the included women in the study by Martinez 1991b 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.

Selective reporting
Only 40% of the included studies reported live birth rates. The remaining studies defined clinical pregnancy rates only (see table Characteristics of included studies).

Other potential sources of bias
Sakhel et al 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.
Effects of interventions

Overall nine studies with a total of 898 couples were included in the meta-analysis. An analysis of agreement between the two review authors on assessment of the method of randomisation and study design resulted in 100% agreement.

Live birth rate per couple

Four trials (Martinez 1991a; Sakhel 2007; Scott 1994; Shalev 1995) reported live birth rates. The results of these studies showed no evidence of a significant difference between different approaches for synchronising ovulation with IUI: hCG versus LH surge (OR 1.0, 95% CI 0.06 to 18; 24 women, one trial) (Analysis 1.1); u-hCG versus r-hCG (OR 1.2, 95% CI 0.68 to 2.0; 284 women, one trial) (Analysis 2.1); and hCG versus GnRH-a (OR 1.1, 95% CI 0.42 to 3.1; 78 women, two trials) (Analysis 4.1).

Pregnancy rate per couple

With the exception of one trial (Claman 2004), all studies reported pregnancy rate per couple. For the comparison hCG versus LH surge detection all four studies provided data. The result revealed no evidence of a statistical significant difference in pregnancy rates per couple (OR 1.3, 95% CI 0.72 to 2.5; 275 women, four trials) (Analysis 1.2). Two studies (Sakhel 2007; Lorusso 2008) compared u-hCG with r-hCG and reported no evidence of a significant difference in pregnancy rates per couple (OR 1.2, 95% CI 0.65 to 1.6; 409 women, two trials) (Analysis 2.2). Three studies (Andrés-Oros 2008; Scott 1994; Shalev 1995) compared hCG with GnRH-a. The meta-analysis showed no evidence of a significant difference in favour of one treatment arm (OR 1.3, 95% CI 0.68 to 2.4; 180 women, three trials) (Analysis 4.2).

Multiple pregnancy rate per pregnancy

Seven studies (Andrés-Oros 2008; Martinez 1991a; Sakhel 2007; Scott 1994; Shalev 1995; Lewis 2006; Lorusso 2008) reported multiple pregnancies. The meta-analysis of two studies (Martinez 1991a; Lewis 2006) revealed no evidence of a statistically significant difference for the comparison hCG versus LH (OR 1.1, 95% CI 0.17 to 7.6; 42 pregnancies, two trials) (Analysis 1.3). Data analysis of two other studies (Lorusso 2008; Sakhel 2007) comparing u-hCG with r-hCG reported no evidence of a significant difference in multiple pregnancy rates either (OR 0.99, 95% CI 0.4 to 2.5; 109 pregnancies, two trials) (Analysis 2.3). The meta-analysis of the studies comparing hCG with GnRH-a (Andrés-Oros 2008; Scott 1994; Shalev 1995) reported three twin pregnancies in the GnRH-a group and none in the hCG group. The analysis showed no evidence of a statistically significant difference (OR 0.15, 95% CI 0.02 to 1.4; 69 pregnancies, three trials) (Analysis 4.3).

Miscarriage rate per pregnancy

Six studies (Andrés-Oros 2008; Lorusso 2008; Martinez 1991a; Sakhel 2007; Scott 1994; Shalev 1995) reported miscarriage rates. Martinez 1991a reported no miscarriages at all. Two studies (Lorusso 2008; Sakhel 2007) comparing r-hCG with u-hCG reported miscarriages per treatment group with no evidence of a statistically significant difference (OR 0.57, 95% CI 0.13 to 2.5; 109 pregnancies, two trials) (Analysis 2.4). The Andrés-Oros 2008, Scott 1994 and Shalev 1995 studies reported 12 miscarriages in total. There was no evidence of a statistically significant difference between the GnRH-a and hCG group (OR 0.84, 95% CI 0.22 to 3.2; 69 pregnancies, three trials) (Analysis 4.4).

OHSS rate per cycle

Four studies (Andrés-Oros 2008; Lorusso 2008; Shalev 1995; Sakhel 2007) reported details on OHSS rate. Both studies (Lorusso 2008; Sakhel 2007) comparing r-hCG with u-hCG reported no cases of (severe) OHSS in a total of 468 cycles. 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. Analysis revealed no evidence of a significant difference between these treatment groups (OR 2.3, 95% CI 0.65 to 7.9; 430 women, two trials) (Analysis 4.5). Finally, Andrés-Oros 2008 reported that no cases of OHSS occurred.

Ectopic pregnancy rate per pregnancy

One study (Sakhel 2007) reported the number of ectopic pregnancies per treatment arm. There was no evidence of a significant difference between u-hCG and r-hCG in ectopic pregnancies (OR 0.92, 95% CI 0.17 to 4.9; 79 pregnancies, one trial) (Analysis 2.5).

Discussion

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 no one of the available methods is superior to another. However, the available evidence is scarce.

hCG injection versus LH surge detection

Although the drop-out rate in the LH surge group was much higher compared to the hCG group (due to no detection of an LH surge in 23% of the cycles) there was no significant difference in live birth and pregnancy rates between these treatment groups (Lewis 2006). No detection of LH surges in urine samples has been reported before, due to a short LH surge or incorrect use of the intervention by the patient (Miller 1996). When counselling patients the advantages of home ovulation predictor tests (no difference in pregnancy outcomes compared to hCG injection, convenience and low costs) and disadvantages (high false-negative results) should be considered in relationship to, on the other hand, the advantages (low 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 percepti-
ble difference between timing with LH surge detection and hCG injection (Cantineau 2007).

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

No evidence of a statistically significant difference in pregnancy rates was found between u-hCG and r-hCG. Other reasons such as costs, injection site reaction, the risk of disease transmission and batch-to-batch inconsistencies should be considered in deciding which to use.

Short (32 to 34 hours) versus long interval (38 to 40 hours)

Retrospective information suggests a broad time interval, from 36 to 48 hours, without any advantage of an early or late hCG to IUI interval. Prospective evidence comparing different hCG to IUI intervals after ovarian stimulation is scarce and only reported as pregnancy rate per cycle. This best available evidence suggests 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).

hCG versus GnRH agonist (GnRH-a)

No statistically significant 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 the timing method with IUI, also considering costs and secondary outcomes such as OHSS rate.

Summary of main results

No evidence of a significant difference in live birth rates and pregnancy rates was found when comparing hCG injection with LH surge detection in cycles with ovarian hyperstimulation combined with IUI. This is the same for the comparison of u-hCG versus r-hCG, short versus longer time interval between hCG and IUI, and hCG versus GnRH-a for timing the insemination. The group sizes were too small to detect significant differences and thus to advise on one particular treatment over another based on this review.

Overall completeness and applicability of evidence

As there was no evidence of benefit for any of the synchronisation methods, no single option could be recommended based on this review. Two studies are still waiting for assessment. One (Propst 2007) reported on the optimal time interval between hCG and IUI. The other (Schmidt-Sarosi 1995) compared a GnRH-a with hCG. Evidence from these studies has to be verified to complete this review. It remains questionable whether definite answers can be given when these data become available.

Quality of the evidence

All the studies had concealed allocation but blinding was not usually applied.

Potential biases in the review process

None

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 no evidence to advise on one of two treatment options (ultrasound combined with hCG injection or LH surge detection in urine) since live births and pregnancy rates do not differ significantly. The choice should be based on hospital facilities, convenience for the patient, medical staff, costs and drop-out levels.

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

Since different time intervals between hCG and IUI did not result in different pregnancy rates a more flexible approach might be allowed.

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 convenience of the treatments.

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

Acknowledgements

Synchronised approach for intrauterine insemination in subfertile couples. (Review)

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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 about the article of Sakhel et al and to Dr Lewis, Dr Andrés Oros, Dr Claman, Dr Scott, Dr Shalev, Dr García-Velasco and Dr Pierson for information on their publications.

REFERENCES

References to studies included in this review

Andrés-Oros 2008 [published and unpublished data]

Claman 2004 [published and unpublished data]

Lewis 2006 [published data only]

Lorusso 2008 [published data only]

Martinez 1991a [published and unpublished data]

Martinez 1991b [published and unpublished data]

Sakhel 2007 [published and unpublished data]

Scott 1994 [published and unpublished data]

Shalev 1995 [published and unpublished data]

Zreik 1999 [published data only]

References to studies excluded from this review

Agarwal 1995 [published data only]

Arici 1994 [published data only]

Baroni 2001 [published data only]

Barratt 1989 [published data only]
Barratt CL, Cooke S, Chauhan M, Cooke ID. A prospective randomized controlled trial comparing urinary luteinizing...

**Cedrin-Durnerin 1993** (published data only)

**Check 1994** (published data only)

**Claman 2000** (published data only)

**Claman 2004a** (published data only)

**Claraz 1989** (published data only)

**Costa Franco 2006** (published data only)

**Diaz 2003a** (published data only)

**Diaz 2003b** (published data only)

**Diaz 2008** (published data only)

**Egbase 2003** (published data only)

**Federman 1990** (published data only)

**Fischer 1993** (published data only)

**Fondop 2005** (published data only)

**George 2007** (published data only)

**Gerris 1995** (published data only)

**Int rhCG study group 2001** (published data only)

**Khattab 2005** (published data only)

**Kossoy 1989** (published data only)
Kotecki 2005 ([published data only])

Lewis 2002 ([published data only])

Lewis 2003 ([published and unpublished data])

Martinez 1994 ([published data only])

Meherji 2004 ([published data only])

Nulsen 1993 ([published data only])

Odem 1991 ([published data only])

Papageorgiou 1995 ([published data only])

Pierson 2002 ([published and unpublished data])

Pirard 2005 ([published data only])

Ragni 1999 ([published data only])

Robinson 1992 ([published data only])

Romeu 1997a ([published data only])

Romeu 1997b ([published data only])

Sakhel 2004 ([published data only])

Scarpellini 1991 ([published data only])

Shanis 1995 ([published data only])

Silverberg 1991 ([published data only])
Silverberg KM, Johnson JV, Olive DL, Schenken RS. A prospective randomized trial to determine the optimal timing of intrauterine insemination following hCG administration after controlled ovarian hyperstimulation. *Fertility and Sterility 1991; 54*:100.

Tavanishtou 2003 ([published data only])

Wang 2001 ([published data only])
References to ongoing studies

Amir Weiss 2009 {unpublished data only}

Additional references

Andersen 1995

Arici 1992

Barratt 1989

Cantineau 2007

Claman 2004

Cohlen 1998

Cohlen 2005

Diaz 2003

Egbase 2002

Fuh 1997

Goverde 2000

Kosmas 2006

Kruger 1993

Lewis 2006

Synchronised approach for intrauterine insemination in subfertile couples. (Review)
Martinez 1991

Miller 1996

Mitwally 2004

Odem 1991

Pierson 2002

Robinson 1992

WHO 1980

WHO 1992

* Indicates the major publication for the study
CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Andrés-Oros 2008

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Participants</td>
<td>120 patients, 290 cycles, at least 2 years of subfertility. Exclusion criteria: patients with PCOS or other cycle disturbances, semen analysis &lt; 5 million after work up. Mean age of women: r-hCG group: 32.2 yrs ± 2.5 and GnRHa group: 32.3 yrs ± 2.5. Type of subfertility: unexplained, endometriosis stage 1 or 2, male factor (WHO 1992), unilateral tubal factor.</td>
</tr>
<tr>
<td>Interventions</td>
<td>GnRH agonist 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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
<tr>
<td>Notes</td>
<td>60 Patients received r-hCG and only 42 patients received GnRH-a. The other 18 patients 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.</td>
</tr>
</tbody>
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Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: &quot;Mediante distribution por numeros aleatorios, por lista de ordenador, las 102 pacientes fueron randomizadas en 2 grupos.&quot;</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Third party</td>
</tr>
</tbody>
</table>
### Andrés-Oros 2008 (Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding? All outcomes</td>
<td>Unclear</td>
<td>Comment: it is not stated if blinding was used.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting? No</td>
<td></td>
<td>Comment: ongoing pregnancy rates and live birth rates were not stated</td>
</tr>
<tr>
<td>Free of other bias? Yes</td>
<td></td>
<td></td>
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</tbody>
</table>

### Claman 2004

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
<td>Single centre, parallel design with random number table. Concealment of allocation: third party</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No blinding used. Duration of the study and follow up not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Power calculation: sample size of 190 with a power of 0.8 to detect an increase in pregnancy rate from 15-30% between groups with an alpha of .05. ITT: no</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td>75 women, 189 cycles, &gt; 2 years subfertility. Exclusion criteria: cycles with endogenous LH surge.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age of women: short hCG-IUI interval: 34.4 yrs ± 3.6 and long hCG-IUI interval: 34.3 yrs ± 3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type of subfertility: unexplained, endometriosis stage 1 or 2, male factor (WHO 1992), clomiphene resistant oligo-ovulation, or combination of factors</td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
<td>Stimulation method: 100-225 IU FSH, 5,000 IU hCG IM or 10,000 IU hCG SC IUI either 32-34 hours or 38-40 hours after injection of hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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 media</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insemination procedure: Tomcat catheter high up in the uterine fundus, one insemination per cycle</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td>Pregnancy rate per cycle: 20/96 (20%) short interval, 14/93 (15%) long interval group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary outcomes not stated. Pregnancy diagnosed: transvaginal ultrasound demonstrating heart activity</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
<td>Inclusion of patients with oligo-ovulation. Setting: Division of Reproductive Medicine, Department of Obstetrics and Gynecology, The Ottawa Hospital. Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No funding.</td>
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### Risk of bias

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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Comment by Claman: a nurse in the clinical care team picked the next random number in the table and crossed it. The random numbers where thus assigned sequentially.</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Third party</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Comment by Claman: the patient and the nurse knew the scheduled time for IUI to be either 33 or 39 hours post HCG.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Quote: “There were 96 completed cycles in the short hCG-IUI interval and 93 in the long hCG-IUI interval groups.” Comment: the outcome data for all these patients is well known.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Comment: ongoing pregnancy rates and live birth rates were not stated. Secondary outcomes were not stated.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**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/pelvic factor.

**Interventions**
- Stimulation method: 100mg 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 33-42 hours later.
- Husband semen and probably donor semen.
- Insemination procedure: not stated. One insemination per cycle.
Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate per couple: LH surge group 25% and hCG group: 31%</td>
<td>Multiple pregnancy rate per couple: LH surge group 11.1% and hCG group: 12.9%.</td>
</tr>
<tr>
<td>Miscarriage rate per couple: LH surge group: 34% and hCG group: 18%</td>
<td>Costs: stated in the abstract. Cost per pregnancy LH group USD3695; cost per pregnancy hCG group USD4830</td>
</tr>
<tr>
<td>Pregnancy diagnosed: rising concentration of hCG. Viable pregnancy is defined as a fetal pole with heart activity by ultrasound</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “Randomization order was assigned by computer program and took place at the time of the baseline ultrasound visit.”</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Third party</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Unclear</td>
<td>Quote: “Treatment group assignment was not known to the patient or treating physician until after informed consent was obtained and the baseline ultrasound was performed.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: from then the study could not be blinded since one group used urine LH testing and the other group received an injection with hCG</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>No</td>
<td>Comment: 2 patients were lost to follow up.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Comment: ongoing pregnancy rates and live birth rates were not stated</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
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 patients 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 2-3 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%. 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

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
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<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: &quot;Patients were randomized to receive rhCG or uhCG by a computer gen-</td>
</tr>
</tbody>
</table>

Synchronised approach for intrauterine insemination in subfertile couples. (Review)
Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Allocation concealment?</th>
<th>Yes</th>
<th>Sealed opaque envelopes.</th>
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<tr>
<td>Blinding?</td>
<td>Unclear</td>
<td>Comment: it is not stated if blinding was used.</td>
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<tr>
<td>All outcomes</td>
<td></td>
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<td>Comment: all outcome data is available of the started cycles</td>
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<td>All outcomes</td>
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<td>No</td>
<td>Comment: ongoing pregnancy rates and live birth rates were not stated</td>
</tr>
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<td></td>
<td></td>
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</tbody>
</table>

### 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
- Type of subfertility: male or idiopathic.

**Interventions**
- Stimulation method: 75-150 IU hMG IM.
- LH surge group: u-LH detection kit two times a day, IUI 16-28 hours after a positive test. hCG group: 10,000 IU hCG, IUI after 36-40 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
### Martinez 1991a (Continued)

#### Risk of bias

<table>
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<tr>
<th>Item</th>
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<td>Comment: not stated.</td>
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<tr>
<td>Allocation concealment?</td>
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<td>Sealed envelopes.</td>
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<tr>
<td>Blinding?</td>
<td>No</td>
<td>Comment: it is not stated if blinding was used. But it seemed to us that there was no blinding since one group used urine-LH home monitoring and the other group used ultrasound monitoring and hCG administration</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>No</td>
<td>In the hCG group 8/48 patients dropped out and 7/48 in the LH group</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Comment: no multiple pregnancy rates stated.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**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: $31.2 \pm 3.8$ yrs for the total group of women
- Mean duration of subfertility: $5.6 \pm 2.6$ 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 21-24 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

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
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<tr>
<td>Allocation concealment?</td>
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<tr>
<td>Blinding? All outcomes</td>
<td>No</td>
<td>Comment: it is not stated if blinding was used. But it seemed to us that there was no blinding since one group used urine-LH home monitoring and the other group used ultrasound monitoring and hCG administration</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Comment: of all included cycles the outcome data was available</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>Comment: both live birth rate and pregnancy rate was stated.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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 drop outs or cycle cancellations were reported

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,
Sakhel 2007 (Continued)

Interventions
Stimulation method: 75-150 IU FSH and hMG, GnRH antagonist. IUI 42 hours after injection of 10,000 IU u-hCG or 250mg 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

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Adequate sequence generation?</td>
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<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Sealed opaque envelopes.</td>
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<tr>
<td>Blinding?</td>
<td>Unclear</td>
<td>Comment: it is not stated if blinding was used.</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Unclear</td>
<td>Comment: it is not stated if blinding was used.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td>Comment: of all included cycles the outcome data was available</td>
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<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>Comment: live birth rate, pregnancy rate and all adverse outcomes were stated</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Comment: the included women in the u-hCG group had a greater mean duration of infertility than the r-hCG group</td>
</tr>
</tbody>
</table>
**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 patient 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 100mg orally each day, from cycle day 5-9

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

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**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “The patients were randomized to receive either LA or hCG in their first cycles.”</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Sealed envelopes</td>
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<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Quote: “The sonologists were blinded to which treatment the patients had received to minimize the risk of observer bias.”</td>
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<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Comment: of all included cycles the outcome data was available</td>
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<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Comment: secondary adverse outcomes not stated.</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

### 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. 0.1 mg triptorelin or 10,000 IU hCG, IUI 24 and 48 hours after injection
- 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 10^6/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, 18.2% GnRH-a group
- Miscarriage rate: 33.3% hCG group, 18.2% 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

**Scott 1994**

(Continued)
### Shalev 1995

(Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Comment: randomisation was performed using a self made computer program. Adequate sequence generation not stated</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Third party.</td>
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<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Comment: Shalev wrote in reaction to an email we sent that the study was blinded. Not further specified</td>
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<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Comment: of all included cycles the outcome data was available</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>Comment: live birth rate, pregnancy rate and all adverse outcomes were stated</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

### Zreik 1999

<table>
<thead>
<tr>
<th>Methods</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>54 women, 53 first cycles. Inclusion criteria: normal hysterosalpingography, a normal endometrium biopsy, history of CC use of &lt; 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.</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
</tbody>
</table>
Notes       Cross-over study design. Only the first cycle pre cross-over data were used. Inclusion of 15 patients with anovulation. Pregnancy rate very low
Setting: Yale Reproductive Medicine Center, New Haven, Connecticut, USA
No funding stated.

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
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<tbody>
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<td>Comment: not stated.</td>
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<td>Allocation concealment?</td>
<td>Yes</td>
<td>Third party since the assignment was not known to the treating physician or the patient</td>
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<td>Blinding?</td>
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<td>Yes</td>
<td>Comment: of all 54 first cycle treatment the outcome data was available</td>
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<td>No</td>
<td>Comment: ongoing pregnancy rates and live birth rates were not stated. Secondary adverse outcomes not stated</td>
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<td>Free of other bias?</td>
<td>Yes</td>
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### Characteristics of excluded studies  [ordered by study ID]

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<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Agarwal 1995</td>
<td>Retrospective study.</td>
</tr>
<tr>
<td>Arici 1994</td>
<td>Compared stimulated with non-stimulated cycles. Double and single insemination used</td>
</tr>
<tr>
<td>Baroni 2001</td>
<td>Compared different timing methods at different follicle sizes at different times to IUI</td>
</tr>
<tr>
<td>Barratt 1989</td>
<td>Endocervical and peri cervical insemination.</td>
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<tr>
<td>Cedrin-Durnerin 1993</td>
<td>Quasi-randomised trial.</td>
</tr>
<tr>
<td>Check 1994</td>
<td>Prospective non-randomized study.</td>
</tr>
<tr>
<td>Claman 2000</td>
<td>Abstract of an included study.</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Claman 2004a</td>
<td>Abstract of an included study.</td>
</tr>
<tr>
<td>Claraz 1989</td>
<td>Intracervical insemination.</td>
</tr>
<tr>
<td>Costa Franco 2006</td>
<td>Retrospective study design.</td>
</tr>
<tr>
<td>Diaz 2003a</td>
<td>Inadequate randomisation; random numbers in an open list.</td>
</tr>
<tr>
<td>Diaz 2003b</td>
<td>Abstract of an excluded study.</td>
</tr>
<tr>
<td>Diaz 2008</td>
<td>Inadequate randomisation; random numbers in an open list. Same study as Diaz 2003a.</td>
</tr>
<tr>
<td>Egbase 2003</td>
<td>Inclusion of PCOS women only.</td>
</tr>
<tr>
<td>Federman 1990</td>
<td>Comparing single versus double insemination. Cross-over study</td>
</tr>
<tr>
<td>Fischer 1993</td>
<td>Investigates the time interval from hCG administration to follicular wall rupture</td>
</tr>
<tr>
<td>Fondop 2005</td>
<td>Cohort study.</td>
</tr>
<tr>
<td>George 2007</td>
<td>Timed intercourse.</td>
</tr>
<tr>
<td>Gerris 1995</td>
<td>Prospective non-randomised study.</td>
</tr>
<tr>
<td>Int rhCG study group 2001</td>
<td>Included anovulatory patients only. Used both IUI and timed intercourse.</td>
</tr>
<tr>
<td>Khattab 2005</td>
<td>Retrospective study design.</td>
</tr>
<tr>
<td>Kossoy 1989</td>
<td>Cohort study.</td>
</tr>
<tr>
<td>Kotecki 2005</td>
<td>Comparison of five different ovarian stimulation protocols.</td>
</tr>
<tr>
<td>Lewis 2002</td>
<td>Abstract of an included study.</td>
</tr>
<tr>
<td>Lewis 2003</td>
<td>Abstract of an included study.</td>
</tr>
<tr>
<td>Martinez 1994</td>
<td>Retrospective study.</td>
</tr>
<tr>
<td>Meherji 2004</td>
<td>Commentary report.</td>
</tr>
<tr>
<td>Odem 1991</td>
<td>Quasi randomized trial. Insemination through cervical cap.</td>
</tr>
<tr>
<td>Papageorgiou 1995</td>
<td>Comparing stimulated with non stimulated cycles.</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pierson 2002</td>
<td>Dose finding study.</td>
</tr>
<tr>
<td>Pirard 2005</td>
<td>Investigated the luteal support between hCG triggered cycles and GnRHa administered cycles</td>
</tr>
<tr>
<td>Ragni 1999</td>
<td>Compared a single peri ovulatory IUI with two double-IUI regimes</td>
</tr>
<tr>
<td>Robinson 1992</td>
<td>Inclusion of donor insemination only.</td>
</tr>
<tr>
<td>Romeu 1997a</td>
<td>Prospective non-randomised trial.</td>
</tr>
<tr>
<td>Romeu 1997b</td>
<td>Failure to use a truly randomized design.</td>
</tr>
<tr>
<td>Sakhel 2004</td>
<td>Abstract of an included study.</td>
</tr>
<tr>
<td>Scarpellini 1991</td>
<td>Also comparing IUI with timed intercourse.</td>
</tr>
<tr>
<td>Shanis 1995</td>
<td>Not truly randomized.</td>
</tr>
<tr>
<td>Silverberg 1991</td>
<td>Comparing single versus double insemination.</td>
</tr>
<tr>
<td>Tavaniotou 2003</td>
<td>Cohort study.</td>
</tr>
<tr>
<td>Wang 2006</td>
<td>Ovulation induction at different follicle sizes.</td>
</tr>
</tbody>
</table>

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

**Propst 2007**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicenter randomised study with a parallel design.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>206 subfertile couples</td>
</tr>
<tr>
<td>Interventions</td>
<td>Single IUI either 12 or 36 hours after receiving hCG.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pregnancy rate per couple: 12 hour group: 27/100 (27%), 36 hour group: 32/102 (31.4%)</td>
</tr>
<tr>
<td>Notes</td>
<td>Randomisation method not clear, concealment of allocation not clear</td>
</tr>
</tbody>
</table>
Schmidt-Sarosi 1995

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective randomised comparison of nafarelin versus hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>26 women</td>
</tr>
<tr>
<td>Interventions</td>
<td>Two doses of 400 ug nafarelin intranasal (IN) versus 5000 IU hCG IM injection. Luteal support was given with nafarelin or hCG in each group</td>
</tr>
<tr>
<td>Notes</td>
<td>Concealment of allocation not stated. Not only trigger for ovulation is compared, but also the luteal support is different</td>
</tr>
</tbody>
</table>

Characteristics of ongoing studies [ordered by study ID]

Amir Weiss 2009

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Optimal Timing of intrauterine insemination (IUI) When Utilizing Superovulation Combined With GnRH Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomized open three arm prospective trial to determine the optimal timing for intrauterine insemination after superovulation With Recombinant Gonadotropins utilizing GnRH Antagonists</td>
</tr>
<tr>
<td>Participants</td>
<td>Women with infertility who are candidates for controlled ovarian stimulation and intrauterine insemination. Including ovulatory disorders, male factor, partial mechanical factor, endometriosis, unexplained infertility</td>
</tr>
<tr>
<td>Interventions</td>
<td>IUI 36 hours after ovulation, IUI 42 hours after ovulation, IUI 48 hours after ovulation</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary Outcome Measures: Achieving pregnancy [Time Frame: two weeks after intervention ]</td>
</tr>
<tr>
<td>Starting date</td>
<td>Not stated</td>
</tr>
<tr>
<td>Contact information</td>
<td>Amir Weiss, MD, HaEmek Medical Center, Israel</td>
</tr>
<tr>
<td>Notes</td>
<td>34Synchronised approach for intrauterine insemination in subfertile couples. (Review)</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. hCG versus LH surge

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

### Comparison 2. u-hCG versus r-hCG

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 live birth rate per couple</td>
<td>1</td>
<td>284</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.17 [0.68, 2.03]</td>
</tr>
<tr>
<td>2 pregnancy rate per couple</td>
<td>2</td>
<td>409</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.02 [0.65, 1.57]</td>
</tr>
<tr>
<td>3 multiple pregnancy rate per pregnancy</td>
<td>2</td>
<td>109</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.99 [0.40, 2.47]</td>
</tr>
<tr>
<td>4 miscarriage rate per pregnancy</td>
<td>2</td>
<td>109</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.57 [0.13, 2.47]</td>
</tr>
<tr>
<td>5 ectopic pregnancy rate per pregnancy</td>
<td>1</td>
<td>79</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.92 [0.17, 4.87]</td>
</tr>
<tr>
<td>6 OHSS rate per cycle</td>
<td>2</td>
<td>468</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

### Comparison 3. short versus long interval

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pregnancy rate per cycle</td>
<td>1</td>
<td>189</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.48 [0.70, 3.15]</td>
</tr>
</tbody>
</table>
### Comparison 4. hCG versus GnRH-a

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 live birth rate per couple</td>
<td>2</td>
<td>78</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.42, 3.07]</td>
</tr>
<tr>
<td>2 pregnancy rate per couple</td>
<td>3</td>
<td>180</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.27 [0.68, 2.40]</td>
</tr>
<tr>
<td>3 multiple pregnancy rate per pregnancy</td>
<td>3</td>
<td>69</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.15 [0.02, 1.38]</td>
</tr>
<tr>
<td>4 miscarriage rate per pregnancy</td>
<td>3</td>
<td>69</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.84 [0.22, 3.19]</td>
</tr>
<tr>
<td>5 OHSS per cycle</td>
<td>2</td>
<td>430</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.27 [0.65, 7.91]</td>
</tr>
</tbody>
</table>

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

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: hCG versus LH surge

Outcome: 1 live birth rate per couple

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>LH surge n/N</th>
<th>Odds Ratio M-H(Fixed, 95% CI)</th>
<th>Weight 100.0 %</th>
<th>Odds Ratio M-H(Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez 1991a</td>
<td>1/12</td>
<td>1/12</td>
<td>1.00 [0.06, 18.08]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>12</strong></td>
<td><strong>12</strong></td>
<td><strong>1.00 [0.06, 18.08]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (hCG), 1 (LH surge)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable
### Analysis 1.2. Comparison of hCG versus LH surge, Outcome 2 pregnancy rate per couple.

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 1 hCG versus LH surge

**Outcome:** 2 pregnancy rate per couple

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>LH surge n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis 2006</td>
<td>23/75</td>
<td>17/75</td>
<td>1.51 [0.73, 3.13]</td>
<td>66.0%</td>
<td>1.51 [0.73, 3.13]</td>
</tr>
<tr>
<td>Martinez 1991a</td>
<td>1/12</td>
<td>1/12</td>
<td>1.00 [0.06, 18.08]</td>
<td>5.1%</td>
<td>1.00 [0.06, 18.08]</td>
</tr>
<tr>
<td>Martinez 1991b</td>
<td>4/24</td>
<td>5/24</td>
<td>0.76 [0.18, 3.26]</td>
<td>23.3%</td>
<td>0.76 [0.18, 3.26]</td>
</tr>
<tr>
<td>Zreik 1999</td>
<td>2/28</td>
<td>1/25</td>
<td>1.85 [0.16, 21.69]</td>
<td>5.5%</td>
<td>1.85 [0.16, 21.69]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>139</td>
<td>136</td>
<td>1.33 [0.72, 2.45]</td>
<td>100.0%</td>
<td>1.33 [0.72, 2.45]</td>
</tr>
</tbody>
</table>

Total events: 30 (hCG), 24 (LH surge)

Heterogeneity: Chi² = 0.79, df = 3 (P = 0.85); I² =0.0%

Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable

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

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 1 hCG versus LH surge

**Outcome:** 3 multiple pregnancy rate per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>LH surge n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis 2006</td>
<td>3/23</td>
<td>2/17</td>
<td>1.13 [0.17, 7.60]</td>
<td>100.0%</td>
<td>1.13 [0.17, 7.60]</td>
</tr>
<tr>
<td>Martinez 1991a</td>
<td>0/1</td>
<td>0/1</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>24</td>
<td>18</td>
<td>1.13 [0.17, 7.60]</td>
<td>100.0%</td>
<td>1.13 [0.17, 7.60]</td>
</tr>
</tbody>
</table>

Total events: 3 (hCG), 2 (LH surge)

Heterogeneity: Not applicable

Test for overall effect: Z = 0.12 (P = 0.90)

Test for subgroup differences: Not applicable
Analysis 2.1. Comparison 2 u-hCG versus r-hCG, Outcome 1 live birth rate per couple.

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 2 u-hCG versus r-hCG

Outcome: 1 live birth rate per couple

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>u-hCG n/N</th>
<th>r-hCG n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakhel 2007</td>
<td>36/144</td>
<td>31/140</td>
<td>1.17 [0.68, 2.03]</td>
<td>100.0 %</td>
<td>1.17 [0.68, 2.03]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>144</strong></td>
<td><strong>140</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.17 [0.68, 2.03]</strong></td>
</tr>
</tbody>
</table>

Total events: 36 (u-hCG), 31 (r-hCG)
Heterogeneity: not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable
Analysis 2.2. Comparison 2 u-hCG versus r-hCG, Outcome 2 pregnancy rate per couple.

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 2 u-hCG versus r-hCG

Outcome: 2 pregnancy rate per couple

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>u-hCG n/N</th>
<th>r-hCG n/N</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorusso 2008</td>
<td>14/61</td>
<td>16/64</td>
<td>0.89 [ 0.39, 2.03 ]</td>
<td>30.4 %</td>
<td></td>
</tr>
<tr>
<td>Sakhel 2007</td>
<td>41/144</td>
<td>38/140</td>
<td>1.07 [ 0.64, 1.80 ]</td>
<td>69.6 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>205</strong></td>
<td><strong>204</strong></td>
<td></td>
<td>100.0 %</td>
<td>1.02 [ 0.65, 1.57 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 = 0.0%

Test for overall effect: Z = 0.07 (P = 0.95)

Test for subgroup differences: Not applicable

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

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 2 u-hCG versus r-hCG

Outcome: 3 multiple pregnancy rate per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>u-hCG n/N</th>
<th>r-hCG n/N</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorusso 2008</td>
<td>0/14</td>
<td>0/16</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sakhel 2007</td>
<td>15/41</td>
<td>14/38</td>
<td>1.00 [ 0.40, 2.47 ]</td>
<td>100.0 %</td>
<td>0.99 [ 0.40, 2.47 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>55</strong></td>
<td><strong>54</strong></td>
<td></td>
<td>100.0 %</td>
<td>0.99 [ 0.40, 2.47 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable
Analysis 2.4. Comparison 2 u-hCG versus r-hCG, Outcome 4 miscarriage rate per pregnancy.

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 2 u-hCG versus r-hCG

Outcome: 4 miscarriage rate per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>u-hCG</th>
<th>r-hCG</th>
<th>Odds Ratio (Fixed, 95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorussi 2008</td>
<td>1/14</td>
<td>1/16</td>
<td>1.15 [0.07, 20.34]</td>
<td>18.0%</td>
</tr>
<tr>
<td>Sakhel 2007</td>
<td>2/41</td>
<td>4/38</td>
<td>0.44 [0.08, 2.53]</td>
<td>82.0%</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>54</td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 3 (u-hCG), 5 (r-hCG)
Heterogeneity: Chi$^2 = 0.32$, df = 1 (P = 0.57); I$^2$ = 0.0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 u-hCG versus r-hCG, Outcome 5 ectopic pregnancy rate per pregnancy.

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 2 u-hCG versus r-hCG

Outcome: 5 ectopic pregnancy rate per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>u-hCG</th>
<th>r-hCG</th>
<th>Odds Ratio (Fixed, 95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakhel 2007</td>
<td>3/41</td>
<td>3/38</td>
<td>0.92 [0.17, 4.87]</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>38</td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 3 (u-hCG), 3 (r-hCG)
Heterogeneity: not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable
### Analysis 2.6. Comparison 2 u-hCG versus r-hCG, Outcome 6 OHSS rate per cycle.

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 2 u-hCG versus r-hCG

**Outcome:** 6 OHSS rate per cycle

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>u-hCG n/N</th>
<th>r-hCG n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorusso 2008</td>
<td>0/88</td>
<td>0/96</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Sakhel 2007</td>
<td>0/144</td>
<td>0/140</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>232</strong></td>
<td><strong>236</strong></td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (u-hCG), 0 (r-hCG)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

### Analysis 3.1. Comparison 3 short versus long interval, Outcome 1 pregnancy rate per cycle.

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 3 short versus long interval

**Outcome:** 1 pregnancy rate per cycle

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>short n/N</th>
<th>long n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claman 2004</td>
<td>20/96</td>
<td>14/93</td>
<td>1.48 [0.70, 3.15]</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>96</strong></td>
<td><strong>93</strong></td>
<td>1.48 [0.70, 3.15]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 20 (short), 14 (long)
Heterogeneity: not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable
### Analysis 4.1. Comparison 4 hCG versus GnRH-a, Outcome 1 live birth rate per couple.

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 4 hCG versus GnRH-a

**Outcome:** 1 live birth rate per couple

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>GnRH-a n/N</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott 1994</td>
<td>1/15</td>
<td>3/15</td>
<td></td>
<td>38.4%</td>
<td>0.29 [0.03, 3.12]</td>
</tr>
<tr>
<td>Shalev 1995</td>
<td>12/24</td>
<td>9/24</td>
<td></td>
<td>61.6%</td>
<td>1.67 [0.53, 5.27]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>39</strong></td>
<td><strong>39</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.14 [0.42, 3.07]</strong></td>
</tr>
</tbody>
</table>

Total events: 13 (hCG), 12 (GnRH-a)

Heterogeneity: $\chi^2 = 1.71$, df = 1 (P = 0.19); $I^2 = 41$

Test for overall effect: Z = 0.25 (P = 0.80)

Test for subgroup differences: Not applicable

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

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 4 hCG versus GnRH-a

**Outcome:** 2 pregnancy rate per couple

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>GnRH-a n/N</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrés-Oros 2008</td>
<td>21/60</td>
<td>15/42</td>
<td></td>
<td>67.4%</td>
<td>0.97 [0.42, 2.21]</td>
</tr>
<tr>
<td>Scott 1994</td>
<td>1/15</td>
<td>3/15</td>
<td></td>
<td>16.5%</td>
<td>0.29 [0.03, 3.12]</td>
</tr>
<tr>
<td>Shalev 1995</td>
<td>18/24</td>
<td>11/24</td>
<td></td>
<td>16.2%</td>
<td>3.55 [1.04, 12.06]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>99</strong></td>
<td><strong>81</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.27 [0.68, 2.40]</strong></td>
</tr>
</tbody>
</table>

Total events: 40 (hCG), 29 (GnRH-a)

Heterogeneity: $\chi^2 = 4.61$, df = 2 (P = 0.10); $I^2 = 57$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable
### Analysis 4.3. Comparison 4 hCG versus GnRH-a, Outcome 3 multiple pregnancy rate per pregnancy.

**Review:** Synchronised approach for intrauterine insemination in subfertile couples.

**Comparison:** 4 hCG versus GnRH-a

**Outcome:** 3 multiple pregnancy rate per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>GnRH-a n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andr ́s-Oros 2008</td>
<td>0/21</td>
<td>1/15</td>
<td></td>
<td>36.3</td>
<td>0.22 [ 0.01, 5.91 ]</td>
</tr>
<tr>
<td>Scott 1994</td>
<td>0/1</td>
<td>0/3</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Shalev 1995</td>
<td>0/18</td>
<td>2/11</td>
<td></td>
<td>63.7</td>
<td>0.10 [ 0.00, 2.36 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>40</strong></td>
<td><strong>29</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>0.15 [ 0.02, 1.38 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 0 (hCG), 3 (GnRH-a)

Heterogeneity: $\chi^2 = 0.12$, df = 1 ($P = 0.73$); $I^2 = 0.0$

Test for overall effect: $Z = 1.68$ ($P = 0.094$)

Test for subgroup differences: Not applicable

---

Synchronised approach for intrauterine insemination in subfertile couples. (Review)

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

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 4 hCG versus GnRH-a

Outcome: 4 miscarriage rate per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>GnRH-a n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrés-Oros 2008</td>
<td>3/21</td>
<td>1/15</td>
<td></td>
<td></td>
<td>21.2 % 2.33 [0.22, 24.92]</td>
</tr>
<tr>
<td>Scott 1994</td>
<td>0/1</td>
<td>0/3</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Shalev 1995</td>
<td>2/11</td>
<td>6/18</td>
<td></td>
<td></td>
<td>78.8 % 0.44 [0.07, 2.74]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>33</strong></td>
<td><strong>36</strong></td>
<td></td>
<td></td>
<td><strong>100.0 % 0.84 [0.22, 3.19]</strong></td>
</tr>
</tbody>
</table>

Total events: 5 (hCG), 7 (GnRH-a)

Heterogeneity: Chi² = 1.19, df = 1 (P = 0.28); I² =16%

Test for overall effect: Z = 0.25 (P = 0.80)

Test for subgroup differences: Not applicable

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

Review: Synchronised approach for intrauterine insemination in subfertile couples.

Comparison: 4 hCG versus GnRH-a

Outcome: 5 OHSS per cycle

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>hCG n/N</th>
<th>GnRH-a n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrés-Oros 2008</td>
<td>0/158</td>
<td>0/132</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Shalev 1995</td>
<td>8/68</td>
<td>4/72</td>
<td></td>
<td></td>
<td>100.0 % 2.27 [0.65, 7.91]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>226</strong></td>
<td><strong>204</strong></td>
<td></td>
<td></td>
<td><strong>100.0 % 2.27 [0.65, 7.91]</strong></td>
</tr>
</tbody>
</table>

Total events: 8 (hCG), 4 (GnRH-a)

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

---

Synchronised approach for intrauterine insemination in subfertile couples. (Review)

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Table 1. Characteristics of studies not included in the meta-analysis

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single centre, parallel design with random number table. Concealment of allocation: third party. No blinding used. Follow up not stated. Power calculation: sample size of 190 with a power of 0.8 to detect an increase in pregnancy rates from 15-30% between groups with an alpha of .05. ITT: no. Duration not stated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 women, 189 cycles, &gt; 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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation method: 100-225 IU FSH, 5,000 IU hCG IM or 10,000 IU hCG SC IUI either 32-34 hours or 38-40 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 media Insemination procedure: Tomcat catheter high up in the uterine fundus, one insemination per cycle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate per cycle: 20% short interval, 15% long interval group Secondary outcomes not stated. Pregnancy diagnosed: transvaginal ultrasound demonstrating heart activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion of patients with oligo-ovulation. Setting: Division of Reproductive Medicine, Department of Obstetrics and Gynecology, The Ottawa Hospital. Canada No funding.</td>
</tr>
</tbody>
</table>

Appendix 1. Search string

MEDLINE
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)
Synchronised approach for intrauterine insemination in subfertile couples. (Review)

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WHAT'S NEW

Last assessed as up-to-date: 5 July 2009.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 July 2009</td>
<td>Amended</td>
<td>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</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 4, 2010

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 November 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

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

Mirjam Janssen:
- writing the protocol;
- performing search, selection of articles;
- reviewing articles for inclusion;
- substantial contribution writing review.

Ben Cohlen:
- formulation of research question;
critical view on protocol;

arbitration with reviewing the articles;

substantial contribution writing review.

**DECLARATIONS OF INTEREST**

None known for any of the review authors.

**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.

The protocol defined 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 drop-out rates and cancelled cycles were accepted.

The first author of the protocol was MJ Janssen. The first author of the review has changed to AEP Cantineau.

**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