Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

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[Intervention Review]

Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

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ABSTRACT

Background

Intrauterine insemination (IUI) combined with ovarian hyperstimulation (OH) has been demonstrated to be an effective form of treatment for subfertile couples. Several ovarian stimulation protocols combined with IUI have been proposed, but it is still not clear which stimulation protocol and which dose is the most (cost-)effective.

Objectives

To evaluate ovarian stimulation protocols for intrauterine insemination for all indications.

Search methods

We searched for all publications which described randomised controlled trials comparing different ovarian stimulation protocols followed by IUI . We searched the Menstrual Disorders and Subfertility Group's Central register of Controlled Trials (CENTRAL) . We searched the electronic databases of MEDLINE (January 1966 to present) and EMBASE (1980 to present).

Selection criteria

Randomised controlled trials only were considered for inclusion in this review. Trials comparing different ovarian stimulation protocols combined with IUI were selected and reviewed in detail.

Data collection and analysis

Two independent review authors independently assess trial quality and extracted data.

Main results

Forty three trials involving 3957 women were included. There were 11 comparisons in this review. Pregnancy rates are reported here since results of live birth rates were lacking.

Seven studies (n = 556) were pooled comparing gonadotrophins with anti-oestrogens showing significant higher pregnancy rates with gonadotrophins (OR 1.8, 95% CI 1.2 to 2.7). Five studies (n = 313) compared anti-oestrogens with aromatase inhibitors reporting

no significant difference (OR 1.2 95% CI 0.64 to 2.1). The same could be concluded comparing different types of gonadotrophins (9 studies included, n = 576). Four studies (n = 415) reported that gonadotrophins alone are more effective than with the addition of a GnRH agonist (OR 1.8 95% CI 1.1 to 3.0). Data of three studies (n = 299) showed no convincing evidence of adding a GnRH antagonist to gonadotrophins (OR 1.5 95% CI 0.83 to 2.8). The results of two studies (n = 297) reported no evidence of benefit in doubling the dose of gonadotrophins (OR 1.2 95% 0.67 to 1.9) although the multiple pregnancy rates and OHSS rates were increased. For the remaining five comparisons only one or none studies were included.

Authors' conclusions

Robust evidence is lacking but based on the available results gonadotrophins might be the most effective drugs when IUI is combined with ovarian hyperstimulation. When gonadotrophins are applied it might be done on a daily basis. When gonadotrophins are used for ovarian stimulation low dose protocols are advised since pregnancy rates do not differ from pregnancy rates which result from high dose regimen, whereas the chances to encounter negative effects from ovarian stimulation such as multiples and OHSS are limited with low dose gonadotrophins. Further research is needed for each comparison made.

PLAIN LANGUAGE SUMMARY

Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Intrauterine insemination (IUI) is an assisted reproduction procedure that places sperm directly into the uterus. Additionally, medication (hormones) are given to hyper stimulate the ovaries, which results most of the time in the release of more eggs which can be fertilized and this in turn, results in higher pregnancy rates, but also in a higher number of multiple pregnancies.

Forty three trials involving 3957 women were included. The review compared different drugs for ovarian hyperstimulation showing that injections result in higher pregnancy rates compared with oral medication. However, the evidence for this result is not very strong. Furthermore, it showed that if stimulation is used it might be done with low dose injections, since multiple pregnancy rates were increased with high dose injections, without resulting in more pregnancies. This review does not show which injection should be used, since there is no convincing evidence of a difference. Finally, this review does not answer the question whether the addition of GnRH agonist or antagonist is useful.

BACKGROUND

Worldwide, intrauterine insemination (IUI), is one of the most frequently used fertility treatments for couples with unexplained or male subfertility (Cohlen 2005; Goverde 2000). A systematic review of randomised controlled trials (RCTs) comparing IUI with timed intercourse reported a three fold increase in the probability of conception with IUI for couples with persistent infertility (Hughes 1997). IUI is often combined with ovarian hyperstimulation (OH) to increase the number of available oocytes and therefore, to further enhance the probability of conception. The use of OH may also correct subtle cycle disorders and allows for optimal timing of the insemination. The use of gonadotrophins to achieve OH for IUI cycles has been shown to be an effective treatment modality for couples with unexplained subfertility compared with IUI in natural cycles (OR 2.4, 95% CI 1.4 to 3.9) (Hughes 1997). A more recent systematic review suggests that ovarian stimulation and IUI is more likely to result in a live birth than IUI in natural cycles (OR 2.0, 95% CI 2.0 to 3.5) (Verhulst 2006). For severe male subfertility (total motile sperm count < 10 million) IUI is more effective compared with timed intercourse, although the benefit of additional ovarian stimulation in these couples has not been proven. On the other hand, OH does seem to improve pregnancy rates in couples with a mild semen defect (total motile sperm count > 10 million) (Cohlen 1997). Mild endometriosis in women with no other cause of infertility is often considered to be comparable to unexplained infertility and in these couples stimulated IUI has been recommended although it is uncertain whether or not un stimulated IUI may also be beneficial (NICE Guidelines 2004).

However, OH is associated with an increased risk of multiple pregnancies, which in turn increases maternal risks, preterm delivery

and perinatal morbidity and mortality. Increasingly, trialists are being encouraged to report BESST (Birth Emphasizing a Successful Singleton at Term) as the primary outcome (Min 2004). Bearing this in mind, it is important that protocols for IUI in combination with OH seek to keep multiple pregnancies to a minimum (Cohlen 2005). Another major adverse event with gonadotrophins is the probability of achieving ovarian hyperstimulation syndrome (OHSS) (Derman 1994). Adverse effects to consider with oral ovarian stimulation protocols are: hot flushes, visual disturbances, anti-oestrogenic effects on the endometrium and cervical mucus.

The benefits of oral ovarian stimulation agents are their convenience and their low cost, although it has been suggested that they are less effective for IUI (Hughes 1997;s Cohlen 1997). Several RCTs have been published that compared oral versus injection agents, but most of them lack sufficient power to draw firm conclusions (Athaullah 2002). Recently, a new oral drug has been added to the armamentarium of ovarian stimulating drugs: aromatase-inhibitors. Gonadotrophin releasing hormone analogues (GnRH-analogue) have also been used in protocols for ovarian stimulation. More recently, gonadotrophin releasing hormone antagonists (GnRH antagonist) have been proposed in IUI programs as an alternative to GnRH agonists (Ragni 2004).

Finally, various dosages of ovarian stimulation agents are being used in order to optimise pregnancy rates, while reducing the number of multiple pregnancies. For example, 150 IU of follicle stimulating hormone (FSH) was associated with a multiple pregnancy rate of 27% (Guzick 1999), whereas other studies that used a lower dose of FSH (50-75 IU) reported singleton pregnancies only (Balasch 1994; Ragni 2004).

In conclusion, the optimal ovarian stimulation protocol should maximise the probability of conception (ideally expressed as singleton live birth at term) and in the mean time minimise the risk of multiple pregnancies and the occurrence of OHSS.

OBJECTIVES

To evaluate ovarian stimulation protocols preceding intrauterine insemination in couples with various causes of subfertility (e.g. unexplained subfertility, male factor subfertility and endometriosis).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials only were considered for inclusion in this review. Trials with a cross-over design were included only in the analysis if first cycle data were available. Quasi-randomised controlled trials were excluded.

Types of participants

Couples who have been trying to conceive for at least one year and for whom OH combined with IUI is a treatment option, including:
- Unexplained subfertility which was defined as a subfertility of at least one year duration without any abnormality found at routine fertility investigation (consisting of the following: ovulatory status confirmed with biphasic basal body temperature chart (BBTC), luteal progesterone (P) or sonographic evidence of ovulation; tubal patency confirmed; normal semen parameters as defined by the WHO).
- Male factor subfertility was defined as semen quality not meeting the criteria for normality as defined by the World Health Organization (WHO) in 1987 (thus at least): sperm concentration < 20 x 106/ml or total motility < 50% or normal morphology < 50%, < 14% normal morphology was considered as abnormal when Kruger criteria were used (Kruger 1993). In 1992 the WHO changed its criteria for sperm morphology from 50% to 30% (WHO 1992).
- Mild endometriosis was diagnosed by laparoscopy.
- Other types of subfertility which were treated with OH combined with IUI.

Types of interventions

IUI with ovarian hyperstimulation, where OH is the same as ovarian stimulation also defined as controlled ovarian hyperstimulation (COH). However, 'controlled stimulation' of the ovaries suggests that some form of control can be performed, which is not the case.
1. Anti-oestrogens versus gonadotrophins
2. Anti-oestrogens versus gonadotrophins with GnRH agonists.
3. Anti-oestrogens versus gonadotrophins with GnRH antagonists.
4. Anti-oestrogens versus aromatase inhibitors.
5. Gonadotrophins alone versus gonadotrophins alone for example FSH versus HMG and u-FSH versus r-FSH.
6. Gonadotrophins alone versus gonadotrophins with GnRH agonists.
7. Gonadotrophins alone versus gonadotrophins with GnRH antagonists.
8. Gonadotrophins alone versus gonadotrophins with anti-estrogens.
9. Different dosage regimens for anti-oestrogens or aromatase inhibitors.

10. Different dosage regimens for gonadotrophins (High dose (>75 IU per day) versus low dose gonadotrophins (75 IU or less per day)).
11. Other comparisons
Studies which compared stimulated IUI with IUI in natural cycles were excluded as this is the topic of other reviews (Cohlen 2000; Verhulst 2006).

Types of outcome measures

Primary outcomes

- Incidence of live births (live birth rate/couple) and incidence of pregnancies beyond 12 weeks (ongoing pregnancy rate/couple) when live births are not mentioned
- Incidence of multiple pregnancies beyond 12 weeks (multiple pregnancy rate/couple)

Secondary outcomes

- Incidence of miscarriages (miscarriages/ couple and per pregnancy)
- Incidence of ovarian hyperstimulation syndrome (OHSS) (OHSS/ couple)
- Incidence of ectopic pregnancy (ectopic pregnancy per couple and per pregnancy)

Search methods for identification of studies

We searched for all publications which described (or might describe) RCTs comparing different stimulation protocols followed by IUI.
(1) We searched the Menstrual Disorders and Subfertility Group's Central register of Controlled Trials (CENTRAL) .
(2) We searched the electronic databases of MEDLINE (January 1966 to present) and EMBASE (1988 to present) through Science Direct.
We searched these databases using the Cochrane search strings for RCTs and the following subject headings and keywords:
intrauterine; intra uterine; intra-uterine; insemination; IUI; artificial insemination; AIH; mild ovarian hyperstimulation; MOH; controlled ovarian hyperstimulation; COH; hyperstimulation; ovarian stimulation; clomiphene citrate; CC; anti-oestrogens; Clomid; Serophene; aromatase inhibitors; letrozole; follicle stimulating hormone; FSH; recFSH; u-FSH; gonadotropins; human menopausal gonadotropins; hMG; highly purified FSH; urinary FSH; Menopur; humegon; menogon; pergonal; Gonal-f; Puregon; Ganirelix; GnRH; GnRH-analogue; LHRH; LHRH analogue; LHRH-analogue; GnRH-antagonist; Cetrorelix; Cetrotide
(3) We handsearched the reference lists of all identified and included studies.
(4) We handsearched abstracts of the American Society for Reproductive Medicine (1987 to 2005) and the European Society for Human Reproduction and Embryology (1987 to 2005) meetings.
If important information is missing from the original publications we tried to contact the authors using different means of communication and sent them a reminder a couple of weeks later. We did not restrict the search by language.

Data collection and analysis

Two review authors (AEPC,MJH) independently selected the trials included according to the aforementioned criteria. Disagreements were resolved through arbitration by BJ Cohlen. Analysis of agreement between the two observers for inclusion was performed using crude percentage agreement. This analysis was performed on the method of randomisation, concealment of allocation, study design and primary outcomes. Type of study, quality of the selected studies, type of participants, type of interventions and type of outcome measures mentioned at the 'criteria for considering studies' section were extracted and assessed by these same two observers as were the data. If specific information was missing, we contacted one of the trial authors by letter, email or fax.

Quality assessment

We extracted the following characteristics from each trial to assess the quality of included studies.
- Method of randomisation; adequately randomised, quasi- randomised or not clear.
Quasi-randomised: e.g. trials using alternating record numbers, dates of birth or odds and even numbers will not be included. Studies where the method of randomisation is not clear: e.g. not stated or stated without further description will be included in the review.
- Concealment of allocation; adequate, inadequate or not clear.
Adequate allocation: e.g. by third party or sealed opaque envelopes. Inadequate allocation: e.g. open list of random numbers or open envelopes/ tables. Not clear: e.g. not stated or stated without further description.
- Trial design; parallel design, cross-over design or not clear.
Parallel designed studies or first data of cross-over studies will be included.
- Power calculation; power calculation beforehand, no power calculation or not clear.
- Drop-outs; details and number of dropouts (couples) or no details on dropouts.
- Cancelled cycles: reason for and number of cancelled cycles given or no details on cancelled cycles given.
- Blinding; when possible and appropriate blinding will be assessed.
- Intention to treat analysis: performed, not performed or not clear.

Data extraction

We extracted the following characteristics of the participants from each trial to define the type of participants in detail and to detect possible clinical heterogeneity:
- Age of the woman;
- Duration of subfertility;
- Type of subfertility;
- Previous fertility treatments;
- Primary or secondary subfertility.

We extracted interventions which might have influenced treatment outcome were extracted from each study as well. The following interventions were considered:
- Dosage of medication for ovarian stimulation
- Trigger for ovulation (endogenous LH surge, hCG);
- Timing of insemination;
- Single or double insemination per cycle (Cantineau 2002);
- Semen preparation technique (Boomsma 2004);
- Number of motile sperm injected;
- Donor semen or husband/partner semen;
- Type of insemination device/ catheter;
- Cancel criteria.

We extracted the following outcomes were extracted from each study when possible:
- Live births and pregnancies beyond 12 weeks;
- Multiple pregnancies beyond 12 weeks;
- Miscarriages;
- OHSS;
- Ectopic pregnancy.

The outcomes 'costs of treatment', 'international units (IU) used (when applicable)' and 'number of dominant follicles' were reported in the original protocol, however these were not stated in the final review since we concluded they were of no relevance and making the review too complicated.

Statistical analysis

We performed statistical analyses in accordance with the guidelines for statistical analysis developed by the Cochrane Menstrual Disorders and Subfertility group (MDSG).

For dichotomous data, the results for each study were expressed if appropriate as odds ratios (OR) with 95% confidence intervals (CI) and combined for meta-analysis with RevMan software. Continuous data were combined for meta-analysis with RevMan software using the weighted mean difference (WMD) with 95% CI.

Heterogeneity between the results of different studies was noted when the confidence intervals did not overlap. This was checked by the results of Chi-squared tests and the I-squared (I2) statistic for inconsistency. The cut-off levels we used were: I^2 below 30% a fixed-effect model should be used and a I^2 above 60% a random-effect model should be used. Between 30 and 60% the choice of model was based on differences of the studies included. If high quality RCTs were included with comparable patients, the fixed-effect model was used. When statistical heterogeneity was presumed, the random-effect model results were reported as well. Then, the trials were re-studied to detect clinical heterogeneity which was taken into account.

Publication bias was investigated by constructing a funnel graph, plotting sample size versus effect size. A funnel plot was not constructed when insufficient studies were available.

The outcome of live birth rates and pregnancy rates was considered a positive consequence of treatment therefore a higher proportion of women with a live birth or a pregnancy 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 the meta-analyses are viewed.

A priori a subgroup analysis was described for trials comparing two different stimulation protocols in couples with different types of subfertility. Enough studies had to be included (at least two) to make meta-analyses of subgroups possible.

A priori it was also planned to perform sensitivity analyses if there are more than five trials included in the review to examine stability regarding the direction of outcomes.

It is the intention of the review authors that a new search for RCTs will be performed every two years and the review updated accordingly.

RESULTS

Description of studies

With the adopted search strategy we were able to retrieve 81 trials. We analysed these trials in detail.

Analysis of agreement between the two observers for inclusion was performed using crude agreement, which occurred for 75 of the 81 trials (93%). After discussion consensus was reached regarding all trials. Of the included trials agreement concerning whether an adequate comparison was made occurred in 98% of the trials. Agreement on the method of randomisation was reached in all cases.

Also See Table 1

Excluded studies

Reviewing the retrieved trials resulted in exclusion of 31 trials for the following reasons: they either did not perform a comparison of interest (n=7) (Arcaini 1996; Doyle 1991; Jaroudi 1998;Nappi 2000; Papageorgiou 1995; Steinkampf 1993;Tummon 1997) or failed to use an adequately randomised design (n=23) (Allegra 1990 I; Allegra 1990 II; Alvarez 1999; Brami 2004; Chang 1993; Check 1992; Crosignani 2005; DiMarzo 1992; Isaza 2000; Isaza 2003; Jacobson 1991; Manganiello 1997; Mitwally 2002; Mitwally 2003 I; Mitwally 2003 II; Mitwally 2004;Mitwally 2005;

Nava 2004;Nuojua-Huttunen 1997; Prentice 1995; Ruddock 2004; Taskin 2005; Vasiljevic 2000). The abstract of Matorras (1999) was excluded since the full text publication of 2000 contained the same data (*see* table 'Characteristics of excluded studies').

Seven studies are awaiting further assessment for the following reasons: 1. Timed intercourse or DIPI was applied in certain cycles and cycles could not be separated (n=4) (Bekuretsion 1999; Fernandez 2001; Karlstrom 2000; Karlstrom 2002); 2. It is questionable whether the trial was adequately randomised (n= 3) (Colombi 1996; Karande 1995;Kotecki 2005);(*see* also table 'Characteristics of studies awaiting assessment').

Attempts were made to contact the authors by e-mail or letter or both to provide us with details that were not reported and further information about the published data. Five replies have been received as of November 2006hich resulted in exclusion of two publications (Isaza 2000; Matorras 1999) and inclusion of the correct data for one publication (Karlstrom 1993). Two authors provided additional information about several publications included (Gerli and Filicori).

Included studies

The remaining 43 studies were eligible for inclusion in this systematic review. These trials comprised 3957 women. The total number of treatment cycles was not exactly known because five trials (Demirol 2002;El Helw 2002;Fatemi 2003;Sammour 2001; Unfer 2004) did not mention their number.

Twenty-nine trials presented data that could be pooled in one of the meta-analyses, while the other eight studies could not be pooled for various reasons; they did not provide information about live births or pregnancy rate per couple, although one of these studies (Nakajima 1999) provided data on secondary outcomes (see table 'Characteristics of included studies'), or it was not possible to derive the correct information from their reports, and we have not received adequate response from requests for the required values through email or letter. This made it impossible to include these studies in the meta-analyses according to the Reviewers' Handbook (Higgins 2005). Furthermore, the results of one cross-over study were not pooled as first cycle data was lacking (Dodson 1991).

The remaining five trials compared ovarian stimulation protocols which we did not define beforehand (such as aromatase inhibitors versus gonadotrophins). Subgroup analyses were not performed since each of these studies compared other interventions (Gerli 2000;Jamal 2005; Kim 1996; Unfer 2004;Wang 2004).

Pregnancy was confirmed mostly by ultrasound after 7 weeks and ongoing pregnancy with a second ultrasound after 12 weeks of pregnancy.

We will describe the studies in detail for each comparison separately.

1. Anti-oestrogens versus gonadotrophins

Seven of the eight trials included for this comparison reported the number of women in each treatment arm, including 556 women in total. Three trials (Kamel 1995; Karlstrom 1998; Nakajima 1999) were published as abstracts only.

Type of participants

All except one study (n = 7) (Balasch 1994; Dankert 2006; Ecochard 2000; Kamel 1995; Karlstrom 1993; Karlstrom 1998; Nakajima 1999) included couples diagnosed with unexplained subfertility or mild male factor subfertility or both. The study of Matorras 2002 included couples diagnosed with severe male factor and as a result donor sperm was used for intrauterine insemination.

Three studies (Ecochard 2000; Karlstrom 1993; Karlstrom 1998) included also other types of subfertility such as endometriosis, ovarian dysfunction and cervical factor.

The reported diagnostic investigations differed among the trials. Five studies (Balasch 1994; Dankert 2006; Ecochard 2000; Karlstrom 1993; Matorras 2002) reported a complete investigative work-up consisting of most of the following tests: semen-analysis, basal body temperature chart (not reported by Matorras 2002), hormone essays (not reported by Dankert 2006 and Ecochard 2000), post-coital testing (not reported by Matorras 2002), hysterosalpingography, endometrial biopsy (not reported by Dankert 2006 and Karlstrom 1993) and diagnostic laparoscopy. The remaining trials were published as abstracts and stated that complete investigation was done or did not state details about diagnostic investigations.

The age of women was stated in five trials (Balasch 1994; Dankert 2006; Ecochard 2000; Karlstrom 1993; Matorras 2002). The mean age in the anti-oestrogen group was 31.2 ± 3.1 years compared to 31.5 ± 3.5 years in the gonadotrophin group. The same trials reported the mean duration of subfertility: 4.3 ± 2.6 years for the anti-oestrogen group and 4.2 ± 2.4 years for the gonadotrophin group.

Three of the studies included (Dankert 2006; Karlstrom 1993; Matorras 2002) reported that none of the included couples underwent previous fertility treatment. Two studies (Dankert 2006; Matorras 2002) reported the percentage of primary infertility which was 100% and 94% respectively.

Type of interventions

Trials comparing clomiphene citrate with gonadotrophins used 50 or 100 mg CC per day for five days and 75 to 150 IU hMG or FSH per day. When 50 mg CC was used for five days this was compared with 75 IU FSH from cycle day 3 to day 7 (Balasch 1994; Kamel 1995). The studies that used 100 mg CC compared this with 75 IU rFSH (Dankert 2006) or 150 IU uFSH or hMG (Karlstrom 1993; Karlstrom 1998; Matorras 2002). Only Ecochard and co-workers used an alternate day scheme for the use of gonadotrophins.

All studies included comparing anti-oestrogens with gonadotrophins used 5000 IU (Dankert 2006; Ecochard 2000; Matorras 2002) or 10.000 IU (Balasch 1994; Kamel 1995; Karlstrom 1993; Karlstrom 1998) hCG. Three studies (Ecochard 2000; Karlstrom 1998; Nakajima 1999) used also LH determina-

tion in urine or blood to adjust timing in cases of an LH surge.
In the studies using hCG only for timing, one insemination was performed between 35 and 42 hours after hCG injection. Studies that used LH determination as well, reported a wider interval for insemination from 24 hours after LH determination until 38 hours when no surge was detected. It is questionable whether anticipating on such an unexpected (premature) LH surge results in favourable outcomes (Cohlen 1998).
The five studies (Balasch 1994; Dankert 2006; Ecochard 2000; Karlstrom 1993; Matorras 2002) which were full publications reported four different semen preparation techniques; swim-up technique, Percoll gradient technique, self-migration with hyaluronic acid and Puresperm respectively. Up until now there is insufficient evidence to recommend any specific preparation technique, due to a lack of large high quality randomised controlled trials, comparing the effectiveness of a gradient or a swim-up or wash and centrifugation technique or all three on clinical outcome (Boomsma 2004).
All trials performed one intrauterine insemination only.
Two studies (Balasch 1994 and Karlstrom 1993) reported the number of inseminated motile sperm for conceptual and non-conceptual cycles, which were comparable in both trials. The number of inseminated motile sperm was reported in three studies (Balasch 1994; Kamel 1995; Karlstrom 1993), and none reported a noteworthy difference between both treatment groups.
In one study (Matorras 2002) donor semen was used. This study included subfertile couples with severe male subfertility or other indications for using donor semen. All other studies mentioned the use of husband semen or the context made clear husband semen was used.
Three studies (Balasch 1994; Karlstrom 1993; Matorras 2002) reported the type of insemination catheter used. Balasch and co-workers used the IUI catheter in their study, Karlstrom used in his study of 1993 the Kremer catheter or the TDT catheter for insemination and Matorras and co-workers used the Frydman catheter in their study of 2002.
Three studies (Dankert 2006; Ecochard 2000; Matorras 2002) reported cycle cancellation criteria to prevent adverse outcomes, such as multiple pregnancies and OHSS. The first study cancelled cycles when more than three follicles were 14 mm. The second study used the same criteria adding that cycles were cancelled as well when E2 levels exceeded 1200 pg/ml. The third study (Matorras 2002) cancelled when more than six follicles were 15 mm or more or E2 levels exceeded 2000 pg/ml.

Type of outcomes

One (Dankert 2006) of the eight studies included comparing anti-oestrogens with gonadotrophins reported live birth rates. All expect one study (Nakajima 1999) reported pregnancy rates per couple. One of these studies (Balasch 1994) reported ongoing pregnancy rates per couple as well. Pregnancy was confirmed by ultrasound after seven weeks and ongoing pregnancy with a second ultrasound after 12 weeks of pregnancy.
Multiple pregnancy rates and miscarriage rates were stated in four publications (Balasch 1994; Dankert 2006; Matorras 2002; Nakajima 1999) and the OHSS rate was stated in two publications (Balasch 1994; Matorras 2002). None of the studies reported ectopic pregnancies.

2. Anti-oestrogens versus gonadotrophins with GnRH agonist

None of the studies included compared anti-oestrogens with gonadotrophins combined with a GnRH agonist.

3. Anti-oestrogens versus gonadotrophins with GnRH antagonist

None of the studies included compared anti-oestrogens with gonadotrophins combined with a GnRH antagonist.

4. Anti-oestrogens versus aromatase inhibitors

Five studies included (Al-Fozan 2004; El Helw 2002; Fatemi 2003; Ozmen 2005; Sammour 2001) compared anti-oestrogens with aromatase inhibitors. Three studies (El Helw 2002; Ozmen 2005; Sammour 2001) were published as abstract of congress meetings only. In total results of 313 couples were pooled.

Type of participants

All studies included couples diagnosed with unexplained subfertility. One study (Ozmen 2005) included mild-moderate male infertility as well.
The reported inclusion criteria varied among these studies. While Al-Fozan and co-workers reported that patients were included if patent tubes were seen on hysterosalpingogram and the semen analysis was normal, Fatemi and co-workers stated more criteria: age below 39 years, body mass index between 18 and 29 kg/m2, presence of ovulatory cycles with duration between 24 to 35 days, FSH concentrations on day 3, normal liver and kidney function, negative history for tubal pathology and normal semen analysis. The three remaining publications (all abstracts) (El Helw 2002; Ozmen 2005; Sammour 2001) did not state inclusion criteria and no further defined unexplained or male factor subfertility.
The age of women was stated in three trials (Al-Fozan 2004; Fatemi 2003; Sammour 2001). The mean age in the anti-oestrogen group was 30.8 ± 0.5 years compared to 30.1 ± 0.5 years in the aromatase inhibitors group. Two trials (Al-Fozan 2004; Sammour 2001) reported the mean duration of subfertility per treatment group: 2.5 ± 0.3 years for the anti-oestrogen group and 2.4 ± 0.2 years for the aromatase-inhibitors group.
None of the studies reported whether included couples underwent previous fertility treatment. Only the full text publications (Al-Fozan 2004;Fatemi 2003) reported that couples with secondary infertility were included as well.

Type of interventions

Both types of drugs were given for five days consecutive in each study, except in one (El Helw 2002) where a single dose of 20 mg of aromatase inhibitor was compared with anti-oestrogens given for five days. The daily dose of aromatase-inhibitors varied among the trials from 2.5 to 7.5 mg; two studies (Fatemi 2003; Sammour 2001) compared 2.5 mg letrozole with 100 mg clomiphene citrate. Ozmen and co-workers compared 5 mg letrozole with 100 mg

clomiphene citrate and Al-Fozan 2004 compared 7.5 mg letrozole with 100 mg clomiphene citrate.

Four studies (Al-Fozan 2004; El Helw 2002; Ozmen 2005; Sammour 2001) used hCG to time insemination. Two of these studies (Al-Fozan 2004; Sammour 2001) timed insemination twice; 24 and 48 hours after hCG injection, whereas the other two studies (El Helw 2002; Ozmen 2005) timed insemination once after 33-36 hours. The fifth included study of Fatemi and co-workers (2003) timed the insemination 24 hours after the endogenous LH surge. This surge was defined as LH concentrations three times higher than the concentration observed in the previous 24 hours.

One study (Ozmen 2005) only reported the type of semen preparation using a density gradient. None of the studies stated explicitly that the husband's semen was used. However, all studies included couples with unexplained subfertility which makes it illogical that they used donor semen. Two studies (El Helw 2002; Sammour 2001) mentioned that no difference was found between the two groups in semen characteristics, but none of the studies reported the number of motile sperm inseminated.

None of the studies stated the type of insemination catheter used, nor cancellation criteria for preventing multiples.

Type of outcomes

None of the studies included reported live birth rates, but they reported pregnancy rates per couple instead. Ongoing pregnancy rates were reported in two studies (Al-Fozan 2004;Fatemi 2003), but without reporting the definition of an ongoing pregnancy. One study (Al-Fozan 2004) reported secondary outcomes (multiple pregnancies, miscarriages and ectopic pregnancies).

5. Gonadotrophins versus gonadotrophins

Two comparisons were created both comparing two different types of gonadotrophins: A. hMG versus r-FSH and B. r-FSH versus u-FSH. Three studies (Filicori 2001; Filicori 2003; Gerli 1993) compared hMG with r-FSH including 132 couples in total. Four studies (Gerli 2004; Gerli 2004 II; Matorras 2000; Pares 2002) compared r-FSH with u-FSH including 444 couples in total. The two remaining studies (Demirol 2002; Gurgan 2004) both compared more than two different types of gonadotrophins. Demirol and co-workers compared hMG with u-FSH and two different r-FSH. Description of this comparison is stated under C. Finally, Gurgan and co-workers compared hMG with u-FSH and r-FSH including 241couples in total. Description of this study is stated under D.

Two publications (Demirol 2002; Gurgan 2004) were published as abstracts only.

A. hMG versus r-FSH:

Type of participants

Both studies of Filicori and co-workers included couples with unexplained or mild male factor subfertility. The remaining study (Gerli 1993) included couples with unexplained subfertility only. Type of subfertility was not defined explicitly in one of the three studies, but inclusion criteria consisted of: no ovulatory dysfunction, a body mass index between 17 to 25 kg/m2, a pelvic ultrasound showing normal uterus and ovaries, hysterosalpingogram and/or laparoscopy demonstrating tubal patency and normal hormone analysis in the studies of Filicori and co-workers. The study of Gerli and co-workers reported inclusion criteria as no ovulatory dysfunction, tubal or uterine factor, or male factor or both.

The age of women included was stated in all three trials. The mean age in the FSH group was 31.6 ± 1.5 years compared to 32.3 ± 1.7 years in the hMG group. One trial (Gerli 1993) reported the mean duration of subfertility per treatment group: 2.3 ± 0.6 years for the FSH group and 2.6 ± 0.8 years for the hMG group. Filicori and co-workers mentioned in both publications that some of the women included had received ovulation induction previously, but not for at least three months preceding the study. Gerli and co-workers did not state whether previous fertility treatment was given. None of the studies reported primary or secondary subfertility.

Type of interventions

Both studies of Filicori and co-workers used 150 IU gonadotrophins in both treatment arms and the third study (Gerli 1993) used 225 IU FSH or hMG. All studies applied a single dose of LHRH agonist in the preceding luteal phase.

All studies (Filicori 2001; Filicori 2003; Gerli 1993) used hCG to time insemination. In both studies Filicori and co-workers performed a single insemination 36 hours after 10.000 IU hCG. Gerli and co-workers performed two inseminations, one 12 hours and one 36 hours after 5000 IU hCG.

All studies used a swim-up technique for semen preparation. Of the three studies one study (Filicori 2003) stated explicitly that partners' semen was used, but it is likely that the other two studies used partners' semen as well. The second study of Filicori 2003, also found no difference between the treatment groups concerning sperm count and sperm motility. However, none of the studies reported the number of motile sperm inseminated.

None of the studies included stated the type of insemination catheter used.

Two studies (Filicori 2003; Gerli 1993) mentioned cancellation criteria. The first study stated that on day 21 when no dominant follicles were seen on ultrasound the cycle was cancelled. The second study reported that patients at risk for OHSS based on ultrasound findings were cancelled.

Type of outcomes

None of the studies included comparing FSH with hMG reported live birth rates but instead all studies reported pregnancy rates per couple. Ongoing pregnancy rates were not stated. Both studies of Filicori (Filicori 2001; Filicori 2003) reported the number of multiple pregnancies and miscarriages. All studies reported that no ovarian hyperstimulation syndrome (OHSS) was observed. None of the studies reported ectopic pregnancies.

B. r-FSH versus u-FSH

Type of participants

All except one study (Gerli 2004 II) included couples with unexplained subfertility, male subfertility and ovulatory dysfunction.

One study (Gerli 2004) included women with endometriosis also, and one study (Pares 2002) included women with endometriosis and women with a cervical factor as well. The remaining study (Gerli 2004 II) included women suffering from PCOS only.

The reported diagnostic investigation and inclusion criteria varied among these studies. Both studies of Gerli (Gerli 2004; Gerli 2004 II) performed a diagnostic screening including gynaecological and ultrasound examination, semen analysis, hormonal assessment and hysterosalpingogram. Matorras 2000 included couples satisfying the following criteria: a history of infertility > two years, women age between 18 to 40 years and at least one normal patent tube. Pares 2002 used the following inclusion criteria: infertility of more than one year; at least a normal Fallopian tube and a sperm test better than 1.5 x 10(6)/ml and motility grade 3.

The age of women was stated in all four trials. The mean age in the r-FSH group was 31.8 ± 3.2 years compared to 31.9 ± 3.3 years in the u-FSH group. All trials reported the mean duration of subfertility per treatment group: 3.5 ± 1.7 years for the r-FSH group and 3.8 ± 2.2 years for the u-FSH group.

One of the studies (Gerli 2004 II) mentioned that all women had received ovulation induction with clomiphene citrate previously. And one study (Pares 2002) stated that

80% of the women included, suffered from primary subfertility and they were equally divided between the two treatment groups.

Type of interventions

Two studies (Gerli 2004;Gerli 2004 II) used a protocol comparing 50 IU r-FSH daily with 75 IU u-FSH daily. The other two included studies (Matorras 2000; Pares 2002) used 150 IU in both treatment arms.

All four studies used hCG to trigger ovulation and to time insemination. Both studies of Gerli (Gerli 2004; Gerli 2004 II reported the use of 10.000 IU hCG. Matorras 2000 used 5000 IU hCG and the fourth study (Pares 2002) did not mention the hCG dosage. Gerli 2004) performed a single insemination 32 to 40 hours after hCG in both studies. Matorras 2000 also performed a single insemination but after 36 hours. Pares and co-workers inseminated twice in one cycle; 20 and 40 hours after hCG. The semen preparation technique was stated in two studies only (Matorras 2000; Pares 2002) reporting Pure sperm and Percoll gradient respectively. None of the studies mentioned explicitly that partner semen was used, although this was most likely. It is noteworthy that one study (Pares 2002) reported an important difference in the number of motile sperm injected between treatment groups (Significant higher in the r-FSH group).

None of the studies included comparing r-FSH with u-FSH stated the type of insemination catheter used.

Three studies reported cycle cancellation criteria; cycles were stopped when > five follicles were 16 mm or more (Gerli 2004 (II)), > six follicles were 15 mm or more and E2 > 1000 pg/ml (Matorras 2000) and finally, > four follicles 18 mm or more and E2 >2000 pg/ml or > six follicles >10 to 16 mm (Pares 2002).

Type of outcomes

None of the studies reported live birth rates. One study (Pares 2002) stated ongoing pregnancy rates and all studies reported pregnancy rates per couple. Multiple pregnancies and miscarriage rate were reported by all studies. Finally, Pares 2002 reported the incidence of ovarian hyperstimulation syndrome (OHSS). None of the studies reported ectopic pregnancies.

C. hMG versus u-FSH versus r-FSH (follitropin alpha) versus r-FSH (follitropin beta)

Type of participants

Demirol and co-workers included 322 couples with minimal and mild endometriosis, male factor and unexplained subfertility . Diagnostic screening included semen analysis, hysterosalpingography or laparoscopy. Couples were included with a history of primary subfertility of > two years, between 20 to 40 years, normo-ovulatory status and patent tubes. Male factor subfertility was defined as subnormal sperm analysis according the WHO criteria. The age of women and duration of subfertility was not stated.

Type of interventions

Ovarian stimulation was started on cycle day 3 with 75 IU gonadotrophins if the body mass index (BMI) was less than 25 kg/m2 and 150 IU if the BMI was > 25 kg/m2. 10.000 IU hCG was used to trigger ovulation and time insemination. A single insemination was performed 36 hours after hCG injection. Semen preparation was performed with pure sperm. It was not been stated whether partner semen was used, although this was most likely. The type of insemination catheter has not been stated. Cycle cancellation criteria were not stated.

Type of outcomes

This study (Demirol 2002) did not mention live birth rates. Clinical pregnancy rates per cycle were mentioned only.

D. hMG versus u-FSH versus r-FSH (follitropin alpha)

Type of participants

Gurgan and co-workers included 241couples with unexplained subfertility. Couples with a history of primary subfertility of more than two years, aged between 20 to 40 years, normal semen analysis, normo-ovulatory status and normal hysterosalpingography or laparoscopy. The age and duration of subfertility of the included couples was not stated.

Type of interventions

Ovarian stimulation was started on cycle day 3 with 75 IU of gonadotrophins if the BMI was less than 25 kg/m2 and 150 IU if the BMI was > 25 kg/m2. To trigger ovulation and time insemination, and injection of 10,000 IU hCG was given. A single insemination per cycle was performed 36 hours after hCG injection. Semen preparation technique was not stated. The type of catheter used was not stated. Cycle cancellation criteria were decreasing estradiol levels or more than four follicles of 16 mm of more.

Type of outcomes

Live birth rates were not stated. Clinical pregnancies were stated only.

6. Gonadotrophins alone versus gonadotrophins combined with

a GnRH agonist

Five studies (Carrera 2002(I); Carrera 2002(II); Dodson 1991; Pattuelli 1996; Sengoku 1994) compared gonadotrophins alone with gonadotrophins combined with a GnRH agonist. One trial (Pattuelli 1996) was published as an abstract only. One study (Dodson 1991) reported data per cycle only. In total data of 391 women could be pooled.

Four studies (Carrera 2002 (I); Dodson 1991; Pattuelli 1996; Sengoku 1994) included couples suffering from unexplained subfertility. Apart from this indication Dodson and co-workers included also the indications: male factor, endometriosis and adnexal adhesions. Carrera 2002 (I) included also male factor subfertility besides unexplained subfertility. The second study of Carrera (Carrera 2002 (II)) included women with PCOS only.

The reported diagnostic investigations differed among the trials. Four studies (Carrera 2002(I); Carrera 2002(II); Dodson 1991; Sengoku 1994) reported a complete investigative work-up consisting of most of the following tests: semen-analysis (except Carrera 2002 (II)), basal body temperature chart (only stated by Sengoku 1994), hormone essays, post-coital testing (only reported by Sengoku 1994), hysterosalpingography, endometrial biopsy (only reported by Sengoku 1994) and diagnostic laparoscopy (not reported by Carrera 2002 (I) and only done when abnormalities were found in the second study of Carrera and co-workers). The remaining trial was published as an abstract and stated only that a fertility work-up was performed.

The age of the women was stated in four trials (Carrera 2002(I); Carrera 2002(II); Dodson 1991; Sengoku 1994). One study (Dodson 1991) reported the age of women and duration of subfertility for the total group of women included. The mean age in the gonadotrophins alone group was 30.8 ± 2.3 years compared to 31.2 ± 2.4 years in the gonadotrophin/GnRH agonist group. The same trials reported the mean duration of subfertility: 4.0 ± 2.1 years for the gonadotrophins alone group and 4.1 ± 2.0 years for the gonadotrophin/GnRH agonist group.

One study (Carrera 2002 (II)) reported that women were previously treated with three cycles with clomiphene citrate. As stated before, this might introduce selection bias.

Both studies of Carrera and co-workers reported the percentage of primary infertility which was 100%.

Type of interventions

Different dosages of drugs and different schedules were used in all trials. The first study of Carrera (Carrera 2002 (I)) stimulated with 100 IU r-FSH per day from cycle day 3 onwards in both groups. Procrin was used as GnRH agonist; 1 mg per day from cycle day 21 of the preceding cycle and 0.5 mg from cycle day 3 of the stimulation cycle. In the second study of Carrera (Carrera 2002 (II)) women were stimulated with 75 IU r-FSH in both treatment groups. Decapeptyl was used as GnRH agonist 0.1 mg per day from the preceding cycle day 21 onwards and 0.05 mg from cycle day 3. The third study (Dodson 1991) stimulated with 75 IU hMG from cycle day 7 in the gonadotrophins only group and in the gonadotrophin/GnRH agonist group leuprolide 1 mg/day was applied in the luteal phase 4 to 7 days before the onset of menstrual period combined with 75 to 225 IU hMG from cycle day 2 onwards. Pattuelli and co-workers applied 150 IU FSH in both treatment groups and LHRH from the mid luteal phase of the preceding cycle in the group where a GnRH agonist was applied. Finally, Sengoku and co-workers stimulated with 150 IU hMG per day in both groups. In the treatment group where a GnRH agonist was applied this was done from cycle day 1; 0.3 mg buserelin acetate three times a day.

All five studies used hCG for timing a single insemination. All but one study (Sengoku 1994) timed insemination 36 to 40 hours after hCG injection. Sengoku and co-workers inseminated after 24 to 28 hours. The semen preparation technique was stated in all studies. Two studies (Carrera 2002 (I) and Carrera 2002 (II)) used the Percoll gradient technique. Two studies (Dodson 1991 and Sengoku 1994) stated a double wash technique and Pattuelli and co-workers used the swim-up technique. None of the studies mentioned explicitly that partner semen was used, although this was most likely. One study (Sengoku 1994) stated the number of inseminated motile sperm. In both studies of Carrera and co-workers a Gynetics catheter was used for insemination. One study (Sengoku 1994) used the Tomcat catheter. The remaining studies (Dodson 1991 and Pattuelli 1996) did not state the type of insemination catheter.

Both studies of Carrera (Carrera 2002 and Carrera 2002 (II)) reported the same cycle cancellation criteria: > three follicles of 18 mm or more or E2 > 1000 pg/ml.

Dodson and co-workers used different cancellation criteria: > seven follicles of 17 mm or more or E2 > 2000 pg/ml. The remaining two studies (Pattuelli 1996; Sengoku 1994) did not state cancellation criteria.

Type of outcomes

None of the studies reported live birth rates and all but one study (Dodson 1991) stated pregnancy rates per couple. Multiple pregnancies were reported by three studies (Carrera 2002 I; Carrera 2002 II; Pattuelli 1996). Both studies of Carrera reported miscarriage rates and OHSS rates. None of the studies reported ectopic pregnancies.

7. Gonadotrophins alone versus gonadotrophins combined with a GnRH antagonist

Five studies (Gomez 2005;Lambalk 2006;Ragni 2001;lScheiber 2003;;Williams 2004) compared gonadotrophins alone with gonadotrophins combined with a GnRH antagonist. One study (Scheiber 2003) was published as abstract only. Two studies (Scheiber 2003; Williams 2004) reported pregnancy rates per cycle only. In total data of 324 women could be pooled.

The studies (Gomez 2005; Lambalk 2006; Ragni 2001) of which the results could be pooled included couples with unexplained and mild male factor subfertility. Scheiber and co-workers included

women with PCOS and Williams and co-workers included couples with unexplained subfertility only.

The diagnostic fertility investigations were comparable for the three studies (Gomez 2005; Lambalk 2006; Ragni 2001). All three performed cycle analysis, hormone analysis, weight measurement of women and hysterosalpingography or laparoscopy or both. Semen analysis was done twice in the study of Gomez and co-workers and once in the study of Lambalk and co-workers. Ragni did not report a semen analysis. The other two studies included (Scheiber 2003 ; Williams 2004) did not state any fertility investigations.

The age of women was stated in four trials (Gomez 2005; Lambalk 2006; Ragni 2001; Williams 2004). The mean age in the gonadotrophins alone group was 32.6 ± 3.6 years compared to 33.4 ± 3.2 years in the gonadotrophin/GnRH antagonist group. The mean duration of subfertility was stated in two studies (Lambalk 2006; Williams 2004) which was 2.5 ± 1.7 years for the GnRH antagonist group and 2.4 ± 1.8 years for the FSH alone group. Whether previous fertility treatment was advocated was not reported in any of the studies. However, two studies used previous treatment as selection criteria; no IUI or IVF previously (Williams 2004) and not more than two previous IUI attempts (Lambalk 2006).

One study (Gomez 2005) reported the percentage of primary subfertility which was more than 90% in both treatment groups.

Type of interventions

Different treatment schedules and dosages of drugs were used in the various trials included. Gomez and co-workers started with 100 IU FSH on cycle day 3 to 4 and when the recruited follicles were 16 mm or larger or E2 levels were > 300 pg/ml, 0.25 mg Ganirelix was subcutaneously injected daily until hCG was given. Lambalk and co-workers started from day 2 to 3 of menstrual cycle with r-FSH of which the dose was determined by the investigator based on patient's characteristics and history. Ganirelix or placebo was given (double-blind design) when one or more follicles > 14 mm were seen, until hCG was given. Ragni and co-workers started with a fixed dose of 150 IU r-FSH from day 3 of the cycle until hCG administration. Cetrorelix was started from the day when a follicle > 14 mm in mean diameter was visualized until hCG injection. Scheiber and co-workers started with 150 IU r-FSH on cycle day 2 to 3 and Ganirelix 0.25 mg was given when the dominant follicle was 14 mm, E2 > 600 pg/ml or LH > 7.5 IU/l. Williams and co-workers started with 150 IU r-FSH on day 2 to 3. On day 6 Ganirelix 0.25 mg was initiated and was continued until administration of hCG.

All five studies used hCG for timing of a single insemination. However, Ragni and co-workers timed an insemination with LH urinary test in the control group. All but one study (Ragni 2001) reported the time interval between hCG injection and insemination. This time interval varied slightly between the studies, but all inseminations were planned 32-42 hours after hCG injection. The semen preparation technique was stated in one study (Gomez 2005) that used a swim-up technique. None of the studies mentioned explicitly that partners semen was used, although this was most likely. One study (Williams 2004) reported the number of sperm inseminated in each group which was comparable. Both Gomez (2005) and Scheiber (2003) stated a slight difference of injected motile sperm between both treatment arms. Only Gomez and co-workers reported the type of insemination catheter (a Lee catheter)

Cancellation criteria were mentioned in two studies (Gomez 2005; Ragni 2001). Gomez and co-workers stated that cycles were cancelled when more than 4 follicles had a diameter of more than 16 mm. Ragni and co-workers stated that cycles were cancelled when more than 6 follicles had a diameter of 14 mm or more or less than 2 follicles had a size of 14 mm. The remaining three studies did not report any cancellation criteria.

Type of outcomes

One of the studies (Gomez 2005) reported live birth rates whereas three studies (Gomez 2005; Lambalk 2006; Ragni 2001) stated pregnancy rates per couple and multiple pregnancies. None of the studies reported miscarriage rates, OHSS rates or ectopic pregnancies.

8. Gonadotrophins alone versus gonadotrophins combined with anti-oestrogens

One study (Ransom 1996) compared gonadotrophins alone with gonadotrophins combined with anti-oestrogens. This publication was a full-text paper. Data of 98 women were available.

All couples who were to undergo OH with IUI were enrolled in this study. Indications were: unexplained and male factor subfertility, endometriosis, cervical factor, ovulatory dysfunction, PCOS and women with surgically corrected pelvic adhesions.

All participants had to have had a preliminary infertility investigation, including hysterosalpingogram, postcoital test, semen analysis and hormonal analysis.

The mean age of the women was 32.9±4.8 years in the group stimulated with gonadotrophins only and 32.3±3.4 years in the group where anti-oestrogens were added. Duration of subfertility was not stated. Previous fertility treatment consisted of at least three unsuccessful cycles with anti-oestrogens. Previous treatment with gonadotrophins was reason for exclusion.

Whether couples suffered from primary subfertility was not reported.

Type of interventions

Ransom and co-workers compared a daily dose of 150 IU hMG from cycle day 3 onwards with 100 mg CC from cycle day 3 to 7 combined with 150 IU hMG on cycle day 7, 9 and 11. When no mature-sized follicles were present by day 12, hMG was continued until a follicle of 18 mm or more was detected.

5000 IU hCG were used to induce ovulation and 34-36 hours later one insemination was performed. A standard swim up technique was used for semen preparation. It was not stated explicitly that partner semen was used, although this was most likely, since therapeutic donor insemination candidates were excluded. The number of injected motile sperm was stated and was not significant

different between both groups (37.2 versus 42.4 x 106). The type of insemination catheter was not reported. An additional hCG injection was applied for luteal support.
Cancellation criteria were not stated.

Type of outcomes
Pregnancy rates per group were stated as well as multiple pregnancy rates, miscarriage rates and ectopic pregnancies. Ransom and co-workers did not report OHSS rates.

9. Different dosage regimen for anti-oestrogens or aromatase inhibitors

One study (Al-Fadhli 2005) compared different dosage regimens for aromatase inhibitors. This trial was published as an abstract only.
Couples with unexplained or mild endometriosis were included. However, diagnostic fertility investigations were not reported in detail.
The age of women and duration of subfertility were not reported. Neither previous fertility treatment nor the percentage of primary subfertility were stated.
Type of interventions
Al-Fadhli 2005 and co-workers compared different dosage regimen of aromatase inhibitors; 2.5 mg letrozole for five days versus 5 mg letrozole for five days. Ovulation was triggered with 10.000 IU hCG and one insemination was performed 24 hours later. The semen preparation technique and the type of insemination catheter were not stated. It was not stated explicitly that partners semen was used, although this was most likely. The number of injected spermatozoa was not reported and cancellation criteria were not stated.
Type of outcomes
Primary outcome was the number of follicles, endometrial thickness and pregnancy rate per cycle. Also the number of multiple pregnancies were stated. Live birth rates, pregnancy rates per couple, miscarriage rates, ectopic pregnancies and OHSS were not reported.

10. Different dosage regimens for gonadotrophins

Four studies (Dhaliwal 2002; Hughes 1998; Ragni 2004; Sengoku 1999) were included comparing different dosage regimens for gonadotrophins.
All four articles were full-text papers. In total data of 297 women could be pooled.
Two studies (Dhaliwal 2002; Sengoku 1999) included couples with unexplained and ovulatory dysfunction with CC failure. Hughes and co-workers included women with endometriosis and tubal disease as well. Ragni 2004 included couples with unexplained subfertility, male factor subfertility, endometriosis and PCOS.
The infertility work-up differed between the four studies. All studies performed cycle analysis, hormone analysis, semen analysis and hysterosalpingography or laparoscopy or both. Cervical mucus testing was done in two studies (Dhaliwal 2002; Sengoku 1999). Additionally, one study (Sengoku 1999) performed an endometrial biopsy and a basal body temperature curve. Ragni 2004) used a body mass index between 19 to 30 to include women.
The age of women was stated in all four trials. Two trials (Dhaliwal 2002; Sengoku 1999) compared low dose gonadotrophins (75 IU/day) with high dose gonadotrophin (150 IU/day) and the mean ages of the women were 30.2±3.9 years and 31.5±4.0 years respectively. One study (Hughes 1998) had three treatment groups. Ragni and co-workers (Ragni 2004) reported a mean age of 33.1±3.0 years in the high dose group and 32.1±6.6 in the low dose group.
The mean duration of subfertility was stated in all 4 studies. Duration of subfertility was comparable between studies. However, Dhaliwal 2002 reported a mean duration of 6.1±2.8 years in the low dose group versus 6.9±2.9 years in the high dose group in contrast to the other three studies (Hughes 1998; Ragni 2004; Sengoku 1999) that reported a mean duration of subfertility of 3.9±2.2 years, 3.1±1.2 years and 4.4±2.3 years respectively.
Previous fertility treatment was reported in all studies but differed. Dhaliwal and co-workers reported five to six cycles CC use, Hughes and co-workers reported that 90% of the included women had CC with IUI before, Ragni (2004) reported previous fertility treatment was performed but no IUI and finally, Sengoku (1999) reported previous CC treatment. Three studies (Dhaliwal 2002; Hughes 1998; Sengoku 1999) reported the percentage of primary subfertility which was 76%, 67% and 70% respectively.
Type of interventions
Dhaliwal 2002 started with 100 mg CC on cycle day 3 for five days in both groups combined with 75 to 150 IU hMG daily from cycle day 5 in the conventional protocol and 150 IU hMG once on cycle day 9 in the minimal stimulation protocol. Hughes 1998 compared three different stimulation protocols: Women in group A applied 150 IU r-FSH on cycle day 4 and 75 IU r-FSH on cycle day 6 and 8; women in group B applied 150 IU r-FSH on cycle day 4, 6 and 8 and women in group C applied 150 IU on cycle day 4, 6, 8 and 10. Ragni (2004) compared two stimulation protocols: 50 IU r-FSH per day combined with a 0.25 mg GnRH antagonist from the day in which a follicle > 13 mm in mean diameter was visualized compared to 50 IU r-FSH on alternate days combined with the same GnRH antagonist. Finally, Sengoku (1999) compared 150 IU u-FSH daily, both from cycle day 3 onwards.
All four studies used hCG for timing of a single insemination. However, timing after hCG differed among the studies; two studies (Hughes 1998 and Sengoku 1999) timed the insemination 24 to 28 hours after hCG injection and two studies (Dhaliwal 2002; Ragni 2004) timed insemination 34 to 40 hours after hCG injection. Furthermore, Sengoku and co-workers adjusted timing of insemination when an LH rise was detected.
The semen preparation technique was stated in two studies: Dhaliwal 2002 used a swim-up technique, and Sengoku 1999 used

a double washing technique. None of the studies mentioned explicitly that partner semen was used, although this was most likely. None of the studies stated the number of injected motile sperm. Two studies (Dhaliwal 2002; Sengoku 1999) reported the type of insemination catheter (IUI cannula and Tomcat catheter).
Cancellation criteria were reported in two studies (Hughes 1998; Ragni 2004). The first study stated that cycles were cancelled if no follicles developed on cycle day 18 or when more than 2 follicles reached a size of 17 mm or more. The second study stated that cycles were cancelled when more than 2 follicles > 14 mm. The remaining studies (Dhaliwal 2002 ; Sengoku 1999) did not state any cancellation criteria.

Type of outcomes
One of the studies (Ragni 2004) reported live birth rates. All studies stated pregnancy rates per couple. All but one study (Hughes 1998) stated multiple pregnancy rate per pregnancy, miscarriage rates and OHSS rates. None of the studies reported ectopic pregnancies as an outcome of interest.

11. Other comparisons
The remaining five studies compared different stimulation protocols, which were not stated beforehand in our protocol; A. oestrogens added to anti-oestrogens (Gerli 2000), B. Aromatase inhibitor versus gonadotrophins (Jamal 2005), C. GnRHa in different dosages (Kim 1996), D. phyto-oestrogens added to anti-oestrogens (Unfer 2004) and E. tamoxifen with gonadotrophins versus anti-oestrogens (Wang 2004). Each has been stated below separately. Two studies (Jamal 2005; Wang 2004) were published as abstracts only.
A. Oestrogens added to anti-oestrogens
Type of participants
Gerli (2000) included patients with a subfertility of at least two years with an oligomenorrhoea or amenorrhoea associated with a positive menstrual response to an progesterone challenge. Diagnostic investigations were not mentioned explicitly, but women whose partners had abnormal semen analysis (according to the WHO), women with uterine or tubal abnormalities and women with a BMI > 25 kg/m2 were excluded.
The mean age of participants was 28±5.6 years for them who received clomiphene citrate (CC) plus ethinyl E2 and 26±4.2 years for patients who received CC alone. The mean duration of subfertility was 48±18.5 months for the CC plus ethinyl E2-group and 36.7±9.6 months for the CC alone group. In all cases, no ovulation induction had been tried before.
Type of intervention
From cycle day 3, 100 mg clomiphene citrate (CC) was given for five days. On cycle day 8, 0.05 mg of ethinyl E2 or placebo was given for five days.
10,000 IU hCG was used for timing and 24 to 36 hours after hCG injection a single intrauterine insemination was performed. The semen preparation technique and the number of injected motile sperm were not stated. The type of insemination catheter was not stated either.
Cancellation criteria were not mentioned. Luteal phase support with 50 mg progesterone daily was given starting three days after IUI.
Type of outcomes
Ongoing pregnancy rates were reported defined as gestations that reached 20 weeks. Miscarriage rate was reported. No other outcome measures of interest were stated.
B. Aromatase inhibitors versus gonadotrophins
Type of participants
Jamal (2005) included women with unexplained subfertility of at least two years duration. Diagnostic investigations were not stated. Inclusion criteria were women between 20 to35 years with FSH < 10 mIU/ml on cycle day 3. Mean age of participants and the mean duration of subfertility were not reported. Whether previous fertility treatment had been performed was stated.
Type of intervention
5 mg aromatase inhibitor (letrozole) daily was administered from cycle day three for five days. This was compared with 75 IU hMG daily starting on cycle day 3 for women below 30 years and 150 IU hMG for women > 30 years.
10000 IU hCG was used to trigger ovulation and IUI was performed 34 to 36 hours later.
Type of outcomes
Clinical pregnancy rates were reported.
C. GnRHa in different dosages
Type of participants
Kim (1996) included subfertile women with various stages of endometriosis diagnosed and staged by laparoscopy. Mean age of participants in the ultra long group was 32.9±2.2 and in the long protocol group 32.4±2.0 years respectively. Duration of subfertility was 3.9±1.3 years and 3.2±1.0 years for the ultra long protocol and long protocol respectively. A part of patients had experienced previous attempts of medical treatment, but none had received any medication for at least 6 months.

Type of intervention
The ultra long protocol consisted of one dose of LHRH agonist (3.75 mg Decapeptyl) administered mid luteal. Four weeks after the single injection daily administration of 0.1 mg LHRH agonist was started and continued for at least two weeks prior to ovarian stimulation. After complete suppression of ovarian function was confirmed by serum oestradiol measurement and pelvic ultrasound scan 150 mg hMG and 150 mg u-FSH were started. u-FSH was given for four days only.
The long protocol consisted of daily administration of 0.1 mg LHRH agonist from the mid luteal phase of the menstrual cycle preceding the stimulation cycle. After two weeks administration complete suppression was checked and started with 150 mg hMG and 150 mg u-FSH. u-FSH was given for four days only.
10.000 IU hCG was given to induce ovulation when one or more follicles of 18 mm or more were identified. A single IUI was per-

formed 36 to 40 hours after hCG injection.
Husband semen was used and Precoll gradient method was used for semen preparation. A Makler insemination catheter was used. The motile sperm concentration was 86±20.3 x 106 in the ultra long protocol and 82.1±24.8 x 106 in the long protocol. Luteal support was supplied (50 mg progesterone).
Cancellation criteria were not stated, but selective embryonic reduction was performed at eight weeks of gestation for triplets or pregnancies of higher order.
Type of outcomes
Clinical pregnancy rate, miscarriage rate and multiple pregnancy rate were reported.
D. phyto-oestrogens (PE) added to anti-oestrogens
Type of participants
Unfer (2004) included women with at least two years of subfertility and oligomenorrhoea or amenorrhoea associated with a positive menstrual response to progesterone challenge test. Hormone status was checked and couples with male factor subfertility, uterine or tubal abnormalities or overweight women were excluded. The mean age was 28 ± 5.6 years in the CC+PE group and 26 ± 4.2 years in the CC alone group. The mean duration of subfertility was 48.1 ± 18.5 months and 36.7 ± 9.6 months for CC + PE and CC alone respectively. None of the patients had received fertility treatment in the past.
Type of intervention
Stimulation started on cycle day 3 with 100 mg clomiphene citrate (CC) for five days. From cycle day three 1500 mg PE or placebo was administered for ten days.
10.000 IU hCG was given to induce ovulation when there was at least one follicle with a minimum diameter of 18 mm. A single IUI was performed 24 to 36 hours after hCG injection. The type of sperm preparation, the number of inseminated motile sperm or the type of insemination catheter used was not stated. Cancellation criteria were not reported.
Type of outcomes
Clinical pregnancy defined by visualization of a gestational sac at the first planned ultrasound examination obtained at six to seven weeks of pregnancy or a serum B-hCG level over 1400 mIU. Ongoing pregnancies were defined as gestations that reached 20 weeks' gestation. Miscarriage rate was reported as well.
E. tamoxifen with gonadotrophins versus anti-oestrogens
Type of participants
Wang (2004) included subfertile couples who failed to develop an endometrial thickness of at least 8 mm in a previous super ovulatory cycle.
The mean age of participants and the duration of subfertility were not reported.
Type of intervention
Ovarian stimulation was initiated with 100 mg CC daily from cycle day 3 for 5 days or 40 mg tamoxifen citrate (TMX) daily from cycle day 3 for 7 days. both in combination with 150 IU of hMG on alternate days starting on cycle day 4.
10.000 IU hCG was given to trigger ovulation when at least one follicle was 20 mm or larger. A single IUI was performed 24-36 hours after hCG injection. The type of semen preparation, the number of inseminated motile sperm or the type of insemination catheter were not stated. Cancelleation criteria were not reported. Luteal phase support was applied with progesterone 200 mg transvaginally per day.
Type of outcomes
Ongoing pregnancy rate and miscarriage rate were reported.

Risk of bias in included studies

See Table 2
Comparison 1: Anti-oestrogens versus gonadotrophins
All but one study (Ecochard 2000) used a parallel design. Discussion remains regarding the most accurate study design. Pros and cons of parallel and cross-over methods have been discussed extensively (Cohlen 1998; Daya 1993; Khan 1996; Olive 1995) and the Handbook of the Cochrane Collaboration advises to include studies with a parallel design only and cross-over trials only when pre cross-over data is available. First data extraction was possible of the study of Ecochard and co-workers.
Two studies (Dankert 2006; Matorras 2002) used a computer generated random list. Ecochard 2000 used a random number table and Nakajima 1999 an open randomisation list. Furthermore, four studies (Balasch 1994; Kamel 1995; Karlstrom 1993; Karlstrom 1998) reported a random design without further description. Concealment of allocation was adequate in two studies (Dankert 2006; Ecochard 2000) using third party and opaque envelopes and inadequate in the study of Nakajima 1999 where an open randomisation list was used. In the remaining five studies concealment of allocation was unclear.
Adequate blinding might prevent bias because patients are often inclined to consider one treatment option as superior. However, none of the seven included studies used placebos. Three studies (Dankert 2006; Ecochard 2000; Matorras 2002) analysed their data according to the intention to treat principle. In two studies (Balasch 1994; Nakajima 1999) it has not been stated whether intention to treat analysis was performed and this could not be derived from the available information. The remaining studies (Kamel 1995; Karlstrom 1993; Karlstrom 1998) did not analyse their data according to the intention to treat principle. Balasch 1994 stated no power calculation was performed. Ecochard 2000 performed a power calculation on the basis of cycle numbers and therefore erroneous. Dankert 2006 performed a power calculation based on cycle numbers as well. Both studies did not reach adequate numbers. The remaining four studies did not report anything about power calculations. Six studies (Dankert 2006; Kamel 1995; Karlstrom 1993; Karlstrom 1998; Matorras 2002; Nakajima 1999) reported the number of drop-outs, which varied from none in the study of Matorras 2002 to 24% for various reasons in the study of Dankert 2006 and 30% in the study of Karlstrom 1998.

Details on drop-outs were not given in the latter study. Cycle cancellation was stated in four studies (Dankert 2006; Ecochard 2000; Kamel 1995; Matorras 2002) explicitly, which varied from 4.9% (Ecochard 2000) to 12.1% (Dankert 2006). Reasons for cycle cancellation were ovarian hyperstimulation, spontaneous ovulation, no follicles, low oestrogen levels and personal reasons. None of the studies reported a source of funding.

Comparison 4: Anti-oestrogens versus aromatase inhibitors

All studies included used a parallel design. Two studies (Al-Fozan 2004; Fatemi 2003) used a computer generated random number table. The other three studies reported a random design without further description. The concealment of allocation was unclear in all five studies. None of the studies used blinding. Two studies (Fatemi 2003; Ozmen 2005) analysed their data according to the intention to treat principle, but did not state this explicitly. In the remaining studies (Al-Fozan 2004; El Helw 2002; Sammour 2001) it has not been stated whether intention to treat analysis was performed and this could not be derived from the available information. Finally, none of the studies reported a power calculation. Sammour 2001 reported that none of the included women dropped out. The other studies did not state drop-outs. None of the studies reported information on cycle cancellation. None of the studies reported a source of funding.

Comparison 5: Gonadotrophins versus gonadotrophins

All studies included used a parallel design. Three studies (Demirol 2002; Gerli 2004; Gerli 2004 II) used a computer generated randomisation table and one study (Matorras 2000) used a computer generated list. The remaining four studies stated that the studies were randomised without further description. Concealment of allocation was adequate in three studies (Gerli 2004; Gerli 2004 (II); Matorras 2000) using a third party. Concealment of allocation in one study (Demirol 2002) was done with sealed envelopes, without reporting whether these were numbered and opaque. The other four studies did not report a concealment of allocation. Three studies (Gerli 2004; Gerli 2004 (II); Matorras 2000) used a single blinding; patients were blinded with regard to the type of treatment. Matorras 2000 blinded also the ultrasound staff, oestradiol analysis and sperm laboratory.

Both studies of Filicori did not state whether they used an intention to treat analysis, however the results showed that the numbers randomised match the numbers analysed.

Gerli and co-workers did not use an intention to treat principle in the publication of 1993 expressing the results as pregnancy rate per cycle. In both publications of 2004, Gerli and co-workers performed an intention to treat analysis of started cycles. However in both studies (Gerli 2004 I and Gerli 2004 II) respectively 2 cycles and 5 cycles were not analysed because these were never started. Two studies (Matorras 2000; Pares 2002) performed an intention to treat analysis for pregnancy rate per couple only and not for pregnancy rate per cycle. Finally, two studies (Demirol 2002; Gurgan 2004) did not state whether they used an intention to treat analysis and this could not be derived from the available data.

None of the studies performed or stated a power calculation. Four studies (Filicori 2003; Gerli 2004; Matorras 2000; Pares 2002) reported the number of drop-outs varying from none (Matorras 2000) to 8% (Pares 2002). Cycle cancellation was reported in all but two studies (Demirol 2002; Gurgan 2004). Cycles were cancelled mostly due to poor response or hyperstimulation. The percentage of cycle cancellation varied from 0% (Filicori 2001) to 15% (Matorras 2000). None of the studies reported a source of funding.

Comparison 6: Gonadotrophins alone versus gonadotrophins combined with a GnRH agonist

Two studies (Dodson 1991; Sengoku 1994) used a cross-over design and the remaining three studies (Carrera 2002; Carrera 2002 II; Pattuelli 1996) a parallel design. One study (Carrera 2002) stated they used a numeric list for randomisation. The other studies stated the study was randomised without further description. Concealment of allocation was unclear in all cases. None of the studies used blinding to prevent bias. Four studies (Carrera 2002; Carrera 2002 II; Dodson 1991; Sengoku 1994) did not state whether they used an intention to treat analysis, however, the results showed that the numbers randomised match the numbers analysed. Pattuelli 1996 did not use an intention to treat analysis for analysing their data. Dodson 1991 reported a power calculation based on cycle numbers which is erroneous. The remaining studies did not state a power calculation. None of the studies reported drop-out rates. All studies reported the number of cycles cancelled. This varied from no cancelled cycles (Sengoku 1994) to 16% (Pattuelli 1996). None of the studies stated a source of funding.

Comparison 7: Gonadotrophins alone versus gonadotrophins combined with a GnRH antagonist

All studies (Gomez 2005; Lambalk 2006; Ragni 2001; Scheiber 2003; Williams 2004) used a parallel design. Four studies (Gomez 2005; Lambalk 2006; Ragni 2001; Williams 2004) used a computer generated list for randomisation. Scheiber 2003 stated the study was randomised without further description. Concealment of allocation was reported by Williams 2004; opaque envelopes were used. The study of Lambalk 2006 had a double-blinded design by using a placebo in the control group. The remaining studies did not report blinding.

Lambalk and co-workers performed an intention to treat analysis for the group defined as all randomised subjects who received at least one dose of r-FSH. In the remaining studies (Gomez 2005; Ragni 2001; Scheiber 2003; Williams 2004) it has not been stated whether intention to treat analysis was performed and this could not be derived from the available information. A power calculation was stated in two studies (Lambalk 2006; Williams 2004). Lambalk and co-workers stated that 100 participants per treatment group were needed to be included to detect a difference of 12 % in PRs between groups. Williams 2004 stated a power calculation based on cycle numbers and therefore erroneous. The study of Lambalk and co-workers stated one drop-out since this

patient had a spontaneous pregnancy before starting treatment cycle. Cycle cancellation was reported in all studies varying from 11% (Lambalk 2006; Williams 2004) and 33% (Ragni 2001). Reasons for drop-outs were: insufficient response, no antagonist because ultrasound was performed too late, no hCG because too many follicles were detected, conversion to IVF and spontaneous ovulation. The study of Lambalk 2006 reported they received reimbursement per patient from Organon covering expenses made for execution of the study. Organon provided the study medication.

Comparison 8: Gonadotrophins alone versus gonadotrophins combined with anti-oestrogens

The only study (Ransom 1996) included had a parallel design. Ransom and co-workers used a random number table without describing concealment of allocation. No blinding was used. This study did not state whether they used an intention to treat analysis, however, the results showed that the numbers randomised match the numbers analysed. Drop-outs and cycle cancellation were not reported. Finally, neither power calculation nor a source of funding was reported.

Comparison 9: Different dosage regimens for anti-oestrogens or aromatase inhibitors

The only study (Al-Fadhli 2005) included had a parallel design. This study was randomised without further description. Concealment of allocation was not reported. The abstract did not state whether an intention to treat analysis was performed and this could not be derived from the available information.It was not stated whether a power calculation was performed. In addition blinding, drop-outs and cycle cancellation were not reported. No source of funding was stated.

Comparison 10: Different dosage regimen for gonadotrophins

All studies (Dhaliwal 2002; Hughes 1998;, Ragni 2004; Sengoku 1999) used a parallel design. And all used a computer generated random number table or a centralized randomisation scheme. Concealment of allocation was adequately in two studies (Ragni 2004 and Sengoku 1999) using sealed opaque envelopes. Hughes and co-workers also used numbered sealed envelopes but did not describe whether these were opaque. Dhaliwal and co-workers did not report concealment of allocation. None of the studies stated a form of blinding. Two studies (Ragni 2004; Sengoku 1999) did not state explicitly whether an intention to treat analysis was performed but the results showed that the numbers randomised match the numbers analysed. Two studies (Dhaliwal 2002; Hughes 1998) did not state whether an intention to treat analysis was performed and this could not be derived from the available data. A power calculation was done in three studies based on cycle numbers and therefore erroneous (Hughes 1998; Ragni 2004; Sengoku 1999). Two studies (Hughes 1998; Ragni 2004) reported drop-outs. Reasons for drop outs were lack of follicle development and spontaneous ovulation in the study of Hughes 1998 and hyperresponse, low response or personal reasons were reported in the study of Ragni 2004. All but one study (Dhaliwal 2002) reported number of cycles cancelled. The number of cycles cancelled varied from none (Sengoku 1999) to 17% in the study of Hughes 1998. None of the studies reported a source of funding.

Comparison 11: Other comparisons

The remaining five studies (Gerli 2000; Jamal 2005; Kim 1996; Unfer 2004; Wang 2004) used a parallel design. Only Kim 1996 defined the randomisation method using a blocked randomisation list. The other studies stated that the study was randomized without further description. Concealment of allocation was unclear in all publications. Four studies (Gerli 2000; Kim 1996; Unfer 2004; Wang 2004) did not state that the analysis was performed by an intention to treat principle but the results showed that the numbers randomised match the numbers analysed. Wang and co-workers only stated this principle for pregnancy rates per cycle. In the remaining study (Jamal 2005) it has not been stated whether intention to treat analysis was performed and this could not be derived from the available information. Power calculations were not reported in any of the studies. Two studies used a placebo in a double-blind manner (Gerli 2000; Unfer 2004). None of the studies reported drop-outs, cycle cancellation or a source of funding.

Effects of interventions

The results of each comparison are presented separately.

Comparison 1: Anti-oestrogens compared with gonadotrophins

Live birth rates

Dankert 2006 reported live birth rates per treatment arm revealing no evidence of benefit of one of the treatments (OR 1.1, 95% CI 0.51 to 2.3). Karlstrom 1993 and Karlstrom 1998 reported live birth rates for the group as a total and not separately per treatment modality. Contact has been made with the authors but no reply has been received until now. The other studies did not collect live birth data.

Pregnancy rate per couple

The results of seven studies (Balasch 1994; Dankert 2006; Ecochard 2000; Kamel 1995; Karlstrom 1993; Karlstrom 1998; Matorras 2002) including 556 couples, could be pooled. The pooled effect revealed a significant difference between gonadotrophins and anti-oestrogens; using gonadotrophins improved the pregnancy rates per couple significantly (OR 1.8, 95% CI 1.2 to 2.7). A random-effects model was used for sensitivity analysis. Using this random-effects model results were no longer significantly different (OR 1.8, 95% CI 0.97 to 3.3). This implies that the results are not very robust. No funnel graph was constructed since insufficient studies were included.

Multiple pregnancy rate

Four studies (Balasch 1994; Dankert 2006; Matorras 2002; Nakajima 1999) reported the number of multiple pregnancies. However, one study (Nakajima 1999) did not report the number

of couples in each treatment arm. Therefore, data of three studies (Balasch 1994; Dankert 2006; Matorras 2002) only could be pooled, expressing multiple pregnancy rates per couple. Balasch and co-workers reported zero multiples in each treatment group. A meta-analysis does not include these 'zero' values in the analysis, but this information is important to show low overall rates. The analysis revealed a non-significant difference between treatment groups (OR 0.53, 95% CI 0.15 to 1.9).

Reporting the results per pregnancy all four studies that could be pooled. With anti-oestrogens five multiples were seen out of 51 pregnancies (MPR per pregnancy: 9.8%); with gonadotrophins seven multiple pregnancies were seen out of 69 pregnancies (MPR per pregnancy: 10%) and therefore no significant difference was found between the two treatment modalities (OR 0.96, 95% CI 0.28 to 3.3).

Miscarriage rate

Four studies (Balasch 1994; Dankert 2006; Matorras 2002; Nakajima 1999) reported miscarriage rates. Three studies (Balasch 1994; Dankert 2006; Matorras 2002) reported the number of couples per treatment arm. Miscarriage rates per couple showed a non-significant difference (OR 1.1, CI 95% 0.48 to 2.3). With anti-oestrogens 14 miscarriages were seen out of 51 pregnancies (miscarriage rate per pregnancy: 27%); with gonadotrophins 15 miscarriages were seen out of 69 pregnancies (miscarriage rate per pregnancy: 22%). Regarding miscarriage rate per pregnancy, no significant difference was found between the two treatment modalities (OR 0.73, 95% CI 0.32 to 1.7).

OHSS rate per couple

When pooling the reported outcomes of Balasch 1994 and Matorras 2002, it showed that there is no significant difference in OHSS rate between gonadotrophins and clomiphene citrate (OR 4.4, 95% CI 0.48 to 41). Data of 200 couples were included.

Ectopic pregnancy rate was not reported in the included publications.

Comparison 2: Anti-oestrogens compared with gonadotrophins with GnRH agonists

This comparison was not the subject of any randomised controlled trial.

Comparison 3: Anti-oestrogens compared with gonadotrophins with GnRH antagonists

This comparison was not the subject of any randomised controlled trial.

Comparison 4: Anti-oestrogens compared with aromatase inhibitors

Live birth rates

None of the included studies reported live birth rates.

Pregnancy rates per couple

The five trials (Al-Fozan 2004; El Helw 2002; Fatemi 2003; Ozmen 2005; Sammour 2001) included 313 couples in total. There is no evidence of benefit in using letrozole compared to clomiphene citrate (OR 1.2, 95% CI 0.64 to 2.1). No funnel graph was constructed since insufficient studies were included.

Multiple pregnancy rates

One study (Al-Fozan 2004) reported multiple pregnancy rates. A total of 154 couples were included and one multiple pregnancy occurred in the CC group and none in the letrozole group. The result per couple was not statistically significant different (OR 0.36, CI 95% 0.01 to 8.9).

Miscarriage rate

One study (Al-Fozan 2004) reported miscarriage rates per pregnancy including 154 couples. In the group treated with aromatase inhibitors no miscarriages were reported; in the anti-oestrogen group four miscarriages were seen. The results per couple showed a non-significant difference (OR 0.26, 95% CI 0.01 to 7.0). The same result was seen for miscarriage rate per pregnancy (OR 0.06, 95% CI 0.001 to 1.3).

OHSS rate per couple

None of the included studies reported the incidence of OHSS per group.

Ectopic pregnancy rate was not reported by any of the included studies.

Comparison 5: Gonadotrophins alone compared with gonadotrophins alone.

In total nine trials compared different types of gonadotrophins. None of these reported live birth rates per couple.

hMG versus FSH

Pregnancy rate per couple

Three studies (Filicori 2001; Filicori 2003; Gerli 1993) compared hMG with FSH including 132 couples. There is no evidence of benefit in using hMG compared to FSH (OR 2.2, 95% CI 0.91 to 5.1). No funnel graph was constructed since insufficient studies were included.

Multiple pregnancy rates

Two studies (Filicori 2001; Filicori 2003) comparing 150 IU FSH daily with 150 IU hMG daily reported multiple pregnancy rates per treatment group. Data of 100 couples were available. Four multiple pregnancies were reported in the hMG-group with 50 couples and five in the r-FSH group with also 50 couples resulting in a non significant difference (OR 1.27, 95% CI 0.32 to 5.0). With 150 IU FSH daily five multiples were seen out of nine pregnancies (MPR per pregnancy: 56%); with 150 IU hMG daily four multiple pregnancies were seen out of 13 pregnancies (MPR per pregnancy: 30%). This result was not statistically significant different (OR 2.88, 95% CI 0.49 to 16.8).

Miscarriage rates

Both studies of Filicori and co-workers reported miscarriage rates per couple and per pregnancy. In both groups of 50 couples each two miscarriages were reported, resulting in a non-significant difference (OR 1.0, 95% CI 0.14 to 7.4). In the FSH group two miscarriages were reported out of nine pregnancies (miscarriage rate per pregnancy: 22%) with hMG two miscarriages were seen out

of 13 pregnancies (miscarriage rate per pregnancy: 15%). There is no statistically significant difference in miscarriage rate per pregnancy between these two gonadotrophins (OR 0.64, 95% CI 0.07 to 5.6).

OHSS rates per couple

None of the studies comparing hMG with FSH reported OHSS rates.

Ectopic pregnancy rate per couple

None of the studies comparing hMG with FSH reported ectopic pregnancies.

u-FSH versus r-FSH

Pregnancy rate per couple

Four studies (Gerli 2004; Gerli 2004 (II); Matorras 2000; Pares 2002) compared u-FSH with r-FSH, including 444 couples. No significant difference in PRs per couple was found between ovarian stimulation with r-FSH and ovarian stimulation with u-FSH (OR 1.2, 95% CI 0.81 to 1.8). No funnel graph was constructed since insufficient studies were included.

Multiple pregnancy rates

A total of 223 couples were included in the r-FSH group and 221 in the u-FSH group. There was a non-significant difference in multiple pregnancy rate per couple (OR 0.86, 95% CI 0.37 to 2.0). With r-FSH 11 multiples were seen out of 86 pregnancies (MPR per pregnancy: 13%); with u-FSH 13 pregnancies were seen out of 78 pregnancies (MPR per pregnancy: 17%).

Miscarriage rates

All four studies included reported miscarriage rates. There was a non-significant difference in miscarriage rate per couple between r-FSH and u-FSH (OR 1.4, 95% CI 0.64 to 3.0). In the r-FSH group 16 miscarriages out of 80 pregnancies were seen (miscarriage rate per pregnancy: 20%). In the u-FSH group 12 miscarriages were reported out of 75 pregnancies (miscarriage rate per pregnancy: 16%).

OHSS rate per couple

Pares 2002 reported one case of OHSS in the group treated with r-FSH compared with no cases of OHSS in the group treated with u-FSH which was not significantly different (OR 0.36, 95% CI 0.01 to 9.1). This study included 116 couples.

Ectopic pregnancy rate per couple

None of the studies comparing u-FSH with r-FSH reported ectopic pregnancy rates.

Comparison 6: Gonadotrophins alone compared with gonadotrophins with GnRH agonists.

Live birth rate per couple

None of the studies included reported live birth rates.

Pregnancy rate per couple

Five studies performing this comparison (Carrera 2002; Carrera 2002 (II); Dodson 1991; Pattuelli 1996; Sengoku 1994). Four trials revealed data on pregnancy rates per couple including 415 couples. The pregnancy rate was significant different between both treatment groups favouring gonadotrophins alone (OR 1.8, 95% CI 1.1 to 3.0). No funnel graph was constructed since insufficient studies were included. Sengoku 1994 used a cross-over design reporting pregnancy rates per couple after the first cycle. Dodson 1991 used a cross-over design as well without stating live births or pregnancy rates before cross-over and was therefore excluded.

Multiple pregnancy rates

Three studies (Carrera 2002; Carrera 2002 (II); Pattuelli 1996) reported multiple pregnancy rates per treatment group. Data were available for 324 couples. Multiple pregnancy rate per couple revealed a non-significant difference between the treatment groups (OR 2.7, 95% CI 0.96 to 7.4). With gonadotrophins alone five multiple pregnancies were seen out of 37 pregnancies (MPR per pregnancy: 14%); gonadotrophins combined with a GnRH agonist resulted in 13 multiple pregnancies out of 33 pregnancies (MPR per pregnancy: 39%). This revealed a statistically significant higher multiple pregnancy rate per pregnancy when a GnRH agonist had been added (OR 4.5, 95% CI 1.4 to 15).

Miscarriage rates

Both studies of Carrera and co-workers reported miscarriage rates for each treated group. Data were available of 300 couples. The miscarriage rate per couple was comparable between both treatment arms (OR 1.0, 95% CI 0.2 to 5.1). With gonadotrophins alone three miscarriages were seen out of 10 pregnancies (miscarriage rate per pregnancy: 30%). In the group gonadotrophins combined with GnRH agonists, there were three miscarriages out of 17 pregnancies (miscarriage rate per pregnancy: 18 %). This result was not statistically significant (OR 0.51, 95% CI 0.08 to 3.13).

OHSS rate per couple

Two studies (Carrera 2002; Carrera 2002 (II)) reported OHSS rates. When using gonadotrophins alone six OHSS were seen out of 60 women compared with 11 OHSS out of 60 women using gonadotrophins combined with a GnRH agonist. This result was not statistically significant (OR 2.0, 95% CI 0.69 to 5.9).

Ectopic pregnancy rate per couple

None of the studies included reported rates of ectopic pregnancies.

Comparison 7: Gonadotrophins alone compared with gonadotrophins with GnRH antagonists.

Live birth rates

One study (Gomez 2005), including 80 couples, reported live birth rates. This result showed a statistically significant difference in live birth rates when a GnRH antagonist is added (OR 3.0, 95% CI 1.1 to 8.6). However, the results are based on one study with small numbers, which implies that this result is not robust.

Pregnancy rates per couple

Five IUI studies (Gomez 2005; Lambalk 2006; Ragni 2001; Scheiber 2003; Williams 2004) compared gonadotrophins alone with gonadotrophins combined with a GnRH antagonist. Data of 299 couples were available. The results of three studies could be pooled. The pooled effect showed that there is no evidence of

benefit in the addition of a GnRH antagonist compared to gonadotrophins alone (OR 1.5, 95% CI 0.83 to 2.8). No funnel graph was constructed since insufficient studies were included.
The remaining two studies (Scheiber 2003; Williams 2004) stated pregnancy rates per cycle only. Scheiber and co-workers found that r-FSH with an antagonist is superior to r-FSH alone in preventing cycle cancellation for premature luteinization without showing a significant improvement in pregnancy rates. Williams and co-workers found that the clinical pregnancy rate per cycle initiated was higher in the GnRH antagonist group without reaching statistical significance.

Multiple pregnancy rates

Three studies (Gomez 2005; Lambalk 2006; Ragni 2001) reported multiple pregnancy rates per treatment group. Data of 424 couples were available. There was a non-significant difference in multiple pregnancy rates per couple between both treatment arms (OR 0.67, 95% CI 0.19 to 2.5). With gonadotrophins alone five multiple pregnancies were seen out of 22 pregnancies (MPR per pregnancy: 23%); with gonadotrophins combined with a GnRH antagonist three multiple pregnancies were seen out of 31 pregnancies (MPR per pregnancy: 9.6%), resulting in a non-significant difference (OR 0.48 95% CI 0.12 to 1.94).

Miscarriage rates

None of the studies comparing gonadotrophins with gonadotrophins combined with GnRH antagonists reported miscarriage rates as secondary outcome.

OHSS rate per couple

None of the studies included reported OHSS rates per treatment group.

Ectopic pregnancy rate per couple

None of the studies included reported ectopic pregnancy rates.

Comparison 8: Gonadotrophins in combination with anti-oestrogens versus gonadotrophins alone.

Live birth rate

The study of Ransom 1996 did not report live birth rates per treatment group.

Pregnancy rate per couple

Ransom 1996 included 98 couples and the results showed a statistically significant difference in favour of hMG alone (OR 3.1, 95% CI 1.3 to 7.6). However, only one study has been included with a small number of participants, therefore this result is not very robust.
Other secondary outcomes (multiple pregnancies, miscarriages, OHSS or ectopic pregnancies) were not stated.

Comparison 9: Different dosage regimens for anti-oestrogens or aromatase inhibitors.

One small trial (Al-Fadhli 2005) including 98 couples, compared two different doses of letrozole (aromatase inhibitor). Pregnancy rates per cycle were stated only, showing that 5.0 mg letrozole significantly improved pregnancy rates (29.6% versus 6.3%). Multiple pregnancy rate was zero in both groups. Other secondary outcomes were not reported.

Comparsion 10: Different dosage regimens for gonadotrophins.

Live birth rates

Live births were reported in one study (Ragni 2004) including 63 couples, comparing daily dose of gonadotrophins 50 IU with alternate day dose of gonadotrophins (50 IU), both combined with a GnRH antagonist. The overall live birth rate per recruited couple was 30% in patients treated daily and 3% for patients treated on alternate days, respectively. The results showed a statistically significant difference in favour of daily treatment with gonadotrophins combined with a GnRH antagonist (OR 14, 95% CI 1.6 to 116). However, these results are probably not robust since a small number of participants were included.

Pregnancy rate per couple

Four studies were included comparing different dosage regimens for gonadotrophins (Dhaliwal 2002; Hughes 1998; Ragni 2004; Sengoku 1999). However, the stimulation protocols were completely different among these studies. Two studies (Dhaliwal 2002; Sengoku 1999) including 297 couples compared 75 IU gonadotrophins daily with 150 IU gonadotrophins daily. The pooled effect revealed that there is no evidence of benefit using 150 IU gonadotrophins per day compared to 75 IU per day (OR 1.2, 95% CI 0.69 to 1.9).
The third study (Hughes 1998) included 63 women in total and compared three ovarian stimulation regimens; Group A: 150 IU r-FSH on day 4 and 75 IU r-FSH on day 6 and 8; Group B: 150 IU r-FSH day 4, 6 and 8; Group C: 150 IU r-FSH day 4, 6, 8 and 10. Cycle completion was the primary objective of this analysis, but pregnancy rates were also stated. Two pregnancies occurred during study cycles, both in Group B, with no statistically significant difference among groups (5.4% versus 0% and 0%).
The fourth study (Ragni 2004) compared 50 IU r-FSH daily combined with a GnRH antagonist with 50 IU r-FSH on alternate days combined with a GnRH antagonist. A preliminary evaluation of results revealed a strong difference between the two groups in terms of pregnancy rate. A statistically significant higher pregnancy rate per couple was observed in the group of patients treated with daily r-FSH (37% versus 6%) (OR 9.0, 95% CI 1.8 to 45).

Multiple pregnancy rate

Two studies (Dhaliwal 2002; Sengoku 1999) compared low dose regimens of gonadotrophins versus high dose regimens. Data of 297 couples were available. There was a non-significant difference in multiple pregnancy rate per couple between both treatment arms (OR 3.1, 95% CI 0.48 to 20). With low dose gonadotrophins one multiple pregnancy was seen out of 42 pregnancies (MPR per pregnancy: 2.4%); with a high dose gonadotrophins four multiple pregnancies were seen out of 46 pregnancies (MPR per pregnancy: 8.7%). However meta-analysis did not show a statistically significant difference per pregnancy (OR 3.4, 95% CI 0.46 to 25).
Ragni 2004 reported zero multiples in both treatment groups.

Miscarriage rate

Two studies (Dhaliwal 2002; Sengoku 1999) comparing low dose with high dose regimens reported miscarriage rates. Data of 297 couples were used. There was a non-significant difference in miscarriage rate per couple between both treatment arms (OR 0.28, 95% CI 0.08 to 1.1). Ten miscarriages were seen in the group treated with high dose gonadotrophins (miscarriage rate per pregnancy: 22%). In the group treated with lower dose gonadotrophins three miscarriages were seen out of 42 pregnancies (miscarriage rate: 7%). Using a low dose regimen of gonadotrophins resulted in a non-significant lower miscarriage rate per pregnancy (OR 0.28, 95% CI 0.07 to 1.1).

OHSS rate per couple

When a high dose of gonadotrophins was given, the OHSS rate was significantly higher than using a low dose of gonadotrophins (OR 5.52, 95% CI 1.85 to 16.52) (Dhaliwal 2002; Sengoku 1999). The random-effects model showed comparable significance (OR 5, 95% CI 1.6 versus 15). However, both models show a wide confidence interval and a relative small number of included participants which implies that results are not very robust. With a low dose gonadotrophins four OHSS were seen out of 149 cycles (OHSS rate per cycle: 2.7%); with a high dose gonadotrophins 19 OHSS were seen out of 148 cycles (OHSS rate per cycle: 13%). Data of 297 couples was used. Clinically, these results are of relevance.

Ectopic pregnancy rate per couple

None of the studies included reported the incidence of ectopic pregnancies.

Other comparisons

A. Oestrogens added to anti-oestrogens

Gerli 2000 included 64 women and the number of ongoing pregnancies was 12/32 in the CC+ ethinyl E2 group and 2/32 in the CC alone group. The results showed a statistically significant improvement of clinical pregnancy rates when ethinyl E2 was applied (OR 9.0, 95% CI 1.8 to 44). However, since the power of the study is limited this result is not robust. The miscarriage rate was statistically significant higher in the CC alone group (6/32 versus 2/32).

B. Aromatase inhibitor versus gonadotrophins

Jamal 2005 included 80 women and the number of clinical pregnancies was not statistically significant different between both groups (7/40 in the letrozole group versus 6/40 in the hMG group).

C. GnRHa in different dosages

Kim 1996 included 80 patients and there was a statistically significant higher clinical pregnancy rate per couple in the ultra long protocol group (19/39 versus 11/41) (OR 2.6, 95% CI 1.02 to 6.6). Miscarriage rate was similar in both groups (4/19 ultra long protocol and 2/11 long protocol), multiple pregnancies were higher in the ultra long protocol group (3/19 in the ultra long protocol group versus 1/11in the long protocol).

D. phyto-oestrogens added to anti-oestrogens

Unfer 2004 included 134 patients and reported ongoing pregnancy rates of 13/65 in the CC+PE group versus 3/69 in the CC alone group. The addition of phytoestrogens improved pregnancy rates significantly (OR 5.5, 95% CI 1.5 to 20). However it is most likely that power of the study is too small to draw firm conclusions as illustrated by the wide confidence interval. Miscarriage rates were statistically significant higher in the CC alone group (6/9 in the CC alone group versus 2/15 in the CC+PE group).

E. tamoxifen with gonadotrophins versus anti-oestrogens

Wang 2004 included 48 women and reported an ongoing pregnancy rate of 4/32 in the CC group and 6/16 in the tamoxifen group. This result was not statistically significantly different. Miscarriage rate was similar between treatment groups (5/9 in the CC group and 1/7 in the tamoxifen group).

DISCUSSION

Intra-uterine insemination combined with OH has been proven effective for couples with unexplained and mild male factor subfertility (Cohlen 2000;Verhulst 2006). Compared with IVF, IUI with OH is less invasive and more cost-effective (Goverde 2000). There remains discussion regarding the optimal stimulation drug and protocol not only taken into account the probability of conception but also unwanted side-effects (multiples, OHSS) and costs.

The aim of this review was to evaluate different ovarian stimulation protocols for intrauterine insemination for all indications with regard to live birth rates, pregnancy rates, multiples, miscarriages and OHSS rate. Data could be pooled for six of the eleven comparisons stated in the method section of this review. Of course there are a number of methodological considerations to be taken into account when interpreting the results. We will discuss each comparisons in detail.

Comparison 1: Anti-oestrogens compared with gonadotrophins

The results demonstrated that in an IUI program ovarian stimulation with gonadotrophins increases pregnancy rates per couple significantly, compared to anti-oestrogens, without effecting adverse outcomes. However, these results are not very robust and clinical differences should be taken into account.

One of the differences between the studies included is that Matorras 2002 used donor sperm for insemination treating severe male factor subfertility (41% azoospermia), single women or couples where protected intercourse was necessary due to a HIV positive status of one of the partners. Thus, one might conclude that they did not treat subfertile women but healthy women not yet subjected to the chance of achieving conception. Although Matorras and co-workers compared FSH with CC, which was the comparison of interest, we performed a sensitivity analysis excluding

this trial. The pooled effect of this latter analysis showed higher pregnancy rates using gonadotrophins compared to clomiphene citrate but this effect was no longer statistically significant (OR 1.4 95% CI 0.86 to 2.3).

Another meta-analysis, performed by Hughes 1997, concluded that gonadotrophins seem to be more effective compared with CC. This statement was based on twenty-two trials of which three investigated this comparison directly. Costello 2004 also reviewed studies comparing CC with gonadotrophins both combined with IUI. They included three studies in their meta-analysis that showed a significant higher pregnancy rate per cycle when treated with gonadotrophins. All three studies included in their review were included in this present review, but in addition we included four more trials.

Other confounding clinical factors that might influence the results of this comparison might be the dosage of anti-oestrogens or gonadotrophins used. All studies used comparable dosages of gonadotrophins (75 to150 IU) and anti-oestrogens (50 to100 mg) but different regimens. Balasch 1994 started with gonadotrophins 75 IU on cycle day 7 only, whereas other studies started on cycle day 3.

Another striking clinical difference was that Ecochard 2000 stimulated with 150 IU gonadotrophins on day 4, 6, 8 and 9 of the cycle instead of daily injections such as in the other six trials. Stimulation on alternating days was also done in an other study (Hughes 1998) with disappointing results, which might indicate that a daily dosage of ovarian stimulation is necessary instead of this form of 'coasting'.

Apart from this, Ecochard 2000 was the only trialist to use a different method for timing insemination depending on the detection of spontaneous LH surges. They inseminated 36 hours after hCG or 24 hours after a detected LH surge, while the other studies inseminated between 35 and 42 hours after hCG injection only. Unfortunately, the study results did not report whether spontaneous LH surges were seen significantly more in one of two treatment groups. Extracting this study from the meta-analysis shows a statistically significant difference in favour of gonadotrophins (OR 2.00 95% CI 1.29 to 3.10).

The methodological quality of the six trials included was similar: all but one (Ecochard 2000) used a parallel design and three trials mentioned an adequate method of randomisation (Dankert 2006; Ecochard 2000;Matorras 2002).

Although it is generally believed that gonadotrophins results in significant higher multiple pregnancy rates compared to clomiphene citrate, we could not conclude this with the available data.

Comparison 4: Anti-oestrogens compared with aromatase inhibitors

None of the trials solely or in combination provided convincing evidence of a significant difference. It has been suggested that clomiphene citrate would result in higher miscarriage rates compared to letrozole as reported by one of the smaller studies included (Al-Fozan 2004). More evidence is needed to confirm this observation. Since costs are important it is important to realize that letrozole costs ten times more than clomiphene citrate (Kompas 2001). This aspect should be considered when there is no evidence of benefit. All trials used a parallel design and two studies mentioned adequate methods of randomization.

Comparison 5: Gonadotrophins alone compared with gonadotrophins alone for example FSH versus HMG

There is no convincing evidence of a difference comparing r-FSH with u-FSH combining both treatments with IUI. However, there are confounding factors that might influence this conclusion.

Among these factors are: 1. Different daily dosages of gonadotrophins were used and compared. Both studies of Gerli 2004 compared a higher dose of urinary FSH (75 IU) with a lower dose of recombinant FSH (50 IU), which might result in lower pregnancy rates with recombinant FSH than expected when the same dose would have been used. However, in view of the apparent increased bioactivity of recombinant FSH over urinary FSH products one might consider this a correct comparison (Out 1995). The other studies in the meta-analysis compared similar dosages of r-FSH and u-FSH (Matorras 2000; Pares 2002) that showed a non-significant trend in favour of r-FSH (OR 1.4 95% CI 0.83 to 2.5). The same has been concluded for patients suffering from clomiphene citrate resistant chronic anovulation (Coelingh Bennink1998), but it has also been refuted by others (Yarali 1999).

2. Timing of insemination. All studies inseminated once between 32 to 40 hours after hCG injection; only Pares 2002 inseminated twice (20 and 40 hours after hCG). A previous Cochrane review did not detect an additional value of a second insemination (Cantineau 2003).

Nowadays costs should be included into decision making, whereas u-FSH is 33 to 50 % cheaper (Kompas 2001;Gerli 2004). On the other hand, according to previous literature recombinant products have certain advantages such as higher batch-to-batch consistency, high purity, avoiding injection of potentially allergenic proteins, the likelihood of reducing the risk of infectious particles, rendering the production independent of urine collection and the elimination of drugs co-extracted from urine. (Matorras 2000;No authors listed 98). All trials were methodological comparable and used a parallel design and adequate randomisation methods.

This review has also shown there is no evidence to suggest which is better FSH or hMG. There was no significant difference between

the treatments, but the trials were too small to draw firm conclusions.

When the studies were compared in detail, clinical heterogeneity was observed; Gerli 1993 used a higher dose of gonadotrophins (225 IU) in both treatment groups compared to the other studies (150 IU).Moreover, a LHRH agonist was given during the luteal phase, which is different from the other studies. When the studies of Filicori were pooled (Filicori 2001; Filicori 2003) neither of the two types of gonadotrophins was significantly better (OR 1.60, 95% CI 0.61 to 4.17).

There was a significant reduction in the total amount of gonadotropins used in favour of hMG, which should be taken into account regarding treatment costs. The same was concluded for in vitro fertilisation and intracytoplasmic sperm injection cycles recently (Al-Inany 2005). All trials used a parallel design and none of the trials mentioned the method of randomisation.

Comparison 6: Gonadotrophins alone compared with gonadotrophins with GnRH agonists

There is evidence that adding a GnRH agonist to gonadotrophins does not improve pregnancy rates, while increasing the probability of achieving a multiple pregnancy.

Comparing the studies in detail did not provide large differences in potential clinical confounding factors. Only Sengoku 1994 used a different timing of insemination; 24 to 28 hours after hCG, which did not show completely bad results in pregnancy rates although previous literature (Andersen 1995) stated that the time interval between hCG injection to follicular rupture is approximately 38 hours, which might be the perfect moment for insemination. One study (Sengoku 1994) had a cross-over design, but the first data only were used. Only one study mentioned their method of randomisation (Carrera 2002). In conclusion, adding GnRH agonists to gonadotrophins does not improve treatment outcome. Bearing these data in mind, together with the fact that GnRH agonists are expensive, their use should be carefully considered in an intrauterine insemination program. This conclusion is in line with a previous publication (Dodson 1991 II).

Comparison 7: Gonadotrophins alone compared with gonadotrophins with GnRH antagonists

Adding a GnRH antagonist showed promising results. Analysing the largest study (Lambalk 2006) in detail that included 100 couples in each treatment arm, reported the use of a placebo which filtered out possible bias. However, the amount of gonadotrophins applied in this trial was unclear because the starting dosage depended on the choice of the investigator treating the patient.

Another study in this analysis (Gomez 2005), which showed a significant difference favouring treatment with a GnRH antagonist, started to apply the antagonist only when the dominant follicle reached a size of 16 mm or when the oestradiol levels were higher than 300 pg/ml. While the other trials started with a GnRH antagonist when dominant follicles reached a size of 14 mm. Moreover, there was a significant difference found in the number of dominant follicles at the moment of hCG injection between treatment groups in this study of Gomez and co-workers (higher number of dominant follicles in the group treated with GnRH antagonists). A placebo was not used and therefore clinicians were not blinded in this study. This might have lead the clinicians to stimulate ovaries more aggressively when an antagonist was added, resulting in significantly more dominant follicles in the antagonist group, and thus more pregnancies. This should be taken into account when the results of the meta-analysis are interpreted. It is clear that future well-randomised trials, consisting of at least 300 couples, should lead to a definite answer whether GnRH antagonist are cost-effective and efficient.

Comparison 10: Different dosage regimens for gonadotrophins (High dose (more than75 IU per day) versus low dose gonadotrophins (75 IU or less per day))

Based on small numbers our results show that doubling the daily dose of gonadotrophins per day from 75 IU to 150 IU does not result in improvement of treatment outcome.

There may be a minimum acquired dose of gonadotrophins because both Hughes and Ragni reported extremely low pregnancy rates when a very low-dose regimen is given on alternating days. This might also be an effect of the alternating day regimen, although the half-life for r-FSH is around 30 to 40 hours (Mannaerts 1996).

Considering cost-effectiveness, this is an important finding. Especially when multiple pregnancies are taken into account as well.

Multiple pregnancy rates have been discussed extensively in literature (Fauser 2005; Nan 1994). Using high dose gonadotrophins seems to lead to more multiple pregnancies without improving pregnancy rates significantly, which is an interesting outcome of this review. Of course, these results are based on relative small numbers with a wide confidence interval. However, there is increasing evidence from national registries, that mild ovarian hyperstimulation combined with national guidelines of cancellation criteria reduces the risks of multiples (< 10 % twins and 1% triplets) with acceptable pregnancy rates per cycle and couple (;Haagen 2006; Steures 2006).

Finally, the results imply, based on available data of 297 couples, that OHSS rate is significantly higher when a high dose stimulation protocol is used. It seems logical to assume that the more aggressive an ovarian stimulation protocol is, the higher OHSS rates will be.

AUTHORS' CONCLUSIONS

Implications for practice

We advise the authors of the NICE guidelines to take into account the up-to-date evidence presented in this review.

1. Based on the available results gonadotrophins might be the most effective drugs when IUI is combined with ovarian hyperstimulation. However, this result is not very robust and more research is needed. Anti-oestrogens appear to be cost effective in IUI programs, although they seem somewhat less effective compared to gonadotrophins. Users should be aware of the fact that anti-oestrogens do not prevent multiples and that an anti-oestrogenic effect on the endometrium has been reported.

2. When gonadotrophins are applied we advise to apply it on a daily basis. Low dose protocols (50 to 75 IU per day) are advised since pregnancy rates do not seem to differ significantly from pregnancy rates with high dose regimens (> 75 IU per day) whereas the changes to encounter negative effects from ovarian stimulation, such as the risk of multiples and the risk of OHSS might be higher with high dose protocols.

3. There seems to be no role for GnRH-agonists in IUI programs as they increase costs tremendously and increase the number of multiples without increasing the probability of conception. We therefore advise not to use GnRH agonists in this setting, if mild ovarian hyperstimulation is applied.

4. Whether or not urinary gonadotrophins should be used as first choice compared with recombinant products is more a discussion of purity, trace ability and costs. There is no convincing evidence of a significant difference in the probability of conception.

5. Whether or not GnRH-antagonists are going to play a role in mild ovarian hyperstimulation/IUI programs needs to be determined in future trials.

6. From the available data there is no convincing evidence that letrozole is superior to clomiphene citrate and therefore the cost should be taken into account when using anti-oestrogens.

Implications for research

In general, it is important to provide data about the efficacy of ovarian stimulation combined with IUI for all women suffering from subfertility. However, clear definition of the study population is also needed to assess the effectiveness of treatment in daily practice. Using placebos in a control group will improve the quality of studies.

Suggested randomised controlled trials that need to be done:

To compare clomiphene citrate with gonadotrophins combined with IUI in a prospective designed randomised study for unexplained subfertility (including power calculation)

To compare clomiphene citrate with gonadotrophins combined with IUI in a prospective designed randomised study for mild male factor subfertility (including power calculation)

To compare gonadotrophins with gonadotrophins combined with a GnRH antagonist in a prospective randomised study including cost-efficacy for unexplained and mild male subfertility.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Al-Fadhli 2005

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	72 women 104 cycles age of women: not stated duration of subfertility: not stated type of subfertility unexplained mild endometriosis previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: letrozole 2,5 mg daily for 5 days letrozole 5,0 mg daily for 5 days trigger for ovulation: hCG (10 000 IU) timing IUI; 24 hrs after hCG frequency of IUI: once semen prep technique: not stated no of sperm injected: not stated type of semen: nl SA, thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	PR/cycle multiples number of ampoules used: not applicable

Al-Fadhli 2005 (*Continued*)

	number of dominant follicle (>17 mm): 2.5 mg letrozole: 1.1±0.0 5 mg letrozole: 1.3±0.1
Notes	comparison 9

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Al-Fozan 2004

Methods	randomisation: computer-generated random table Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	154 women 238 cycles age of women: letrozole 30.7± 0.5 CC 31.5±0.5 duration of subfertility: letrozole 2.6±0.2 CC 2.9±0.3 (yrs) type of subfertility unexplained previous fertility treatment; not stated primary subfertility; letrozole 44 women CC 57 women
Interventions	stimulation method/ dosage: letrozole 7,5 mg daily for 5 days CC 100 mg daily for 5 days trigger for ovulation: hCG (10000 IU) timing IUI; 24 and 48 hrs after hCG frequency of IUI:

Al-Fozan 2004 (*Continued*)

	twice semen prep technique: not stated no of sperm injected: not stated type of semen: not stated explicitly but normal SA catheter used: not stated cancellation criteria: not stated
Outcomes	ongoing PR/ women PR/cycle ectopic pregnancy miscarriage rate per pregnancy multiple PRs number of ampoules used: not applicable number of dominant follicle: letrozole: 1.3±0.1 CC: 1.1±0.1
Notes	comparison 4

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Balasch 1994

Methods	randomisation: stated without further description Trial design: parallel power calculation: no drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	100 women 192 cycles age of women: FSH 31.8±3.2 CC 32.6±2.9 duration of subfertility: FSH 6.5±2.5 CC 6.1±2.3 (yrs) type of subfertility

	unexplained male factor previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: FSH 75 IU daily from CD 7 CC 50 mg daily for 5 days trigger for ovulation: hCG (10.000) timing IUI; 35-36 hrs after hCG frequency of IUI: once semen prep technique: swim up into medium no of motile sperm injected: CC: 3.3±1.7 x106 FSH: 3.7±1.9 type of semen: husband semen catheter used: IUI catheter cancellation criteria: not stated
Outcomes	ongoing PR/ women PR/cycle miscarriage rate per pregnancy multiple PRs OHSS number of ampoules used: not stated number of dominant follicle: not stated
Notes	comparison 1

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Carrera 2002

Methods	randomisation: numeric list Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: Group A: 10% Group B: 3% blinding: no ITT: not stated
Participants	60 women 60 cycles age of women: Group A: 32.1± 2.8 Group B: 32.5±2.6 duration of subfertility: Group A 3.2±1.6 Group B 3.4±1.8 (yrs) type of subfertility unexplained male factor previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: Group A: rFSH 100 IU/d from CD3 Group B: GnRHagonist 1 mg/d from CD 21 + rFSH 100 IU/d from CD 3 and 0.5 mg/d GnRHa from CD 3 (Procrin) trigger for ovulation: hCG (10000) timing IUI; 36-38 hrs after hCG frequency of IUI: once semen prep technique: Percoll gradient no of motile sperm injected: A: 9.6±4.3 x10 6 B: 8.8±4.9 x 10 6 type of semen: husband semen catheter used: Gynetics catheter cancellation criteria: >3 foll > 18 mm E2 > 1000 pg/ml
Outcomes	ongoing PR/ women PR/cycle miscarriage rate per pregnancy multiple PRs

Carrera 2002 (*Continued*)

	OHSS number of ampoules used: Group A: 11.3 Group B: 16.5 number of dominant follicle (>17 mm): Group A: 1.5 Group B: 2.2
Notes	comparison 6 number of dominant follicles significant higher in group B

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Carrera 2002 (II)

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: Group A: 6.6% Group B: 13.3% blinding: no ITT: not stated
Participants	60 women 60 cycles age of women: Group A: 28.6± 0.9 Group B: 29.1±0.8 duration of subfertility: Group A 3.1±1.5 Group B 3.3±1.4 (yrs) type of subfertility PCOS previous fertility treatment; 3 cycles with CC primary subfertility; not stated
Interventions	stimulation method/ dosage: Group A: rFSH 75 IU/d from CD3 Group B: GnRHagonist 0.1 mg/d from CD 21 + rFSH 75 IU/d from CD 3 + GnRHa 0.05 mg

Carrera 2002 (II) (*Continued*)

	(Decapeptyl) trigger for ovulation: hCG (10000) timing IUI; 36-38 hrs after hCG frequency of IUI: once semen prep technique: Percoll gradient no of motile sperm injected: A: 11.9±4.3 x106 B: 12.7±4.1 type of semen: not stated catheter used: Gynetics catheter cancellation criteria: >3 foll > 18 mm E2 > 1000 pg/ml
Outcomes	ongoing PR/ women PR/cycle miscarriage rate per pregnancy multiple PRs OHSS number of ampoules used: Group A: 17.6 Group B: 20.8 number of dominant follicle (>17 mm): Group A: 1.8±0.7 Group B: 2.3±0.6
Notes	comparison 6

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dankert 2006

Methods	randomisation: computer generated list Trial design: parallel power calculation: not stated drop-outs: 21 CC group 12 FSH group patients (24%) cycle cancellation: CC group: 17 cycles FSH group: 18 cycles blinding: no ITT: not stated
Participants	138 women 410 cycles age of women: not stated duration of subfertility: at least 2 years type of subfertility unexplained mild male factor previous fertility treatment; not stated primary subfertility; 100%
Interventions	stimulation method/ dosage: CC 100 for 5 days rFSH 75 IU/d from CD3 trigger for ovulation: hCG (5000) timing IUI; 38-40 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	ongoing PR/ women PR/cycle miscarriage rate per pregnancy multiple PRs number of ampoules used: not stated

Dankert 2006 (*Continued*)

	number of dominant follicle: not stated
Notes	comparison 1 also unpublished data

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Demirol 2002

Methods	randomisation: computer-generated random table Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	322 women cycles not stated age of women: 20-40 years duration of subfertility: at least 2 years type of subfertility unexplained endometriosis male factor previous fertility treatment; not stated primary subfertility; 100%
Interventions	stimulation method/ dosage: rFSH, uFSH and hMG BMI < 25 75 IU BMI> 25 150 IU from CD 2-3 trigger for ovulation: hCG timing IUI; 36 hrs after hCG

Demirol 2002 (*Continued*)

	frequency of IUI: once semen prep technique: Puresperm no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	PR/cycle number of ampoules used: Gonal-f: 11 Puregon: 10 Metrodin: 15 Pergonal: 16 number of dominant follicle (>15 mm) Gonal-f 2.6 Puregon 2.4 Metrodin 1.4 Pergonal 1.6
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Dhaliwal 2002

Methods	randomisation: computer-generated random table Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no
Participants	200 women 420 cycles age of women: CC/hMG minimal 28.5± 4.2 CC/hMG convent 30.1±4.6

	duration of subfertility: CC/hMG minimal 6.1±2.8 CC/hMG convent 6.9±2.9 (yrs) type of subfertility unexplained ovulatory dysfunction with CC failure previous fertility treatment; CC use primary subfertility; CC/hMG minimal 74% CC/hMG conventional 78%
Interventions	stimulation method/ dosage: CC/hMG convent 100 mg CC daily day 3-7 hMG 75-150 IU daily day 5-9 CC/hMG minimal CC 100 mg daily day 3-7 hMG 150 IU once day 9 trigger for ovulation: hCG (5000) timing IUI; 36-40 hrs after hCG frequency of IUI: once semen prep technique: swim-up no of motile sperm injected: not stated type of semen: husband semen catheter used: IUI cannula cancellation criteria: not stated
Outcomes	ongoing PR/ women PR/cycle multiple pregnancy rates per pregnancy miscarriage rate per pregnancy OHSS number of ampoules used: minimal: 2 conventional: 12±5.4 number of dominant follicle minimal 1.8±0.7 convent 3.2±1.5
Notes	comparison 10

Risk of bias	***Risk of bias***

Dhaliwal 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dodson 1991

Methods	randomisation: stated without further description Trial design: cross-over power calculation: yes drop-outs: not stated cycle cancellation: hMG: 8 (10%) hMG/leuprolide: 9 (11%) blinding: no ITT: not stated
Participants	97 women first cycles not stated 159 cycles age of women of study population: 33.0± 4.1 duration of subfertility: 4.3±2.7 (yrs) type of subfertility male factor endometriosis adnexal adhesion unexplained previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: hMG: 75 IU daily from CD 7 hMG/leuprolide: 4-7 days before onset of menstrual period leuprolide 1 mg/day sc. until hCG injection hMG: CD 2-3 75-225 IU trigger for ovulation: hCG (5000) timing IUI; 40 hrs after hCG frequency of IUI: once semen prep technique: double wash no of motile sperm injected: not stated type of semen:

Dodson 1991 (*Continued*)

	nl SA thus husband semen catheter used: not stated cancellation criteria: >7 foll > 17 mm E2 > 2000 pg/ml
Outcomes	live births ongoing pregnancy ectopic pregnancy for the total group miscarriage rate for total group multiple PRs for total group OHSS number of ampoules used: hMG/leuprolide: 30.3±11.3 hMG: 21.8±6.1 number of dominant follicle (>16 mm): hMG 3.0±1.7 hMG+leuprolide 3.0±1.5
Notes	comparison 6 no first data available

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ecochard 2000

Methods	randomisation: random number table Trial design: cross-over power calculation: yes drop-outs: not stated cycle cancellation: CC 7 cycles hMG 2 cycles blinding: no ITT: yes
Participants	58 women 56 first cycles 174 cycles in total age of women: CC: 30.4± 3.5 hMG: 31.5±3.7 duration of subfertility:

	CC 4.0±2.0 (yrs) hMG 3.3±2.0 type of subfertility female factor male factor unexplained previous fertility treatment; not stated primary subfertility; not stated
Interventions	Stimulation method/ dosage: CC: 50-100 mg daily day 3-7 hMG: 150 IU/d day 4,6,8,9 trigger for ovulation: hCG (5000) timing IUI; 36 hrs after hCG or 24 hrs after LH surge + hCG frequency of IUI: once semen prep technique: Percoll density gradient no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: >3 foll > 14 mm E2 > 1200 pg/ml
Outcomes	pregnancy/cycle miscarriages for total group multiple PRs for total group OHSS for total group number of ampoules used: not stated number of dominant follicle (>16 mm): hMG 1.5±0.6 CC 1.8±0.9
Notes	comparison 1 first data available

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Ecochard 2000 (*Continued*)

Allocation concealment (selection bias)	Low risk	A - Adequate

El Helw 2002

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	53 women cycles not stated age of women: not stated duration of subfertility: not stated type of subfertility unexplained previous fertility treatment; not stated primary subfertility; not stated
Interventions	Stimulation method/ dosage: Letrozole: 20 mg single dose CD3 CC: 100 mg/d day 3-7 trigger for ovulation: hCG (5000) timing IUI; 36 hrs after hCG frequency of IUI: once semen prep technique: not stated number of motile sperm injected: not stated, but not sign diff type of semen: not stated explicitly but normal SA catheter used: not stated cancellation criteria: not stated
Outcomes	pregnancy/ couple number of ampoules used: not applicable number of dominant follicle comparable in both groups

El Helw 2002 (*Continued*)

Notes	comparison 4

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fatemi 2003

Methods	randomisation: computer-generated random number table Trial design: parallel power calculation: not performed drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	15 women cycles not stated age of women: letrozole: 28.9 CC: 28.2 (yrs) duration of subfertility: not stated type of subfertility unexplained previous fertility treatment; not stated primary subfertility; and secondary SF
Interventions	Stimulation method/ dosage: Letrozole: 2,5 mg CD3-7 CC: 100 mg/d day 3-7 trigger for ovulation: endogeneousLH surge timing IUI; 24 hrs after LH surge frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: not stated explicitly but normal SA catheter used: not stated

Fatemi 2003 (*Continued*)

	cancellation criteria: not stated
Outcomes	pregnancy/ couple PR/cycle number of ampoules used: not applicable number of dominant follicle (>16 mm): CC 2.0 letrozole 1.0
Notes	comparison 4

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Filicori 2001

Methods	randomisation: stated without further description Trial design: parallel power calculation: not performed drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	50 women 50 cycles age of women: FSH: 32±1 hMG: 33±1 duration of subfertility: not stated type of subfertility unexplained mild male factor previous fertility treatment: ovulation induction in some women primary subfertility: not stated
Interventions	Stimulation method/ dosage: LHRHagonist single dose in MLP-phase r-FSH 150 IU/d hMG: 150 IU/d

Filicori 2001 (*Continued*)

	trigger for ovulation: hCG (10000) timing IUI; 36 hrs after hCG frequency of IUI: once semen prep technique: swim up technique no of motile sperm injected: not stated type of semen: not stated explicitly, but seems husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate OHSS miscarriage rate per pregnancy number of ampoules used: FSH:33.6±2.4 hMG:23.6±1.1 number of dominant follicle (> 14 mm) hMG 6.3±0.5 rFSH 8.4±0.8
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Filicori 2003

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: Group A: 2 patients Group B: 0 cycle cancellation: not stated blinding: no

Filicori 2003 (*Continued*)

Participants	50 women 50 cycles age of women: rFSH: 31.9±0.7 hMG: 32.6±0.5 duration of subfertility: not stated type of subfertility unexplained mild male factor previous fertility treatment: ovulation induction in some women (9 in rFSH group and 13 in hMG) primary subfertility: not stated
Interventions	Stimulation method/ dosage: LHRHagonist single dose in MLP-phase rFSH: 150 IU/d hMG: 150 IU/d trigger for ovulation: hCG (10000) timing IUI; 36 hrs after hCG frequency of IUI: once semen prep technique: swim up technique no of motile sperm injected: not stated type of semen: partners semen catheter used: not stated cancellation criteria: when on day 21 no dominant follicles were seen on ultrasound
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy OHSS miscarriage rate per pregnancy number of ampoules used: FSH: 25.3±1.3 hMG:21.7±0.8 number of dominant follicle (> 14 mm) hMG 6.8±0.5 rFSH 5.7±0.7
Notes	comparison 5

Risk of bias	***Risk of bias***

Filicori 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gerli 1993

Methods	randomisation: stated without further description Trial design: parallel power calculation: not performed drop-outs: not stated cycle cancellation: 3 cycles cancelled blinding: no ITT: not stated
Participants	32 women 34 cycles age of women: FSH: 30.9±2.7 hMG: 31.4±3.6 duration of subfertility: FSH: 2.3±0.6 hMG: 2.6±0.8 type of subfertility unexplained previous fertility treatment: not stated primary subfertility: not stated
Interventions	Stimulation method/ dosage: both groups LHRHagonist single dose in MLP-phase r-FSH 225 IU/d hMG: 225 IU/d trigger for ovulation: hCG (5000) timing IUI; 12 and 36 hrs after hCG frequency of IUI: twice semen prep technique: swim up technique no of motile sperm injected: not stated type of semen: not stated explicitly, but seems husband semen catheter used: not stated cancellation criteria: patients at risk for OHSS based on ultrasound hCG was withheld

Gerli 1993 (*Continued*)

Outcomes	pregnancy/ couple PR/cycle OHSS number of ampoules used: FSH:40.2±7.5 hMG:35.0±8.0 number of dominant follicle hMG 4.9±3.4 rFSH 5.1±3.0
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gerli 2000

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: yes ITT: not stated
Participants	64 women 64 cycles age of women: CC/EE: 28.0±5.6 CC/placebo: 26.0±4.2 duration of subfertility: CC/EE: 48.1± 18.5 (months) CC/placebo: 36.7.±9.6 type of subfertility ovulatory factor previous fertility treatment; no primary subfertility; not stated
Interventions	Stimulation method/ dosage: CC 100 mg for 5 days

Gerli 2000 (*Continued*)

	CC/ ethinyl E2: 100 mg CC for 5 days + E E2 0.05 mg day 8-12 CC/placebo: 100 mg day 2-7 and placebo day 8-12 trigger for ovulation: hCG (10000) timing IUI; 24-36 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: > 5 follicles > 16 mm
Outcomes	pregnancy/ couple PR/cycle miscarriage rate per pregnancy number of ampoules used: not applicable number of dominant follicle not stated
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gerli 2004

Methods	randomisation: randomisation table Trial design: parallel power calculation: not stated drop-outs: 2 patients cycle cancellation: uFSH: 4 rFSH: 5 blinding: no ITT: yes
Participants	67 women138 cycle sage of women:uFSH: 31.7±3.4rFSH: 31.2±3.2duration of subfertility:uFSH: 2.8± 1.3rFSH: 2.9±1.5type of subfertility ovulatory factor male factor unexplained fertility treatment;not stated primary subfertility;not stated

Interventions	Stimulation method/ dosage: rFSH: 50 IU/d uFSH: 75 IU/d from CD 2 trigger for ovulation: hCG (10000) timing IUI; 32-40 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	pregnancy/ couple PR/cycle OHSS miscarriage rate per pregnancy multiple pregnancies number of ampoules used: uFSH: 10.9±3.6 rFSH: 11.9± 4.1 number of dominant follicle (>17 mm): u-FSH: 2.6±1.7 r-FSH: 2.9±1.4
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Gerli 2004 (II)

Methods	randomisation: random number table Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: u-FSH: 13 cycles r-FSH: 16 cycles blinding: no ITT: yes
Participants	170 women 379 cycles age of women: u-FSH: 28.6+2.7 r-FSH: 29.1+2.4 duration of subfertility: u-FSH: 2.2+1.4 r-FSH: 2.3+1.3 type of subfertility: PCOS women with a history of at least two years of subfertility previous fertility treatment: ovulation induction with CC primary subfertility: not stated
Interventions	stimulation method/dosage: u-FSH: 75 IU/d r-FSH: 50 IU/d trigger for ovulation: hCG (10.000) timing IUI: 32-40 hours after hCG frequency of IUI: once semen preparation technique: not stated no of motile sperm injected: not stated type of semen: semen analysis thus husband semen is likely. catheter used: not stated cancellation criteria: >5 follicles > 16 mm
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate miscarriage rate number of ampoules: u-FSH: 11.3±4.3 r-FSH: 10.8±4.9 number of dominant follicle (>17 mm): u-FSH: 2.3±1.5 r-FSH: 2.4±1.7
Notes	comparison 5

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Gerli 2004 (II) (*Continued*)

Allocation concealment (selection bias)	Low risk	A - Adequate

Gomez 2005

Methods	randomisation: computer generated list Trial design: parallel power calculation: not stated drop-outs: none cycle cancellation: FSH/GnRHanta: 1 cycle FSH alone: 1 cycle blinding: no ITT: not stated
Participants	82 women 82 cycles age of women: FSH/GnRHanta: 33.9±2.6 FSH alone: 32.1±3.3 duration of subfertility: at least 1 year type of subfertility unexplained mild male factor previous fertility treatment: not stated primary subfertility: FSH/GnRHanta: 36 women FSH alone: 39 women
Interventions	Stimulation method/ dosage: FSH/GnRHanta: 100 IU/d 5 days GnRHanta from DF 16 mm or when E2 > 300 pg/ml 0.25 mg sc FSH alone: 100 IU/d from CD3-4 trigger for ovulation: hCG (5000) timing IUI; 36-38 hrs after hCG frequency of IUI: once semen prep technique: swim up technique

Gomez 2005 (*Continued*)

	no of motile sperm injected: anta: 23.4±9.3 control: 19.9±18.4 type of semen: nl SA thus husband semen catheter used: Lee catheter cancellation criteria: > 4 follicles > 16-20 mm
Outcomes	live birth rate pregnancy/ couple PR/cycle multiple pregnancy rate OHSS miscarriage rate per pregnancy number of ampoules used: FSH/GnRHanta: 10±3 FSH alone: 9±3 number of dominant follicle (>15 mm): FSH/GnRHanta: 2.4±1.4 FSH alone: 1.7±1.2
Notes	comparison 7

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gurgan 2004

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	241 women 241 cycles age of women: 20-40 years duration of subfertility:

	> 2 years type of subfertility unexplained previous fertility treatment: not stated primary subfertility: 100%
Interventions	Stimulation method/ dosage: BMI < 25 75 IU/d CD 2-3 BMI> 25 150 IU/d CD 2-3 for rFSH, uFSH and hMG trigger for ovulation: hCG (10000) timing IUI; 36 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated number of cancellation criteria: low E2 levels, > 4 follicles > 15 mm
Outcomes	pregnancy/ couple PR/cycle number of ampoules used: Gonal-f: 11 uFSH: 15 hMG: 16 number of dominant follicle rFSH: 2.6 uFSH: 1.4 hMG: 1.6
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gurgan II 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Hughes 1998

Methods	randomisation: centralised randomisation scheme Trial design: parallel power calculation: yes drop-outs: Group A: 3 Group B: 1 cycle cancellation: 17% in each group blinding: no ITT: not stated
Participants	63 women 59 cycles age of women: Group A: 32.2±3.4 Group B: 33.0±5.0 Group C: 32.1±4.0 (years) duration of subfertility: Group A: 47.2±20 Group B: 51.3±35.1 Group C: 43.9±22.8 (months) type of subfertility unexplained endometriosis tubal disease previous fertility treatment: in most patients (90%) CC and IUI primary subfertility: 67%

Interventions	Stimulation method/ dosage: A: rFSH day 4 150 IU, day 6 and 8 75 IU/d B: rFSH day 4, 6 and 8 150 IU/d C; rFSH day 4,6,8,10 150 IU/d trigger for ovulation: hCG (5000) timing IUI; 24 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: no follicle development on day 18. >2 follicles > 17 mm
Outcomes	pregnancy/ couple PR/cycle number of ampoules used: A: 4, B: 6, C: 8 number of dominant follicle (>14 mm) A; 1.1 B; 1.2 C; 1.4
Notes	comparison 10

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Jamal 2005

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	80 women 80 cycles age of women: 20-35 years duration of subfertility: at least 2 years type of subfertility unexplained previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: letrozole 5 mg/d CD 3-7 hMG 75 IU/d CD 3 for < 30 years hMG 150 IU/d CD 3 for > 30 years trigger for ovulation: hCG (10000) timing IUI; 34-36 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: not stated catheter used: not stated number of dominant follicle letrozole 1.8±1.3 hMG 3.2± 1.6 cancellation criteria: not stated
Outcomes	PR/ women PR/cycle number of dominant follicle letrozole 1.8±1.3 hMG 3.2± 1.6

Jamal 2005 (*Continued*)

	number of ampoules used: not stated
Notes	-

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kamel 1995

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: CC: 4 hMG: 2 cycle cancellation: not stated blinding: no ITT: not stated
Participants	60 women 60 cycles age of women: not stated duration of subfertility: at least 2 years type of subfertility unexplained male factor previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: CC 50 mg/d CD 3-7 hMG 75 IU/d CD 3 trigger for ovulation: hCG (10000) timing IUI; 36-42 hrs after hCG frequency of IUI: once semen prep technique: not stated

Kamel 1995 (*Continued*)

	no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	PR/ women PR/cycle number of ampoules used: not stated number of dominant follicle (>17 mm): CC: 1.7±0.3 hMG: 2.1±0.4
Notes	comparison 1

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Karlstrom 1993

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: CC: 4 hMG: 9 cycle cancellation: not stated blinding: no ITT: not stated
Participants	32 women 32 cycles age of women: CC 31.7 hMG 32.0 years duration of subfertility: CC: 5.1 hMG: 4.9 type of subfertility unexplained endometriosis previous fertility treatment; none

Karlstrom 1993 (*Continued*)

	primary subfertility; not stated for the subgroup IUI
Interventions	stimulation method/ dosage: CC 100 mg/d CD 3-7 hMG: 150 IU/d from CD 2-3 trigger for ovulation: hCG (10000) timing IUI; 36-41 hrs after hCG frequency of IUI: once semen prep technique: method of self-migration in hyaluronic acid no of motile sperm injected: CC: 10.7 x 106 hMG: 16.6 x 106 type of semen: husband semen catheter used: Kremer de la fontaine or TDT catheter cancel criteria: not stated
Outcomes	PR/ women PR/cycle number of ampoules used: not stated number of dominant follicles: not stated
Notes	comparison 1 Not only IUI but also DIPI and DIPI with IUI combined!!

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Karlstrom 1998

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: 32 in total cycle cancellation: not stated blinding: no ITT: not stated
Participants	74 women 74 cycles age of women: not stated duration of subfertility: not stated type of subfertility unexplained endometriosis male subfertility cervical factor previous fertility treatment; not stated primary subfertility; not stated
Interventions	stimulation method/ dosage: CC 100 mg/d CD 3-7 hMG: 150 IU/d from CD 2-3 trigger for ovulation: hCG (10000) or LH surge in CC group timing IUI; 38 hrs after hCG or day after LH peak Frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	PR/ women PR/cycle number of ampoules used: not stated

Karlstrom 1998 (*Continued*)

	number of dominant follicle: not stated
Notes	comparison 1 extended study from study 1993

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kim 1996

Methods	randomisation: blocked randomisation design Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	80 women 80 cycles age of women: ultra long: 32.9±2.2 long: 32.4±2.0 years duration of subfertility: ultra long: 3.9±1.3 long: 3.2±1.0 type of subfertility endometriosis type I tm IV previous fertility treatment; In 13 patients previous treatment with GnRHa primary subfertility; ultra long: 59% long: 61%
Interventions	stimulation method/ dosage: ultra long: GnRHa 3.75 mg IM 4 weeks before starting daily with GnRHa 0.1 mg combined with FSH/hMG long: GnRHa 0.1 mg 2 weeks daily followed by FSH/hMG

Kim 1996 (*Continued*)

	trigger for ovulation: hCG (10000) timing IUI; 36-40 hrs after hCG frequency of IUI: once semen prep technique: Percoll gradient no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: Makler cannula cancellation criteria: not stated
Outcomes	live birth rate/women PR/ women PR/cycle multiple pregnancy rate miscarriage rate per pregnancy number of ampoules used: ultra long: 36.4±8.4 long: 35.3±8.3 number of dominant follicle: ultra long: 10.3±4.7 long: 10.9±4.8
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Lambalk 2006

Methods	randomisation: blocked randomisation list Trial design: parallel power calculation: yes drop-outs: GnRHanta: 11 FSH alone: 15 cycle cancellation: GnRHantagonist: 11 cycles placebo: 15 cycles blinding: yes ITT: not stated
Participants	204 women 203 cycles age of women: GnRHanta: 32.7±3.3 years FSH alone: 32.5±3.9 years duration of subfertility: GnRH anta: 3.1±1.7 years FSH alone: 3.4±1.8 years type of subfertility unexplained male factor previous fertility treatment; not more than 3 previous IUI attempts primary subfertility; not stated
Interventions	stimulation method/ dosage: GnRHanta: rFSH starting dose decided by the investigator + GnRHantagonist when DF >14mm FSH alone: rFSH + placebo from DF > 14 mm trigger for ovulation: hCG (5000 or 10000) timing IUI; 34-42 hr after hCG injection frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: not explicitly stated catheter used: not stated cancellation criteria: not if more than 3 follicles were more or equal 14 mm
Outcomes	ongoing PR/ women PR/cycle multiple pregnancy rates

	miscarriage rate number of ampoules used: GnRHanta: 8 FSH alone: 8 number of dominant follicle GnRHanta (>18 mm): 1.3±0.6 FSH alone:1.2±1.0
Notes	comparison 7

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Matorras 2000

Methods	randomisation: computer generated list Trial design: parallel power calculation: not stated drop-outs: none cycle cancellation: rFSH: 24 cycles uFSH: 27 cycles blinding: single blinded ITT: yes
Participants	91 women 345 cycles age of women: rFSH: 33.3±3.4 uFSH: 33.9±3.1 duration of subfertility: rFSH: 4.6±2.0 uFSH: 5.3±2.5 type of subfertility unexplained male factor ovulatory dysfunction previous fertility treatment: not stated primary subfertility: not stated

Matorras 2000 (*Continued*)

Interventions	Stimulation method/ dosage: rFSH: 150 IU/d uFSH: 150 IU/d trigger for ovulation: hCG (5000) timing IUI; 36 hrs after hCG frequency of IUI: once semen prep technique: Pure sperm no of motile sperm injected: not stated type of semen: husband semen catheter used: not stated cancellation criteria: > 6 follicles >15 mm and E2 > 2000 pg/ml
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate miscarriage rate per pregnancy number of ampoules used: rFSH: 19.2±7.0 uFSH: 23.8±10.8 number of dominant follicle (>15 mm): r-FSH: 3.8±2.3 u-FSH: 4.5±2.2
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Matorras 2002

Methods	randomisation: computer generated number list Trial design: parallel power calculation: not stated drop-outs: none cycle cancellation: CC: 3 cycles FSH: 29 cycles blinding: no ITT: not stated
Participants	100 women 470 cycles age of women: CC: 31.7±2.8 FSH: 30.7±3.7 duration of subfertility: CC: 5.3±3.4 FSH: 4.7±2.6 type of subfertility abnormal sperm single women HIV positive previous fertility treatment: none primary subfertility: 94% in total group
Interventions	Stimulation method/ dosage: CC: 100 mg/d CD 5-9 uFSH: 150 IU/d from CD2 trigger for ovulation: hCG (5000) timing IUI; 36 hrs after hCG frequency of IUI: once semen prep technique: Pure sperm no of motile sperm injected: not stated type of semen: donor catheter used: Frydman catheter cancellation criteria: > 6 follicles >15 mm and E2 > 2000 pg/ml
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate miscarriage rate per pregnancy

Matorras 2002 (*Continued*)

	OHSS number of ampoules used: not stated number of dominant follicle (>17 mm): FSH: 3.2±1.7 CC: not stated
Notes	comparison 1

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nakajima 1999

Methods	randomisation: open randomized trial Trial design: parallel power calculation: not stated drop-outs: 2 patients withdrew cycle cancellation: not stated blinding: no ITT: not stated
Participants	22 women 55 cycles age of women: not stated duration of subfertility: at least 18 months type of subfertility unexplained previous fertility treatment: not stated primary subfertility: not stated
Interventions	Stimulation method/ dosage: dosages of CC not stated dosages of rFSH not stated trigger for ovulation: hCG (dose ?) timing IUI; 28-36 hrs after hCG or after positive ovulation prediction kit

Nakajima 1999 (*Continued*)

	frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: not stated catheter used: not stated cancellation criteria: not stated
Outcomes	PR/cycle multiple pregnancy rate miscarriage rate per pregnancy number of ampoules used: not stated number of dominant follicle not stated
Notes	comparison 1 donor!

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Ozmen 2005

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	43 women 43 cycles age of women: not stated duration of subfertility: not stated type of subfertility unexplained mild-moderate male factor

	previous fertility treatment: not stated primary subfertility: not stated
Interventions	Stimulation method/ dosage: letrozole: 5 mg/d CD 3-7 CC: 100 mg/d CD 3-7 trigger for ovulation: hCG (dose unknown) timing IUI; 33-36 hrs after hCG frequency of IUI: once semen prep technique: density gradient no of motile sperm injected: not stated type of semen: not stated explicitly catheter used: not stated cancellation criteria: not stated
Outcomes	pregnancy/ couple PR/cycle number of ampoules used: not applicable number of dominant follicle (>17 mm): letrozole: 2.1 CC: 1.9
Notes	comparison 4

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pares 2002

Methods	randomisation: stated without further description Trial design: parallel power calculation: no drop-outs: rFSH: 6 uFSH: 4 cycle cancellation: rFSH: 7/172 uFSH: 6/226 blinding: not clear ITT: yes
Participants	126 women 398 cycles age of women: rFSH 33.7± 3.6 uFSH 33.2±4.0 duration of subfertility: rFSH 4.0±2.1 uFSH 4.7±3.8 (yrs) type of subfertility endometriosis unexplained male factor cervical factor ovulatory dysfunction previous fertility treatment; not stated primary subfertility; 80% of each group
Interventions	stimulation method/ dosage: rFSH 150 IU daily from CD 3 uFSH 150 IU daily from CD 3 trigger for ovulation: hCG (dose unknown) timing IUI; 20 and 40 hrs after hCG frequency of IUI: twice semen prep technique: Percoll gradient no of motile sperm injected: rFSH: 14.3±13.5 uFSH: 11.3±11.4 x106 type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: >4 follicles > 18 mm E2 > 2000 pg/ml or > 6 follicles > 10-16 mm

Pares 2002 (*Continued*)

Outcomes	ongoing PR/ women PR/cycle miscarriage rate per pregnancy multiple pregnancy rate OHSS number of ampoules used: rFSH: 13.7±4.9 uFSH: 15.2±6.5 number of dominant follicle (>17 mm): rFSH: 1.5±0.9 uFSH: 1.4±0.9
Notes	comparison 5

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pattuelli 1996

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	204 women 204 cycles age of women: not stated duration of subfertility: not stated type of subfertility unexplained previous fertility treatment: not stated primary subfertility: not stated

Pattuelli 1996 (*Continued*)

Interventions	Stimulation method/ dosage: LHRH in mid luteal phase FSH 150 IU CD1-5 subsequent dose was adjusted individually FSH 150 IU/d CD2-6 trigger for ovulation: hCG (10000) timing IUI; 38-40 hrs after hCG frequency of IUI: once semen prep technique: swim up technique no of motile sperm injected: not stated type of semen: husband semen catheter used: not stated cancellation criteria not stated
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate OHSS number of ampoules used: not stated number of dominant follicle: not stated
Notes	comparison 6

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ragni 2001

Methods	randomisation: computer generated list Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: Group A: 7 cycles Group B: 9 cycles blinding: no ITT: not stated
Participants	41 women 48 cycles age of women:

	GnRH anta: 33±3.5 FSH alone: 32.9±3 duration of subfertility: more than 2 years type of subfertility unexplained male factor previous fertility treatment: not stated primary subfertility: not stated
Interventions	Stimulation method/ dosage: Group A: FSH 150 IU/d from CD3; when DF>14 0.25 mg GnRHantagonist Group B: FSH 150 IU CD3 trigger for ovulation: hCG (?) Or urinary LH test in group B timing IUI; not stated frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: not stated catheter used: not stated cancellation criteria: >6 follicles > 14 mm or < 2 follicles > 14 mm
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rates number of ampoules used: Group A: 15±4 Group B: 15±3 number of dominant follicle (>14 mm): Group A: 2.7±1.1 Group B: 3.2±1.4
Notes	comparison 7

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ragni 2004

Methods	randomisation: blocked randomisation list Trial design: parallel power calculation: yes drop-outs: Group A: 3 patients withdrew cycle cancellation: Group A: 2 cycles Group B: 1 cycle blinding: no ITT: not stated
Participants	69 women 69 cycles age of women: Group A: 33.1±3.0 Group B: 32.1±6.6 duration of subfertility: Group A: 3.2±1.1 Group B: 3.0±1.2 type of subfertility unexplained male factor endometriosis PCOS previous fertility treatment: no IUI primary subfertility: not stated
Interventions	Stimulation method/ dosage: Group A: FSH 50 IU/d; when DF>14 0.25 mg GnRHantagonist Group B: FSH 50 IU alternate days/ GnRHantagonist when DF >14mm trigger for ovulation: hCG (5000) timing IUI; 34 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: >2 follicles > 14 mm
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate

Ragni 2004 (*Continued*)

	miscarriage rate per pregnancy OHSS number of ampoules used: not stated number of dominant follicle (>16 mm): Group A: 1.5±0.5 Group B: 1.2±0.5
Notes	comparison 10

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ransom 1996

Methods	randomisation: random number table Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	98 women 240 cycles age of women: Group hMG: 32.9±4.8 Group hMG+CC: 32.3±3.4 duration of subfertility: not stated type of subfertility unexplained male factor endometriosis ovulatory dysfunction PCOS cervical factor previous fertility treatment: no IUI max 3 cycles of CC primary subfertility: not stated

Ransom 1996 (*Continued*)

Interventions	Stimulation method/ dosage: Group A: hMG 150 IU/d CD 3 Group B: CC 100 mg CD 3-7 + hMG 150 IU CD 7,9, 11 trigger for ovulation: hCG (5000) timing IUI; 34-36 hrs after hCG frequency of IUI: once semen prep technique: standard swim-up no of motile sperm injected: rA: 37.2±25.5 B: 42.4±31.7 x106 type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	pregnancy/ couple PR/cycle multiple pregnancy rate miscarriage rate per pregnancy number of ampoules used: not stated number of dominant follicle: Group A: 3.9±2.0 Group B: 4.1±2.1
Notes	comparison 8

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sammour 2001

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: none cycle cancellation: none blinding: no ITT: not stated
Participants	49 women cycles not stated age of women: letrozole: 30.7 CC 32.8 duration of subfertility: Letrozole: 26 CC: 24 (months) type of subfertility unexplained previous fertility treatment: not stated primary subfertility: not stated
Interventions	stimulation method/dosage: letrozole: 2,5 mg CD 3-7 CC: 100 mg CD 3-7 trigger for ovulation: hCG (10000) timing IUI; 24 and 48 hrs after hCG frequency of IUI: twice semen prep technique: not stated no of motile sperm injected: not stated type of semen: not stated explicitly catheter used: not stated cancellation criteria: not stated
Outcomes	pregnancy/ couple number of ampoules used: not applicable number of dominant follicle: letrozole: 6.0 CC: 5.5
Notes	comparison 4

Sammour 2001 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Scheiber 2003

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: in total 15 cycles blinding: no ITT: not stated
Participants	62 women 96 cycles age of women: not stated duration of subfertility: not stated type of subfertility PCOS previous fertility treatment: not stated primary subfertility: not stated
Interventions	Stimulation method/ dosage: Group A: rFSH 150 IU/d CD2-3 + GnRHantagonist from DF> 14 mm Group C: rFSH 150 IU/d CD2-3 trigger for ovulation: hCG (10000) timing IUI; 32-40 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not significant type of semen:

Scheiber 2003 (*Continued*)

	nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	PR/cycle number of ampoules used: not stated number of dominant follicle not stated
Notes	comparison 7

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sengoku 1994

Methods	randomisation: stated without further description Trial design: cross-over power calculation: not stated drop-outs: not stated cycle cancellation: none blinding: no ITT: not stated
Participants	91 women 91 cycles age of women: Group A: 31.6±3.3 Group B: 32.0±3.7 duration of subfertility: Group A: 5.8±3.1 Group B: 5.7±2.9 (yrs) type of subfertility unexplained previous fertility treatment; not stated primary subfertility; Group A: 32 (71%) Group B: 34 (74%)

Sengoku 1994 (*Continued*)

Interventions	stimulation method/ dosage: Group A: hMG 150 IU/d CD3 Group B: hMG 150 IU/d CD3 + GnRHa 300 uG 3 dd 1 from CD1 trigger for ovulation: hCG (10000) timing IUI; 24 -28 hrs after hCG frequency of IUI: once semen prep technique: washed twice by centrifugation no of motile sperm injected: A: 18.2±8.9 B: 18.8±9.5 x106 type of semen: nl SA thus husband semen catheter used: Tom cat catheter cancellation criteria: not stated
Outcomes	live birth ongoing PR/ women PR/cycle miscarriage rate per pregnancy multiple pregnancy rate not from first cycle OHSS number of ampoules used: Group A: 19±8 Group B: 19±6 number of dominant follicle (>12 mm): hMG alone: 6.3±3.4 hMG+GnRHa: 7.7±3.6
Notes	comparison 6

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sengoku 1999

Methods	randomisation: random number table Trial design: parallel power calculation: yes drop-outs: not stated cycle cancellation: none blinding: no ITT: not stated
Participants	97 women 97 cycles age of women: Group I: 31.8±3.5 Group II: 32.9±3.3 duration of subfertility: Group I: 4.2± 2.5 Group II: 4.6±2.0 type of subfertility unexplained previous fertility treatment; CC treatment primary subfertility; Group I: 33 (69%) Group II: 35 (71.4%)
Interventions	Stimulation method/ dosage: uFSH: 150 IU/d from CD 3 uFSH: 75 IU/d from CD 3 trigger for ovulation: hCG (5000) timing IUI; 24-28 hrs after hCG When LH surge was detected IUI was the next morning performed frequency of IUI: once semen prep technique: washed twice no of motile sperm injected: not stated type of semen: husband catheter used: Tomcat catheter cancellation criteria: not stated
Outcomes	pregnancy/ couple PR/cycle multiple PR/pregnancy miscarriage rate per pregnancy OHSS number of ampoules used:

Sengoku 1999 (*Continued*)

	uFSH (150): 19±7 uFSH (75): 13± 6 number of dominant follicle (>14 mm): uFSH (150): 4.3±3.2 uFSH (75): 2.2±1.0
Notes	comparison 10

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Unfer 2004

Methods	randomisation: stated without further description Trial design: parallel power calculation: no drop-outs: not stated cycle cancellation: not stated blinding: yes ITT: not stated
Participants	134 women cycles not stated age of women: Group A: 28± 5.6 Group B: 26± 4.2 duration of subfertility: Group A: 48.1±18.5 Group B: 36.7±9.6 (months) type of subfertility oligo/amenorroe previous fertility treatment; none primary subfertility; not stated
Interventions	stimulation method/ dosage: Group A: CC 100 mg/d CD 3-7 + phytooestrogens 1500 mg/d CD3-12 Group B: CC 100 mg/d CD 3-7 + placebo trigger for ovulation: hCG (10000) timing IUI; 24-36 hrs after hCG

Unfer 2004 (*Continued*)

	frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	ongoing PR/ women miscarriage rate for the total group OHSS number of ampoules used: not applicable number of dominant follicle not stated
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Wang 2004

Methods	randomisation: stated without further description Trial design: parallel power calculation: not stated drop-outs: not stated cycle cancellation: not stated blinding: no ITT: not stated
Participants	48 women 60 cycles age of women: not stated duration of subfertility: not stated type of subfertility not stated previous fertility treatment;

Wang 2004 (*Continued*)

	super ovulatory cycles with IUI primary subfertility; not stated
Interventions	stimulation method/ dosage: - CC 100 mg daily for 5 days - TMX 40 mg daily for 5 days + hMG 150 IU on alternate days from CD 4 trigger for ovulation: hCG (10000) timing IUI; 24-36 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: not stated type of semen: not stated catheter used: not stated cancellation criteria: not stated
Outcomes	PR/ women PR/cycle miscarriage rate per pregnancy multiple pregnancy rate number of ampoules used: not applicable number of dominant follicle CC: 3.7±1.4 TMX: 3.1±1.4
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Williams 2004

Methods	randomisation: computer-generated random system Trial design: parallel power calculation: yes drop-outs: not stated cycle cancellation: Group A: 4 cycles Group B: 9 cycles blinding: no ITT: not stated
Participants	54 women 118 cycles age of women: GnRH anta: 34.0 FSH alone: 33.0 duration of subfertility: GnRHanta: 23 (months) FSH alone: 17 (months) type of subfertility unexplained previous fertility treatment; not IUI or IVF primary subfertility; not stated
Interventions	stimulation method/ dosage: Group A: rFSH 150 IU/d from CD 2-3 + GnRHantagonist from CD 6 Group B: rFSH 150 IU/d from CD 2-3 trigger for ovulation: hCG (10000) timing IUI; 34-40 hrs after hCG frequency of IUI: once semen prep technique: not stated no of motile sperm injected: FSH+anta: 34 FSH: 26 x 106 type of semen: nl SA thus husband semen catheter used: not stated cancellation criteria: not stated
Outcomes	PR/cycle multiple pregnancy rate stated but not per pregnancy number of ampoules used: not stated number of dominant follicle (>16 mm) Group A: 1.8

Williams 2004 (*Continued*)

	Group B: 2.1
Notes	comparison 7

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

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

Study	Reason for exclusion
Allegra 1990	retrospective study also intracervical insemination
Allegra 1990 (II)	retrospective study
Alvarez 1999	not randomized Not only IUI but also directed coitus was performed
Arcaini 1996	superovulation with IUI was compared with superovulation alone which is not the comparison of interest
Brami 2004	comment/ translation of a review
Chang 1993	retrospective study
Check 1992	quasi-randomised study randomised by date of birth
Crosignani 2005	review article
DiMarzo 1992	retrospective study
Doyle 1991	ovarian stimulation with hMG and timed coitus was compared with hMG combined with intrauterine insemination
Isaza 2000	
Isaza 2003	Quasi-randomised study randomised by odds-even
Jacobson 1991	not adequately randomised.
Jaroudi 1998	ovarian stimulation combined with IUI was compared with ovarian stimulation combined with timed intercourse

(*Continued*)

Manganiello 1997	observational study
Matorras 1999	abstract contains same data as included trial with the reference: Matorras 2000
Mitwally 2002	observational cohort study
Mitwally 2003	non-randomised prospective study
Mitwally 2003 (II)	not the comparison of interest literature review
Mitwally 2004	non-randomized study
Mitwally 2005	retrospective study
Nappi 2000	not the comparison of interest overview
Nava 2004	quasi-randomised study
Nuojua-Huttunen 1997	non- randomised study
Papageorgiou 1995	IUI in natural cycles compared with IUI after mild ovarian stimulation
Prentice 1995	ovarian stimulation combined with IUI compared with expectant management quasi-randomized by alternating record numbers
Ruddock 2004	not the comparison of interest case report
Steinkampf 1993	ovarian stimulations compared without IUI
Taskin 2005	clinical trial, not randomized
Tummon 1997	ovarian stimulation combined with IUI compared with no treatment for infertility
Vasiljevic 2000	non randomized study

DATA AND ANALYSES

Comparison 1. anti-estrogens versus gonadotrophins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	1	138	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.51, 2.26]
2 pregnancy rate per couple	7	556	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [1.16, 2.66]
3 multiple pregnancy rate per couple	3	338	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.15, 1.86]
4 multiple pregnancy rate per pregnancy	4	120	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.28, 3.28]
5 miscarriage rate per couple	3	338	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.48, 2.29]
6 miscarriage rate per pregnancy	4	120	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.32, 1.67]
7 OHSS rate per couple	2	200	Odds Ratio (M-H, Fixed, 95% CI)	4.44 [0.48, 41.25]
8 ectopic pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. anti-estrogens versus aromatase inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 pregnancy rate per couple	5	313	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.64, 2.08]
3 multiple pregnancy rate per couple	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.87]
4 multiple pregnancy rate per pregnancy	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 7.03]
5 miscarriage rate per couple	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.16]
6 miscarriage rate per pregnancy	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.31]
7 OHSS rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 ectopic pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. different types of gonadotrophins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 A). hMG versus FSH	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 B). r-FSH versus u-FSH	2	4	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 pregnancy rate per couple	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 A). hMG versus FSH	5	373	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.59, 1.75]
2.2 B). r-FSH versus u-FSH	5	605	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.95, 1.94]
3 multiple pregnancy rate per couple	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 A). hMG versus FSH	2	100	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.20, 3.09]
3.2 B). r-FSH versus u-FSH	4	444	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.37, 1.97]
4 multiple pregnancy rate per pregnancy	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 A). hMG versus FSH	2	22	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.06, 2.03]
4.2 B). r-FSH versus u-FSH	4	164	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.30, 1.76]
5 miscarriage rate per couple	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 A). hMG versus FSH	2	100	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 7.39]
5.2 B). r-FSH versus u-FSH	4	444	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.64, 3.04]
6 miscarriage rate per pregnancy	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 A). hMG versus FSH	2	22	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.07, 5.62]
6.2 B). r-FSH versus u-FSH	4	155	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.58, 3.01]
7 OHSS rate per couple	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 A). hMG versus FSH	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 B). r-FSH versus u-FSH	1	116	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 9.11]
8 ectopic pregnancy rate per couple	0		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 A). hMG versus FSH	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 B). r-FSH versus u-FSH	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 pregnancy rate per couple	4	415	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.10, 2.97]
3 multiple pregnancy rate per couple	3	324	Odds Ratio (M-H, Fixed, 95% CI)	2.66 [0.96, 7.35]
4 multiple pregnancy rate per pregnancy	3	70	Odds Ratio (M-H, Fixed, 95% CI)	4.45 [1.36, 14.55]
5 miscarriage rate per couple	2	120	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.19, 5.14]
6 miscarriage rate per pregnancy	2	27	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.08, 3.13]
7 OHSS rate per couple	2	120	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.70, 5.87]

8 ectopic pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. gonadotrophins alone versus gonadotrophins with GnRH antagonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	1	80	Odds Ratio (M-H, Fixed, 95% CI)	3.04 [1.07, 8.57]
2 pregnancy rate per couple	3	299	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.83, 2.76]
3 multiple pregnancy rate per couple	3	299	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.45]
4 multiple pregnancy rate per pregnancy	3	53	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.12, 1.94]
5 miscarriage rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 miscarriage rate per pregnancy	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 OHSS rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 ectopic pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. gonadotrophins alone versus gonadotrophins with anti-estrogens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 pregnancy rate per couple	1	98	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [1.29, 7.58]
3 multiple pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 multiple pregnancy rate per pregnancy	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 miscarriage rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 miscarriage rate per pregnancy	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 OHSS rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 ectopic pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 10. Different dosage regimen for gonadotrophins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 live birth rate per couple	1	63	Odds Ratio (M-H, Fixed, 95% CI)	13.71 [1.62, 116.34]
2 pregnancy rate per couple	2	297	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.69, 1.92]
3 multiple pregnancy rate per couple	2	297	Odds Ratio (M-H, Fixed, 95% CI)	3.11 [0.48, 20.13]
4 multiple pregnancy rate per pregnancy	2	88	Odds Ratio (M-H, Fixed, 95% CI)	3.35 [0.46, 24.58]
5 miscarriage rate per couple	2	297	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 1.05]
6 miscarriage rate per pregnancy	2	88	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.07, 1.09]
7 OHSS rate per couple	2	297	Odds Ratio (M-H, Fixed, 95% CI)	5.52 [1.85, 16.52]
8 ectopic pregnancy rate per couple	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 11. Other comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 estrogens added to anti-estrogens	1	64	Odds Ratio (M-H, Fixed, 95% CI)	9.0 [1.82, 44.59]
2 aromatase inhibitors versus gonadotrophins	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.37, 3.95]
3 GnRH agonist in different dosages	1	80	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [1.02, 6.59]
4 phyto-estrogens added to anti-estrogens	1	134	Odds Ratio (M-H, Fixed, 95% CI)	5.5 [1.49, 20.32]
5 tamoxifen with gonadotrophins versus anti-estrogens	1	48	Odds Ratio (M-H, Fixed, 95% CI)	4.2 [0.98, 18.03]

Analysis 1.1. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 1 live birth rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 1 live birth rate per couple

Study or subgroup	anti-estrogens n/N	gonadotrophins n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dankert 2006	20/71	18/67		100.0 %	1.07 [0.51, 2.26]
Total (95% CI)	**71**	**67**		**100.0 %**	**1.07 [0.51, 2.26]**

Total events: 20 (anti-estrogens), 18 (gonadotrophins)
Heterogeneity: not applicable
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 2 pregnancy rate per couple

Study or subgroup	Gonadotrophins n/N	Anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	12/50	4/50		8.9 %	3.63 [1.08, 12.18]
Dankert 2006	17/67	19/71		40.2 %	0.93 [0.43, 1.99]
Ecochard 2000	3/29	6/29		15.7 %	0.44 [0.10, 1.97]
Kamel 1995	4/28	2/26		5.2 %	2.00 [0.33, 11.97]
Karlstrom 1993	3/15	1/17		2.2 %	4.00 [0.37, 43.38]
Karlstrom 1998	8/40	4/34		10.1 %	1.88 [0.51, 6.88]
Matorras 2002	30/49	16/51		17.7 %	3.45 [1.51, 7.88]
Total (95% CI)	**278**	**278**		**100.0 %**	**1.76 [1.16, 2.66]**

Total events: 77 (Gonadotrophins), 52 (Anti-estrogens)

Heterogeneity: Chi^2 = 10.40, df = 6 (P = 0.11); I^2 =42%

Test for overall effect: Z = 2.68 (P = 0.0074)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 3 multiple pregnancy rate per couple.

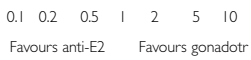
Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 3 multiple pregnancy rate per couple

Study or subgroup	anti-E2 n/N	gonadotrophins n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	0/50	0/50			Not estimable
Dankert 2006	2/71	1/67		14.5 %	1.91 [0.17, 21.60]
Matorras 2002	2/51	6/49		85.5 %	0.29 [0.06, 1.53]
Total (95% CI)	**172**	**166**		**100.0 %**	**0.53 [0.15, 1.86]**

Total events: 4 (anti-E2), 7 (gonadotrophins)
Heterogeneity: Chi^2 = 1.57, df = 1 (P = 0.21); I^2 =36%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 4 multiple pregnancy rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 4 multiple pregnancy rate per pregnancy

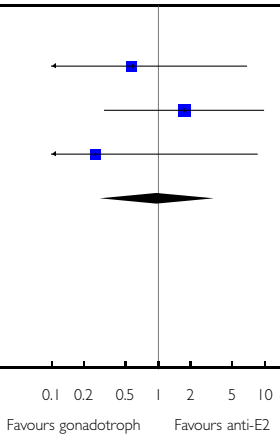
Study or subgroup	gonadotrophins n/N	Anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	0/12	0/4			Not estimable
Dankert 2006	1/23	2/27		33.9 %	0.57 [0.05, 6.70]
Matorras 2002	6/30	2/16		40.2 %	1.75 [0.31, 9.88]
Nakajima 1999	0/4	1/4		26.0 %	0.26 [0.01, 8.52]
Total (95% CI)	**69**	**51**		**100.0 %**	**0.96 [0.28, 3.28]**

Total events: 7 (gonadotrophins), 5 (Anti-estrogens)

Heterogeneity: $Chi^2 = 1.18$, df = 2 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 5 miscarriage rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 5 miscarriage rate per couple

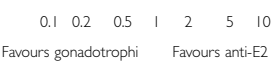
Study or subgroup	gonadotrophins n/N	Anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	1/50	2/50		15.9 %	0.49 [0.04, 5.58]
Dankert 2006	5/67	7/71		50.9 %	0.74 [0.22, 2.45]
Matorras 2002	8/49	5/51		33.2 %	1.80 [0.54, 5.92]
Total (95% CI)	**166**	**172**		**100.0 %**	**1.05 [0.48, 2.29]**

Total events: 14 (gonadotrophins), 14 (Anti-estrogens)

Heterogeneity: Chi^2 = 1.49, df = 2 (P = 0.48); I^2 =0.0%

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

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 6 miscarriage rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 6 miscarriage rate per pregnancy

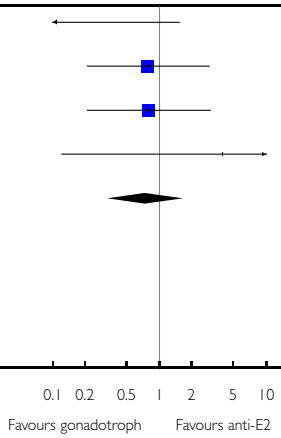
Study or subgroup	gonadotrophins n/N	anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	1/12	2/4		21.3 %	0.09 [0.01, 1.55]
Dankert 2006	5/23	7/27		39.0 %	0.79 [0.21, 2.95]
Matorras 2002	8/30	5/16		37.0 %	0.80 [0.21, 3.03]
Nakajima 1999	1/4	0/4		2.7 %	3.86 [0.12, 126.73]
Total (95% CI)	**69**	**51**		**100.0 %**	**0.73 [0.32, 1.67]**

Total events: 15 (gonadotrophins), 14 (anti-estrogens)

Heterogeneity: $Chi^2 = 2.98$, df = 3 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 7 OHSS rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 7 OHSS rate per couple

Study or subgroup	gonadotrophins n/N	Estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	0/50	0/50			Not estimable
Matorras 2002	4/49	1/51		100.0 %	4.44 [0.48, 41.25]
Total (95% CI)	**99**	**101**		**100.0 %**	**4.44 [0.48, 41.25]**

Total events: 4 (gonadotrophins), 1 (Estrogens)
Heterogeneity: not applicable
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 anti-estrogens versus aromatase inhibitors, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 4 anti-estrogens versus aromatase inhibitors

Outcome: 2 pregnancy rate per couple

Study or subgroup	aromatase inhibitor n/N	anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Al-Fozan 2004	13/74	15/80		57.8 %	0.92 [0.41, 2.10]
El Helw 2002	5/27	3/26		12.1 %	1.74 [0.37, 8.18]
Fatemi 2003	2/7	3/8		9.7 %	0.67 [0.08, 5.88]
Ozmen 2005	4/22	3/21		12.2 %	1.33 [0.26, 6.83]
Sammour 2001	4/24	2/24		8.1 %	2.20 [0.36, 13.34]
Total (95% CI)	**154**	**159**		**100.0 %**	**1.15 [0.64, 2.08]**

Total events: 28 (aromatase inhibitor), 26 (anti-estrogens)

Heterogeneity: Chi^2 = 1.32, df = 4 (P = 0.86); I^2 =0.0%

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 anti-estrogens versus aromatase inhibitors, Outcome 3 multiple pregnancy rate per couple.

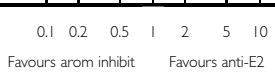
Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 4 anti-estrogens versus aromatase inhibitors

Outcome: 3 multiple pregnancy rate per couple

Study or subgroup	Aromatase inhibitors n/N	Anti-E2 n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Al-Fozan 2004	0/74	1/80		100.0 %	0.36 [0.01, 8.87]
Total (95% CI)	**74**	**80**		**100.0 %**	**0.36 [0.01, 8.87]**

Total events: 0 (Aromatase inhibitors), 1 (Anti-E2)
Heterogeneity: not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4 anti-estrogens versus aromatase inhibitors, Outcome 4 multiple pregnancy rate per pregnancy.

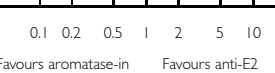
Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 4 anti-estrogens versus aromatase inhibitors

Outcome: 4 multiple pregnancy rate per pregnancy

Study or subgroup	aromatase inhibitor n/N	anti-E2 n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Al-Fozan 2004	0/13	1/11		100.0 %	0.26 [0.01, 7.03]
Total (95% CI)	**13**	**11**		**100.0 %**	**0.26 [0.01, 7.03]**

Total events: 0 (aromatase inhibitor), 1 (anti-E2)
Heterogeneity: not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4 anti-estrogens versus aromatase inhibitors, Outcome 5 miscarriage rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 4 anti-estrogens versus aromatase inhibitors

Outcome: 5 miscarriage rate per couple

Study or subgroup	Aromatase inhibitors n/N	Anti-E2 n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Al-Fozan 2004	0/74	4/80		100.0 %	0.11 [0.01, 2.16]
Total (95% CI)	**74**	**80**		**100.0 %**	**0.11 [0.01, 2.16]**
Total events: 0 (Aromatase inhibitors), 4 (Anti-E2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: Not applicable					

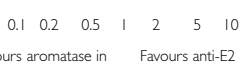
Analysis 4.6. Comparison 4 anti-estrogens versus aromatase inhibitors, Outcome 6 miscarriage rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 4 anti-estrogens versus aromatase inhibitors

Outcome: 6 miscarriage rate per pregnancy

Study or subgroup	aromatase inhibitors n/N	anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Al-Fozan 2004	0/13	4/11		100.0 %	0.06 [0.00, 1.31]
Total (95% CI)	**13**	**11**		**100.0 %**	**0.06 [0.00, 1.31]**
Total events: 0 (aromatase inhibitors), 4 (anti-estrogens)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.074)					
Test for subgroup differences: Not applicable					



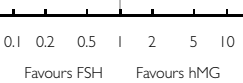
Analysis 5.1. Comparison 5 different types of gonadotrophins, Outcome 1 live birth rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 1 live birth rate per couple

Study or subgroup	hMG n/N	FSH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 A). hMG versus FSH					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (hMG), 0 (FSH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 B). r-FSH versus u-FSH					
Gerli 2004	0/1	0/1			Not estimable
Gerli 2004 (II)	0/1	0/1			Not estimable
Subtotal (95% CI)	**2**	**2**			**Not estimable**
Total events: 0 (hMG), 0 (FSH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

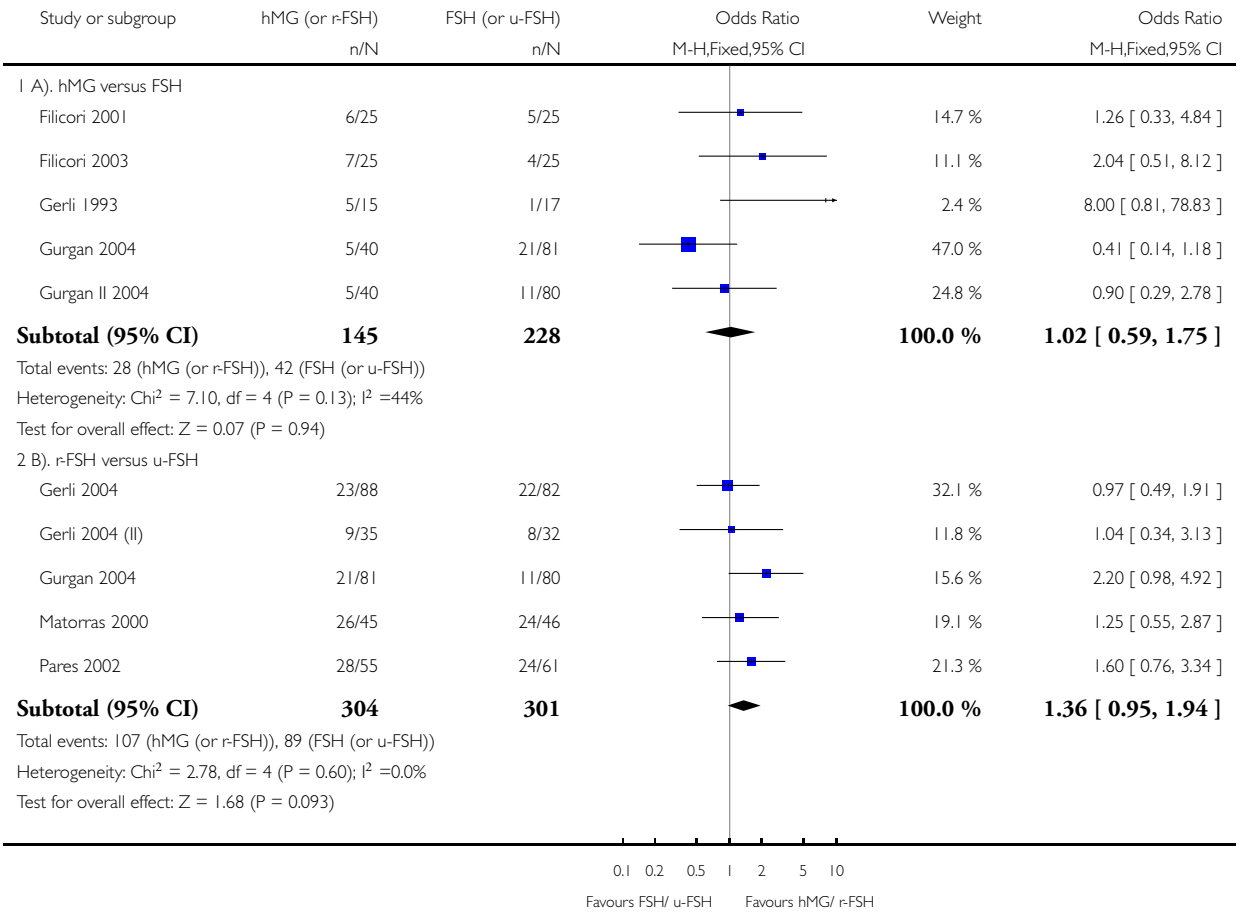


Analysis 5.2. Comparison 5 different types of gonadotrophins, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 2 pregnancy rate per couple

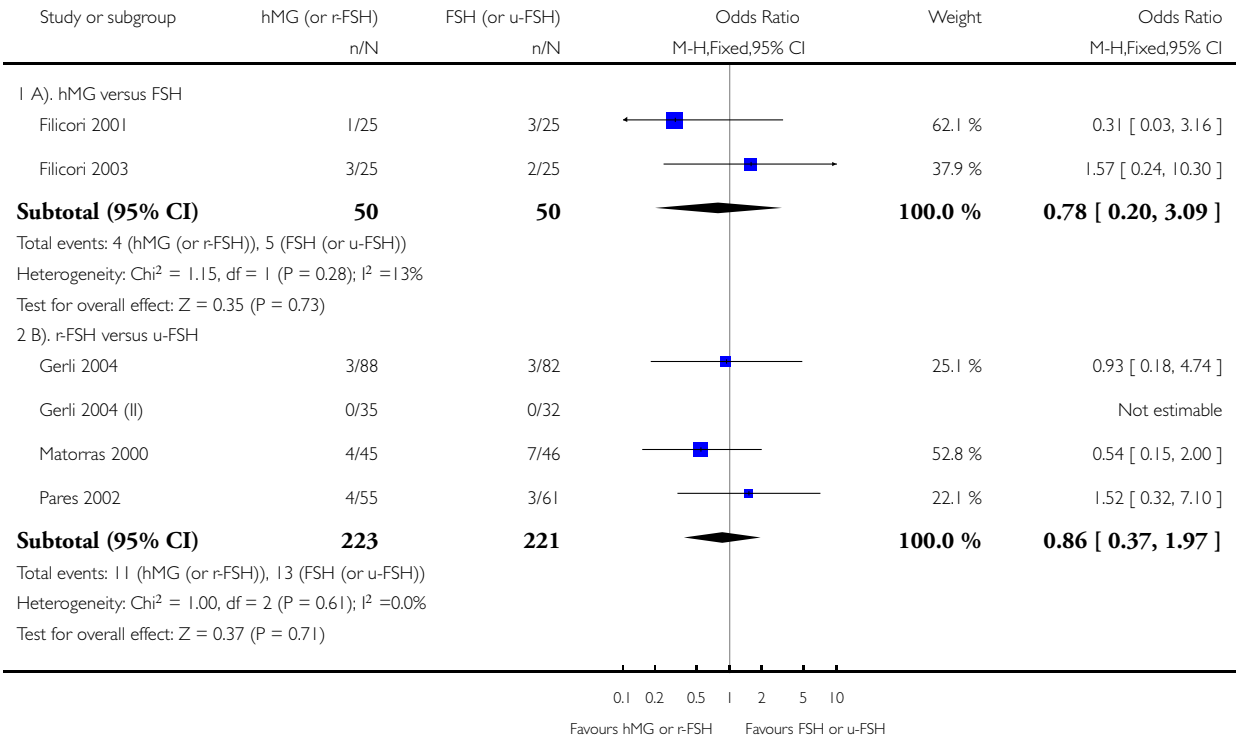


Analysis 5.3. Comparison 5 different types of gonadotrophins, Outcome 3 multiple pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 3 multiple pregnancy rate per couple

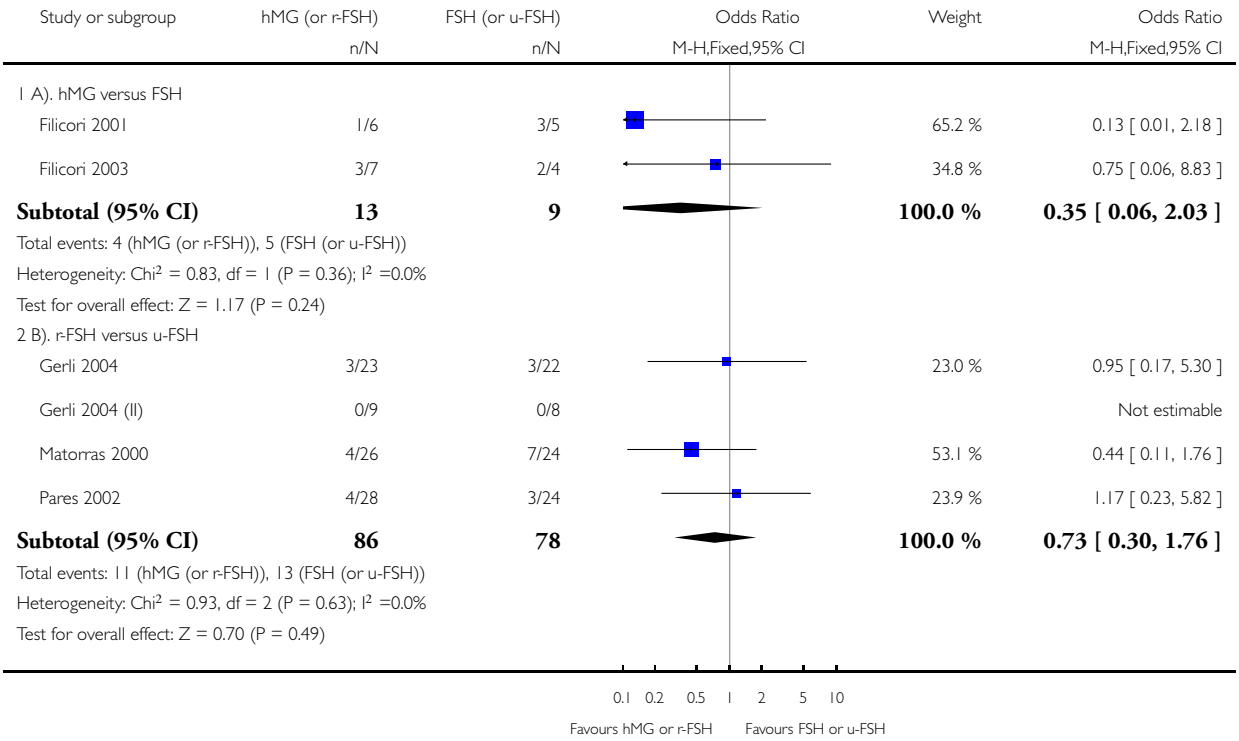


Analysis 5.4. Comparison 5 different types of gonadotrophins, Outcome 4 multiple pregnancy rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 4 multiple pregnancy rate per pregnancy



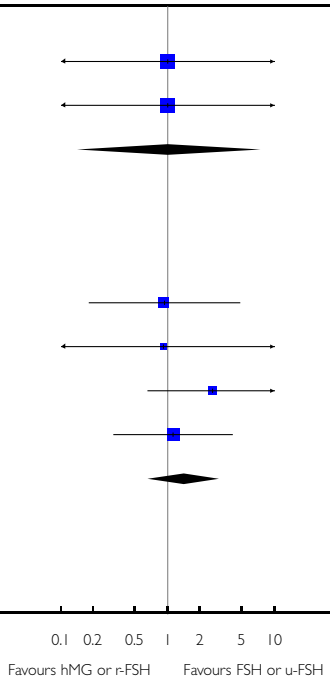
Analysis 5.5. Comparison 5 different types of gonadotrophins, Outcome 5 miscarriage rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 5 miscarriage rate per couple

Study or subgroup	hMG (or r-FSH) n/N	FSH (or u-FSH) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 A). hMG versus FSH					
Filicori 2001	1/25	1/25		50.0 %	1.00 [0.06, 16.93]
Filicori 2003	1/25	1/25		50.0 %	1.00 [0.06, 16.93]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**1.00 [0.14, 7.39]**
Total events: 2 (hMG (or r-FSH)), 2 (FSH (or u-FSH))					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 B). r-FSH versus u-FSH					
Gerli 2004	3/88	3/82		27.7 %	0.93 [0.18, 4.74]
Gerli 2004 (II)	1/35	1/32		9.4 %	0.91 [0.05, 15.21]
Matorras 2000	7/45	3/46		23.1 %	2.64 [0.64, 10.94]
Pares 2002	5/55	5/61		39.8 %	1.12 [0.31, 4.10]
Subtotal (95% CI)	**223**	**221**		**100.0 %**	**1.40 [0.64, 3.04]**
Total events: 16 (hMG (or r-FSH)), 12 (FSH (or u-FSH))					
Heterogeneity: Chi^2 = 1.21, df = 3 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 0.85 (P = 0.40)					

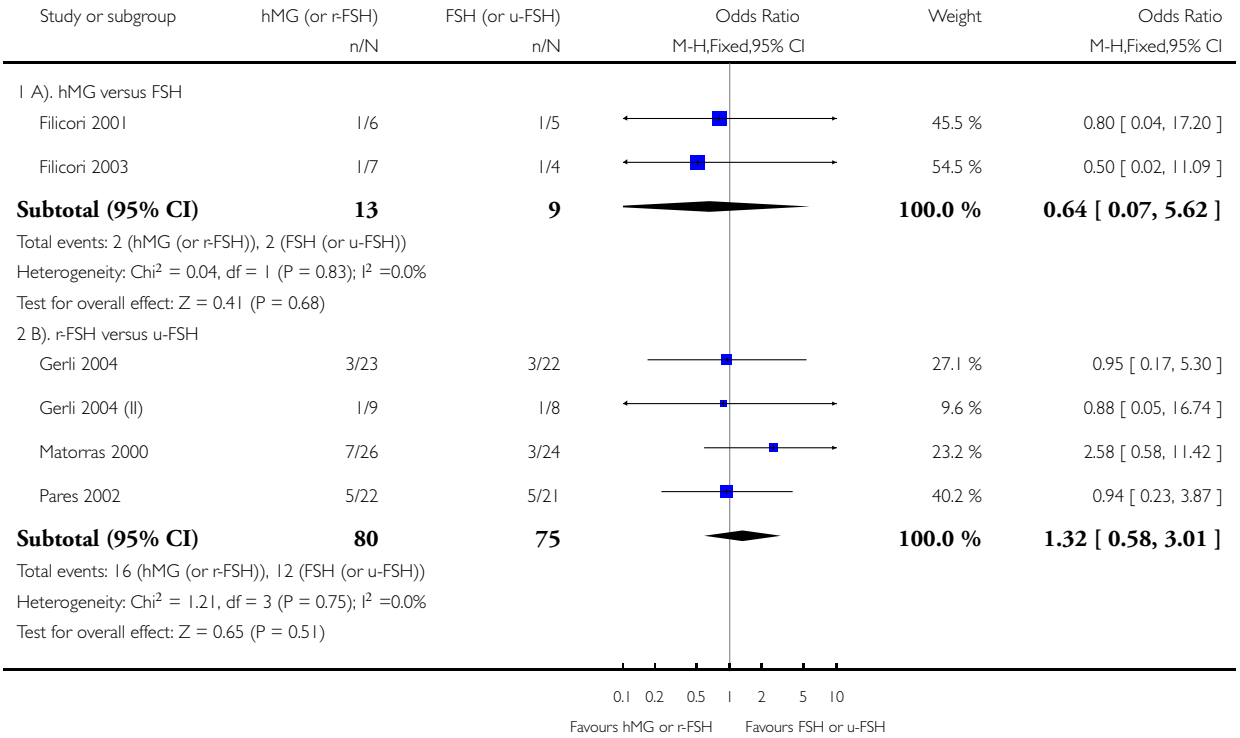


Analysis 5.6. Comparison 5 different types of gonadotrophins, Outcome 6 miscarriage rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 6 miscarriage rate per pregnancy

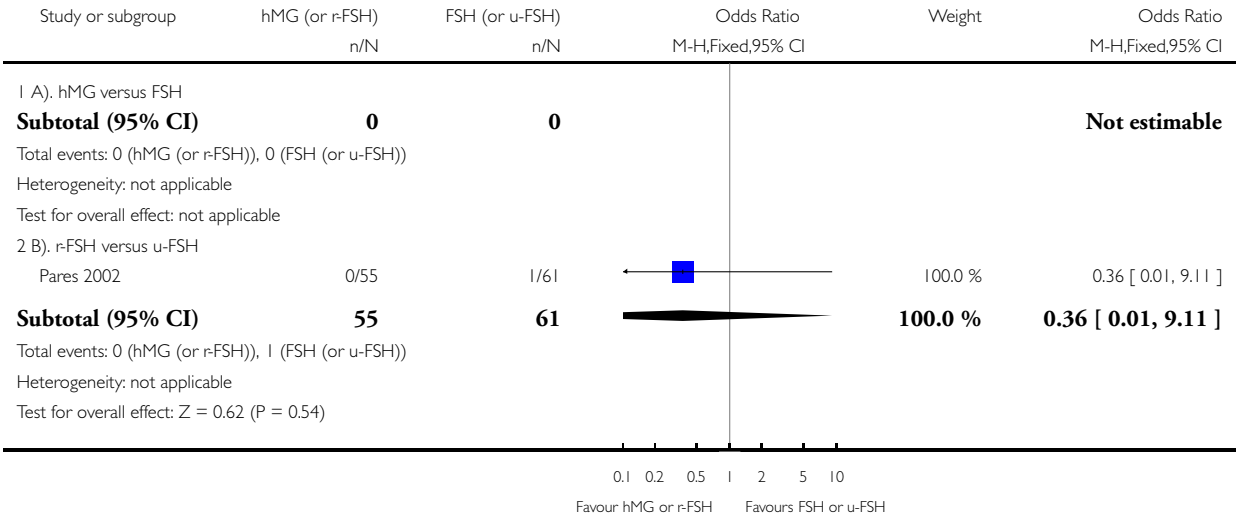


Analysis 5.7. Comparison 5 different types of gonadotrophins, Outcome 7 OHSS rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 7 OHSS rate per couple

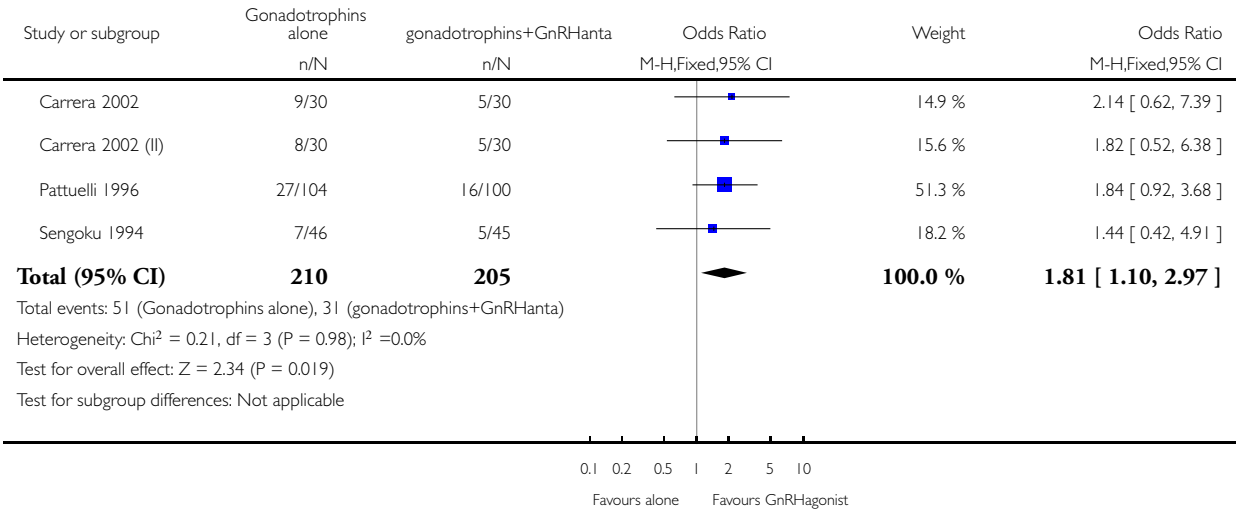


Analysis 6.2. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 2 pregnancy rate per couple



Analysis 6.3. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 3 multiple pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 3 multiple pregnancy rate per couple

Study or subgroup	Gonadotrophins+GnRHa n/N	Gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Carrera 2002	2/30	0/30		9.3 %	5.35 [0.25, 116.31]
Carrera 2002 (II)	3/30	1/30		18.1 %	3.22 [0.32, 32.89]
Pattuelli 1996	8/100	4/104		72.6 %	2.17 [0.63, 7.46]
Total (95% CI)	**160**	**164**		**100.0 %**	**2.66 [0.96, 7.35]**

Total events: 13 (Gonadotrophins+GnRHa), 5 (Gonadotrophins alone)

Heterogeneity: $Chi^2 = 0.33$, df = 2 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable

Analysis 6.4. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 4 multiple pregnancy rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 4 multiple pregnancy rate per pregnancy

Study or subgroup	Gonadotrophins+GnRHa n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Carrera 2002	2/9	0/5		17.2 %	3.67 [0.15, 92.65]
Carrera 2002 (II)	3/8	1/5		28.2 %	2.40 [0.18, 32.88]
Pattuelli 1996	8/16	4/27		54.6 %	5.75 [1.36, 24.39]
Total (95% CI)	**33**	**37**		**100.0 %**	**4.45 [1.36, 14.55]**

Total events: 13 (Gonadotrophins+GnRHa), 5 (gonadotrophins alone)

Heterogeneity: $Chi^2 = 0.35$, df = 2 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 2.47 (P = 0.014)

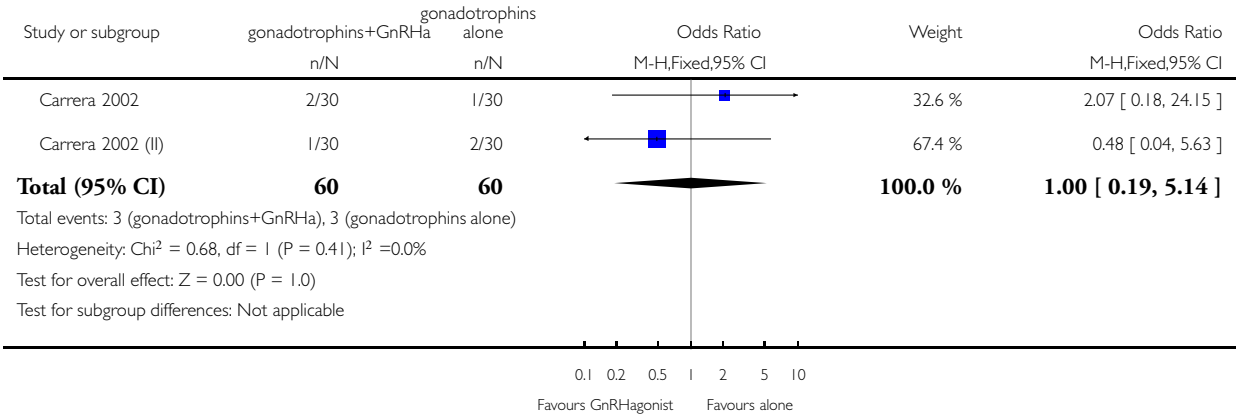
Test for subgroup differences: Not applicable

Analysis 6.5. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 5 miscarriage rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 5 miscarriage rate per couple



Analysis 6.6. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 6 miscarriage rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 6 miscarriage rate per pregnancy

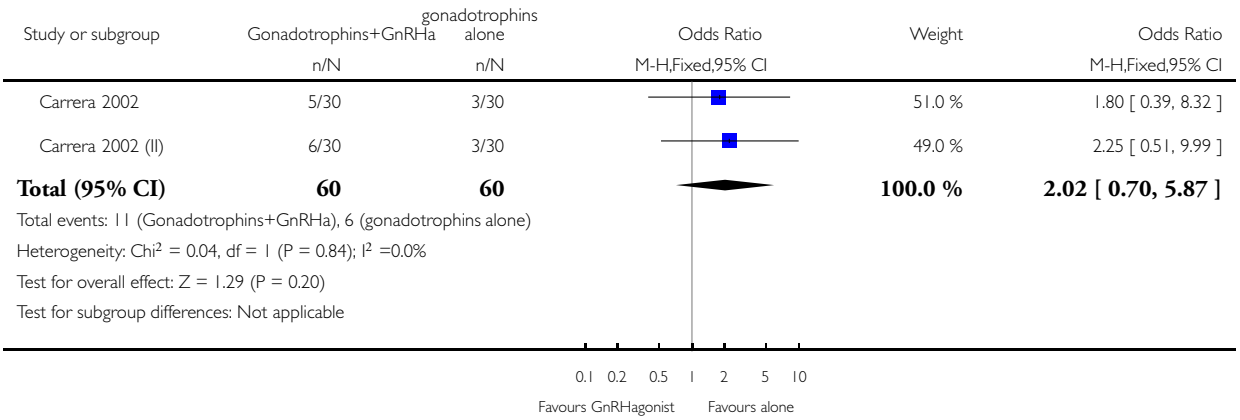
Study or subgroup	gonadotrophins+GnRHa n/N	Gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Carrera 2002	2/9	1/5		31.7 %	1.14 [0.08, 16.95]
Carrera 2002 (II)	1/8	2/5		68.3 %	0.21 [0.01, 3.37]
Total (95% CI)	**17**	**10**		**100.0 %**	**0.51 [0.08, 3.13]**
Total events: 3 (gonadotrophins+GnRHa), 3 (Gonadotrophins alone)					
Heterogeneity: Chi^2 = 0.72, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 0.73 (P = 0.47)					
Test for subgroup differences: Not applicable					

Analysis 6.7. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 7 OHSS rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 7 OHSS rate per couple



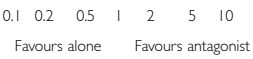
Analysis 7.1. Comparison 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist, Outcome 1 live birth rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist

Outcome: 1 live birth rate per couple

Study or subgroup	gonadotrophins+antag n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gomez 2005	15/39	7/41		100.0 %	3.04 [1.07, 8.57]
Total (95% CI)	**39**	**41**		**100.0 %**	**3.04 [1.07, 8.57]**
Total events: 15 (gonadotrophins+antag), 7 (gonadotrophins alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.10 (P = 0.036)					
Test for subgroup differences: Not applicable					



Analysis 7.2. Comparison 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist

Outcome: 2 pregnancy rate per couple

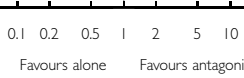
Study or subgroup	gonadotrophins+antag n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gomez 2005	15/39	7/41		24.2 %	3.04 [1.07, 8.57]
Lambalk 2006	13/93	12/85		62.2 %	0.99 [0.42, 2.30]
Ragni 2001	3/19	3/22		13.5 %	1.19 [0.21, 6.72]
Total (95% CI)	**151**	**148**		**100.0 %**	**1.51 [0.83, 2.76]**

Total events: 31 (gonadotrophins+antag), 22 (gonadotrophins alone)

Heterogeneity: $Chi^2 = 2.77$, df = 2 (P = 0.25); $I^2 = 28\%$

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist, Outcome 3 multiple pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist

Outcome: 3 multiple pregnancy rate per couple

Study or subgroup	gonadotrophins+antag n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gomez 2005	1/39	0/41		8.3 %	3.23 [0.13, 81.79]
Lambalk 2006	2/93	2/85		35.9 %	0.91 [0.13, 6.62]
Ragni 2001	0/19	3/22		55.8 %	0.14 [0.01, 2.95]
Total (95% CI)	**151**	**148**		**100.0 %**	**0.67 [0.19, 2.45]**

Total events: 3 (gonadotrophins+antag), 5 (gonadotrophins alone)

Heterogeneity: $Chi^2 = 2.00$, df = 2 (P = 0.37); $I^2 = 0\%$

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

Analysis 7.4. Comparison 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist, Outcome 4 multiple pregnancy rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist

Outcome: 4 multiple pregnancy rate per pregnancy

Study or subgroup	Gonadotrophins+antag n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gomez 2005	1/15	0/7		11.1 %	1.55 [0.06, 42.91]
Lambalk 2006	2/13	2/12		32.4 %	0.91 [0.11, 7.72]
Ragni 2001	0/3	3/3		56.4 %	0.02 [0.00, 1.35]
Total (95% CI)	**31**	**22**		**100.0 %**	**0.48 [0.12, 1.94]**

Total events: 3 (Gonadotrophins+antag), 5 (gonadotrophins alone)

Heterogeneity: $Chi^2 = 3.00$, df = 2 (P = 0.22); $I^2 = 33\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

Analysis 8.2. Comparison 8 gonadotrophins alone versus gonadotrophins with anti-estrogens, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 8 gonadotrophins alone versus gonadotrophins with anti-estrogens

Outcome: 2 pregnancy rate per couple

Study or subgroup	gonadotroph+anti-E2 n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Ransom 1996	25/53	10/45		100.0 %	3.13 [1.29, 7.58]
Total (95% CI)	**53**	**45**		**100.0 %**	**3.13 [1.29, 7.58]**
Total events: 25 (gonadotroph+anti-E2), 10 (gonadotrophins alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.52 (P = 0.012)					
Test for subgroup differences: Not applicable					

Analysis 10.1. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 1 live birth rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 1 live birth rate per couple

Study or subgroup	daily dose n/N	alternate day dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Ragni 2004	9/30	1/33		100.0 %	13.71 [1.62, 116.34]
Total (95% CI)	**30**	**33**		**100.0 %**	**13.71 [1.62, 116.34]**
Total events: 9 (daily dose), 1 (alternate day dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.40 (P = 0.016)					
Test for subgroup differences: Not applicable					

Analysis 10.2. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 2 pregnancy rate per couple

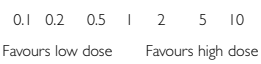
Study or subgroup	high dose n/N	low dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dhaliwal 2002	39/100	35/100		78.3 %	1.19 [0.67, 2.11]
Sengoku 1999	7/48	7/49		21.7 %	1.02 [0.33, 3.18]
Total (95% CI)	**148**	**149**		**100.0 %**	**1.15 [0.69, 1.92]**

Total events: 46 (high dose), 42 (low dose)

Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 3 multiple pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 3 multiple pregnancy rate per couple

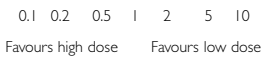
Study or subgroup	high dose n/N	low dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dhaliwal 2002	2/100	0/100		34.0 %	5.10 [0.24, 107.62]
Sengoku 1999	2/48	1/49		66.0 %	2.09 [0.18, 23.81]
Total (95% CI)	**148**	**149**		**100.0 %**	**3.11 [0.48, 20.13]**

Total events: 4 (high dose), 1 (low dose)

Heterogeneity: $Chi^2 = 0.20$, df = 1 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



Analysis 10.4. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 4 multiple pregnancy rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 4 multiple pregnancy rate per pregnancy

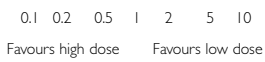
Study or subgroup	High dose n/N	low dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dhaliwal 2002	2/39	0/35		40.9 %	4.73 [0.22, 102.05]
Sengoku 1999	2/7	1/7		59.1 %	2.40 [0.16, 34.93]
Total (95% CI)	**46**	**42**		**100.0 %**	**3.35 [0.46, 24.58]**

Total events: 4 (High dose), 1 (low dose)

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



Analysis 10.5. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 5 miscarriage rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 5 miscarriage rate per couple

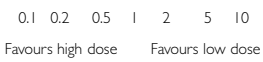
Study or subgroup	high dose n/N	low dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dhaliwal 2002	2/100	9/100		89.9 %	0.21 [0.04, 0.98]
Sengoku 1999	1/49	1/48		10.1 %	0.98 [0.06, 16.12]
Total (95% CI)	**149**	**148**		**100.0 %**	**0.28 [0.08, 1.05]**

Total events: 3 (high dose), 10 (low dose)

Heterogeneity: $Chi^2 = 0.91$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable



Analysis 10.6. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 6 miscarriage rate per pregnancy.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 6 miscarriage rate per pregnancy

Study or subgroup	high dose n/N	low dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dhaliwal 2002	2/35	9/39		90.4 %	0.20 [0.04, 1.01]
Sengoku 1999	1/7	1/7		9.6 %	1.00 [0.05, 19.96]
Total (95% CI)	**42**	**46**		**100.0 %**	**0.28 [0.07, 1.09]**
Total events: 3 (high dose), 10 (low dose)					
Heterogeneity: Chi^2 = 0.85, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 1.83 (P = 0.067)					
Test for subgroup differences: Not applicable					

Analysis 10.7. Comparison 10 Different dosage regimen for gonadotrophins, Outcome 7 OHSS rate per couple.

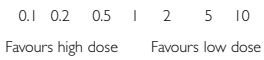
Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 10 Different dosage regimen for gonadotrophins

Outcome: 7 OHSS rate per couple

Study or subgroup	high dose n/N	low dose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dhaliwal 2002	6/100	0/100		13.9 %	13.83 [0.77, 248.79]
Sengoku 1999	13/48	4/49		86.1 %	4.18 [1.25, 13.94]
Total (95% CI)	**148**	**149**		**100.0 %**	**5.52 [1.85, 16.52]**

Total events: 19 (high dose), 4 (low dose)
Heterogeneity: Chi^2 = 0.59, df = 1 (P = 0.44); I^2 =0.0%
Test for overall effect: Z = 3.06 (P = 0.0022)
Test for subgroup differences: Not applicable



Analysis 11.1. Comparison 11 Other comparisons, Outcome 1 estrogens added to anti-estrogens.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 11 Other comparisons

Outcome: 1 estrogens added to anti-estrogens

Study or subgroup	CC+E2 n/N	CC alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gerli 2000	12/32	2/32		100.0 %	9.00 [1.82, 44.59]
Total (95% CI)	**32**	**32**		**100.0 %**	**9.00 [1.82, 44.59]**

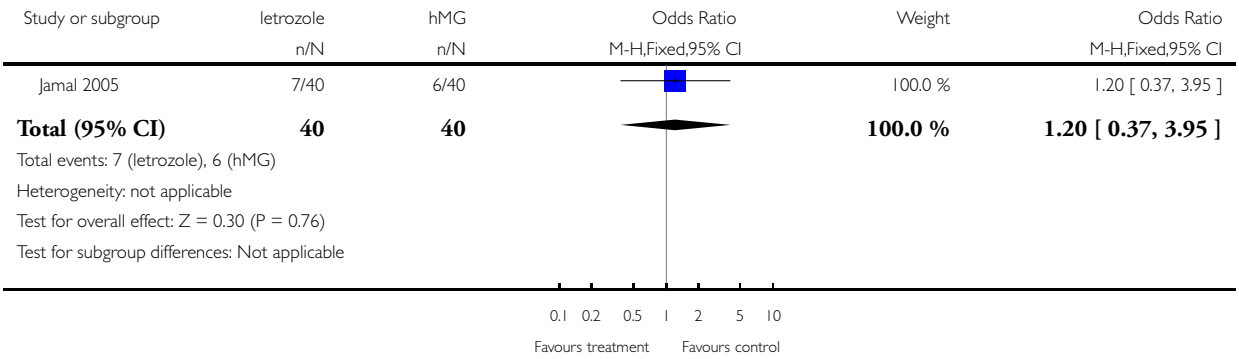
Total events: 12 (CC+E2), 2 (CC alone)
Heterogeneity: not applicable
Test for overall effect: Z = 2.69 (P = 0.0071)
Test for subgroup differences: Not applicable

Analysis 11.2. Comparison 11 Other comparisons, Outcome 2 aromatase inhibitors versus gonadotrophins.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 11 Other comparisons

Outcome: 2 aromatase inhibitors versus gonadotrophins

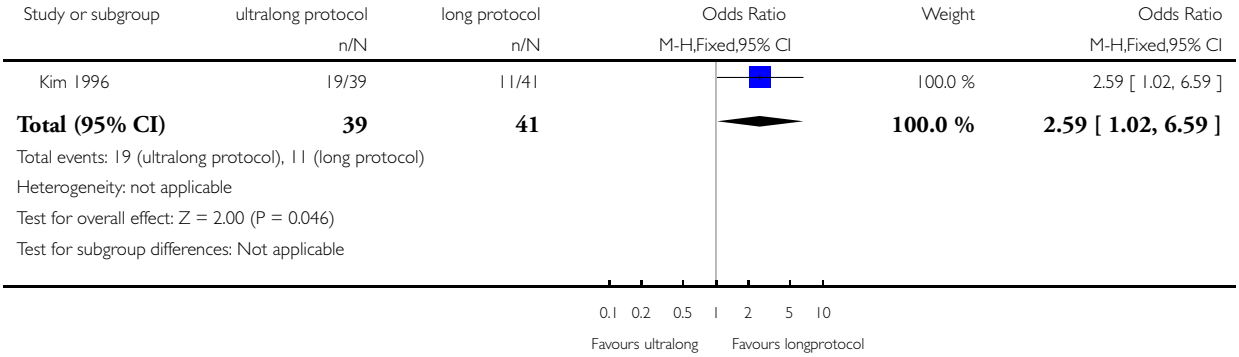


Analysis 11.3. Comparison 11 Other comparisons, Outcome 3 GnRH agonist in different dosages.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 11 Other comparisons

Outcome: 3 GnRH agonist in different dosages

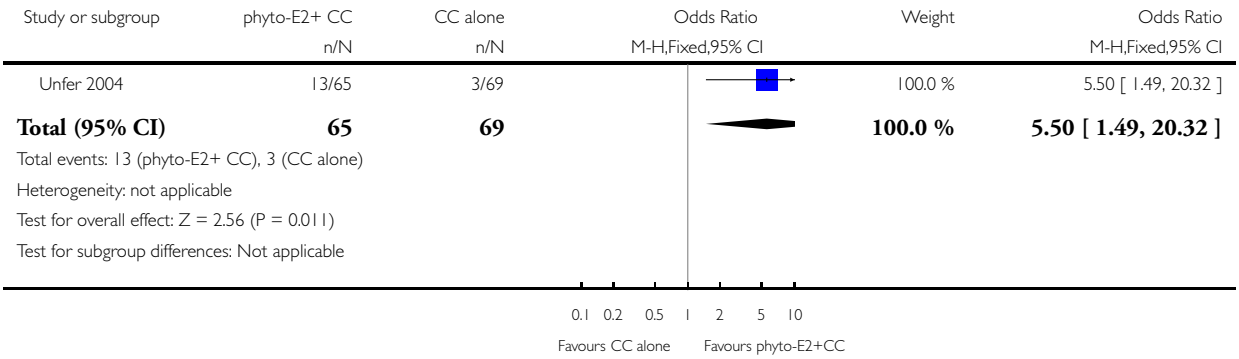


Analysis 11.4. Comparison 11 Other comparisons, Outcome 4 phyto-estrogens added to anti-estrogens.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 11 Other comparisons

Outcome: 4 phyto-estrogens added to anti-estrogens

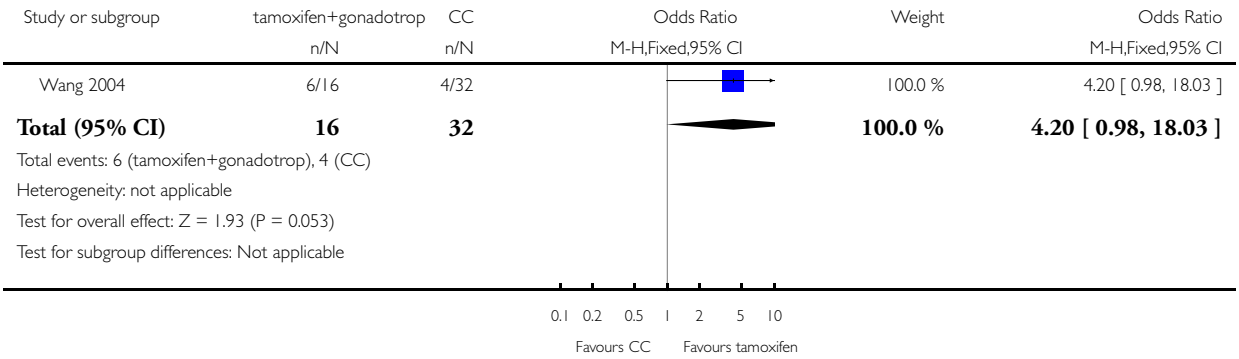


Analysis 11.5. Comparison 11 Other comparisons, Outcome 5 tamoxifen with gonadotrophins versus anti-estrogens.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 11 Other comparisons

Outcome: 5 tamoxifen with gonadotrophins versus anti-estrogens



ADDITIONAL TABLES

Table 1. studies awaiting assessment

Studies	Reason for awaiting
Bekuretsion 1999	Abstract from congress meeting; At the weekend couples were instructed to have intercourse. If data of IUI cycles can be extracted this data could be included
Colombi 1996	Abstract from congress meeting; It is stated that study prospective and randomised but the group size differs too much 233 versus 192 cycles
Fernandez 2001	Abstract from congress meeting; 5.6% of the cycles were followed by timed intercourse. If data from IUI cycles can be extracted this can be included
Karande 1995	Trial stated randomisation method for insemination technique. It is not clear whether randomisation is used for ovarian stimulation
Karlstrom 2000	118 couples received DIPI and 33 couples IUI. At the weekends couples were instructed to have intercourse. If data of IUI cycles is available these couples with one insemination could be included
Karlstrom 2002	Abstract from congress meeting; not clear which couple received IUI or intercourse
Kotecki 2005	This trial is stated as randomised but the treatment groups have totally different sizes

Table 2. study quality

study	concealment of alloc	randomisation	blinding	intention to treat	power calculation
Balasch 1994	unclear	stated without further description	no	not stated	no
Dankert 2005	unclear	computer generated list	no	not stated	no
Ecochard 2000	adequate	random number table	no	yes	yes
Kamel 1995	unclear	stated without further description	no	not stated	no
Karlstrom 1993	unclear	stated without further description	no	not stated	no
Karlstrom 1998	unclear	stated without further description	no	not stated	no
Nakajima 1999	inadequate	open randomized list	no	not stated	no
Matorras 2002	unclear	computer generated random list	no	not stated	no
Al-Fozan 2004	unclear	computer generated random table	no	not stated	no
El Helw 2002	unclear	stated without further description	no	not stated	no
Fatemi 2003	unclear	random number table	no	not stated	no
Ozmen 2005	unclear	stated without further description	no	not stated	no
Sammour 2001	unclear	stated without further description	no	not stated	no
Filicori 2001	unclear	stated without further description	no	not stated	no

Table 2. study quality (*Continued*)

Filicori 2003	unclear	stated without further description	no	not stated	no
Gerli 1993	unclear	stated without further description	no	not stated	no
Gerli 2004	adequate	randomisation table	no	yes	no
Gerli 2004 II	adequate	randomsation table	no	yes	no
Matorras 2000	adequate	computer generated list	single-blinded	yes	no
Pares 2002	unclear	stated without further description	no	yes	no
Demirol 2002	adequate	computer generated random number table	no	not stated	no
Gurgan 2004	unclear	stated without further description	no	not stated	no
Carrera 2002	unclear	numeric list	no	not stated	no
Carrera 2002	unclear	stated without further description	no	not stated	no
Dodson 1991	unclear	stated without further description	no	not stated	yes
Pattuelli 1996	unclear	stated without further description	no	not stated	no
Sengoku 1994	unclear	stated without further description	no	not stated	no
Gomez 2005	unclear	computer generated list	no	not stated	no
Lambalk 2006	unclear	stated without further description	double-blinded	yes	yes

Table 2. study quality (*Continued*)

Ragni 2001	unclear	computer generated list	no	not stated	no
Scheiber 2003	unclear	stated without further description	no	not stated	no
Williams 2004	adequate	computer generated list	no	not stated	yes
Ransom 1996	unclear	random number table	no	not stated	no
Al Fadhli 2005	unclear	stated without further description	no	not stated	no
Dhaliwal 2002	unclear	computer generated random number table	no	not stated	no
Hughes 1998	unclear	central randomisation scheme	no	not stated	yes
Ragni 2004	adequate	blocked randomisation list	no	not stated	yes
Sengoku 1999	adequate	random number table	no	not stated	yes
Gerli 2000	unclear	stated without further description	no	not stated	no
Jamal 2005	unclear	stated without further description	no	not stated	no
Kim 1996	unclear	blocked randomisation design	no	not stated	no
Unfer 2004	unclear	stated without further description	no	not stated	no

Table 2. study quality (*Continued*)

Wang 2004	unclear	stated without further description	no	not stated	no

WHAT'S NEW

Last assessed as up-to-date: 23 January 2007.

Date	Event	Description
12 November 2010	Amended	The results of comparison 6.2 and 6.3 have been edited in the text and data/analysis section

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 2, 2007

Date	Event	Description
24 January 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AEP Cantineau took lead in developing the protocol.

MJ Heineman and BJ Cohlen commented drafts of the protocol.

DECLARATIONS OF INTEREST

Recently, we started a large randomised controlled trial comparing recFSH with a GnRH antagonist with recFSH alone. This is an investigators-initiated trial.

Medication used in this trial has been supplied by Serono B.V. only. Serono B.V. is unable to interfere with the results of this RCT and they have had no influence on this Cochrane review. In conclusion, all three authors have involvement in primary research in the subject area of our review, but no personal financial support has been gained.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- MDSG, New Zealand.

INDEX TERMS

Medical Subject Headings (MeSH)

Estrogen Antagonists [therapeutic use]; Gonadotropin-Releasing Hormone [*agonists; *antagonists & inhibitors]; Gonadotropins [therapeutic use]; Infertility [*therapy]; Insemination, Artificial [*methods]; Ovulation Induction [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans