Long-acting FSH versus daily FSH for women undergoing assisted reproduction (Review)

Pouwer AW, Farquhar C, Kremer JAM

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[Intervention Review]

Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Annefloor W Pouwer[1], Cindy Farquhar[2], Jan AM Kremer[3]

[1]Faculty of Medical School, Radboud University Nijmegen, Nijmegen, Netherlands. [2]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [3]Department of Obstetrics and Gynaecology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Contact address: Annefloor W Pouwer, Faculty of Medical School, Radboud University Nijmegen, Geert Grooteplein 9, PO Box 9101, Nijmegen, 6500HB, Netherlands. a.pouwer@student.ru.nl.

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ABSTRACT

Background

Assisted reproduction techniques (ART) such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) can help subfertile couples to create a family. It is necessary to induce multiple follicles; this is achieved by follicle stimulating hormone (FSH) injections. Current treatment regimens prescribe daily injections of FSH (urinary FSH with or without luteinizing hormone (LH) injections or recombinant FSH (rFSH)).

Recombinant DNA technologies have produced a new recombinant molecule which is a long-acting FSH, named corifollitropin alfa (Elonva) or FSH-CTP. A single dose of long-acting FSH is able to keep the circulating FSH level above the threshold necessary to support multi-follicular growth for an entire week. The optimal dose of long-acting FSH is still being determined. A single injection of long-acting FSH can replace seven daily FSH injections during the first week of controlled ovarian stimulation (COS) and can make assisted reproduction more patient friendly.

Objectives

To compare the effectiveness of long-acting FSH versus daily FSH in terms of pregnancy and safety outcomes in women undergoing IVF or ICSI treatment cycles.

Search methods

We searched the following electronic databases, trial registers and websites: the Cochrane Central Register of Controlled Trials (CENTRAL), the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, MEDLINE, EMBASE, PsycINFO, CINAHL, electronic trial registers for ongoing and registered trials, citation indexes, conference abstracts in the ISI Web of Knowledge, LILACS, Clinical Study Results (for clinical trial results of marketed pharmaceuticals), PubMed and OpenSIGLE (10 October 2011). We also carried out handsearches.

Selection criteria

All randomised controlled trials (RCTs) comparing long-acting FSH versus daily FSH in women who were part of a couple with subfertility and undertaking IVF or ICSI treatment cycles with a GnRH antagonist or agonist protocol were included.

Data collection and analysis

Data extraction and assessment of risk of bias was independently done by two review authors. Original trial authors were contacted in the case of missing data. We calculated Peto odds ratios for each outcome; our primary outcomes were live birth rate and ovarian hyperstimulation syndrome (OHSS) rate.

Main results

We included four RCTs with a total of 2335 participants. A comparison of long-acting FSH versus daily FSH did not show evidence of difference in effect on overall live birth rate (Peto OR 0.92; 95% CI 0.76 to 1.10, 4 RCTs, 2335 women) or OHSS (Peto OR 1.12; 95% CI 0.79 to 1.60, 4 RCTs, 2335 women). We compared subgroups by dose of long-acting FSH. There was evidence of reduced live birth rate in women who received lower doses (60 to 120 μg) of long-acting FSH compared to daily FSH (Peto OR 0.60; 95% CI 0.40 to 0.91, 3 RCTs, 645 women). There was no evidence of effect on live births in the medium dose subgroup (Peto OR 1.03; 95% CI 0.84 to 1.27) and no evidence of effect on clinical pregnancy rate, ongoing pregnancy rate, multiple pregnancy rate, miscarriage rate or ectopic pregnancy rate.

Authors' conclusions

The use of a medium dose of long-acting FSH is a safe treatment option and equally effective compared to daily FSH. Further research is needed to determine if long-acting FSH is safe and effective for use in hyper- or poor responders and in women with all causes of subfertility.

PLAIN LANGUAGE SUMMARY

Long-acting FSH versus daily FSH for women undergoing assisted reproduction

For definitions of terminology see the Glossary

Assisted reproduction techniques such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) can help subfertile couples to create a family. In a normal cycle only one egg will mature and is suitable for fertilisation. When IVF or ICSI are performed, the fertilisation of the egg takes place outside the woman's body. Multiple eggs are needed for IVF and ICSI to increase the number of suitable fertilised eggs for transfer to the woman. After the eggs are fertilised, they become embryos. One, two and sometimes three embryos are transferred; the other embryos can be cryopreserved and transferred in a later treatment cycle.

The development of multiple eggs is achieved by controlled ovarian stimulation (COS) with follicle stimulation hormone (FSH). Current treatment regimens prescribe daily injections of FSH during the first seven days of COS. A new treatment is available and one single injection of long-acting FSH, called corifollitropin alfa, can replace the first seven injections of FSH. The optimal dose of long-acting FSH is still being determined.

The aim of this review was to compare the effectiveness of long-acting FSH versus daily FSH in terms of pregnancy and safety outcomes in women undergoing IVF or ICSI treatment cycles. We included four trials involving a total of 2335 women. The results suggested that a medium dose of long-acting FSH provides similar numbers of live births as daily FSH. The serious adverse event ovarian hyperstimulation syndrome (OHSS) occurred equally with both treatments.

It can be concluded that medium dose long-acting FSH is a safe treatment option and is equally effective compared to daily FSH injections.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Long-acting FSH (all doses) versus daily FSH for women undergoing assisted reproduction

Patient or population: women undergoing assisted reproduction
Settings:
Intervention: long-acting FSH (all doses) versus daily FSH

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Long-acting FSH (all doses) versus daily FSH				
Live birth rate - Low dose (60-120 μg)	Study population		OR 0.61 (0.41 to 0.91)	645 (3 studies)	⊕⊕◯◯ low[1,2,3]	
	288 per 1000	198 per 1000 (142 to 269)				
	Medium risk population					
	352 per 1000	249 per 1000 (182 to 331)				
Live birth rate - Medium dose (150-180 μg)	Study population		OR 1.03 (0.84 to 1.27)	1657 (3 studies)	⊕⊕◯◯ low[1,2,3]	
	336 per 1000	343 per 1000 (298 to 391)				
	Medium risk population					
	343 per 1000	350 per 1000 (305 to 399)				
Live birth rate - High dose (240 μg)	Study population		OR 0.32 (0.05 to 1.9)	33 (1 study)	⊕⊕◯◯ low[1,2,3]	

	375 per 1000	**161 per 1000** (29 to 533)			
	Medium risk population				
	375 per 1000	**161 per 1000** (29 to 533)			
Ovarian hyperstimulation syndrome - Low dose (60-120 μg)	**Study population**		**OR 1.23** (0.54 to 2.82)	645 (3 studies)	⊕⊕◯◯ **low**[1,2,3]
	42 per 1000	**51 per 1000** (23 to 110)			
	Medium risk population				
	47 per 1000	**57 per 1000** (26 to 122)			
Ovarian hyperstimulation syndrome - Medium dose (150-180 μg)	**Study population**		**OR 1.07** (0.72 to 1.58)	1657 (3 studies)	⊕⊕◯◯ **low**[1,2,3]
	62 per 1000	**66 per 1000** (45 to 95)			
	Medium risk population				
	63 per 1000	**67 per 1000** (46 to 96)			
Ovarian hyperstimulation syndrome - High dose (240 μg)	**Study population**		**OR 1.81** (0.08 to 41.62)	33 (1 study)	⊕⊕◯◯ **low**[1,2,3]
	0 per 1000	**0 per 1000** (0 to 0)			
	Medium risk population				
	0 per 1000	**0 per 1000** (0 to 0)			

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Open-label studies included
[2] Total number of events is less than 300
[3] Number of studies is not sufficient to assess publication bias

BACKGROUND

For definitions of terminology see the Glossary (Appendix 1)

Description of the condition

Infertility affects 10% to 15% of couples trying to conceive (Evers 2002; Gnoth 2005). Assisted reproduction techniques (ART) such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) can help these couples to create a family. In ART it is necessary to induce multiple follicles. This is achieved by controlled ovarian stimulation (COS) with follicle stimulating hormone (FSH) injections.

Current treatment regimens prescribe daily injections of FSH (urinary FSH with or without luteinizing hormone (LH) injections or recombinant FSH (rFSH)). The FSH injections are usually started from cycle day two. Prevention of a premature ovulation due to a LH surge can be accomplished with gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists. Some clinicians consider antagonists to be the first choice in COS due to their immediate action, lack of side effects (for example lower incidence of ovarian hyperstimulation syndrome (OHSS)), the need for fewer injections and the same live birth rate as with agonists (Al-Inany 2011; Tarlatzis 2007). Other clinicians consider agonists as the first choice in COS due to a higher pregnancy rate (Maheshwari 2011). Antagonist injections start on day five or six (see Figure 1) whereas agonist injections start two to four weeks prior to the stimulation (see Figure 2).

Figure 1. Schematic representation of therapeutic interventions during ovarian stimulation with rFSH in a GnRH antagonist protocol (Source:De Greef 2010)

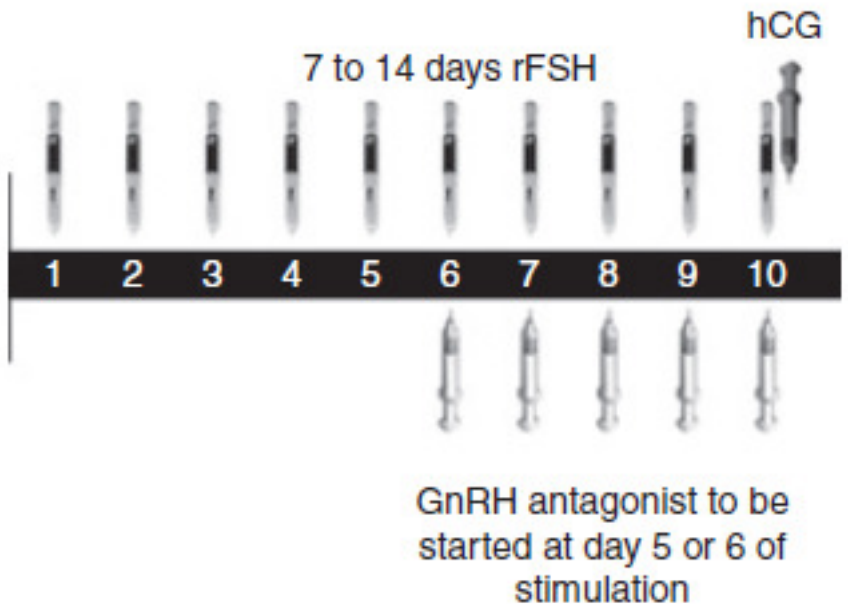
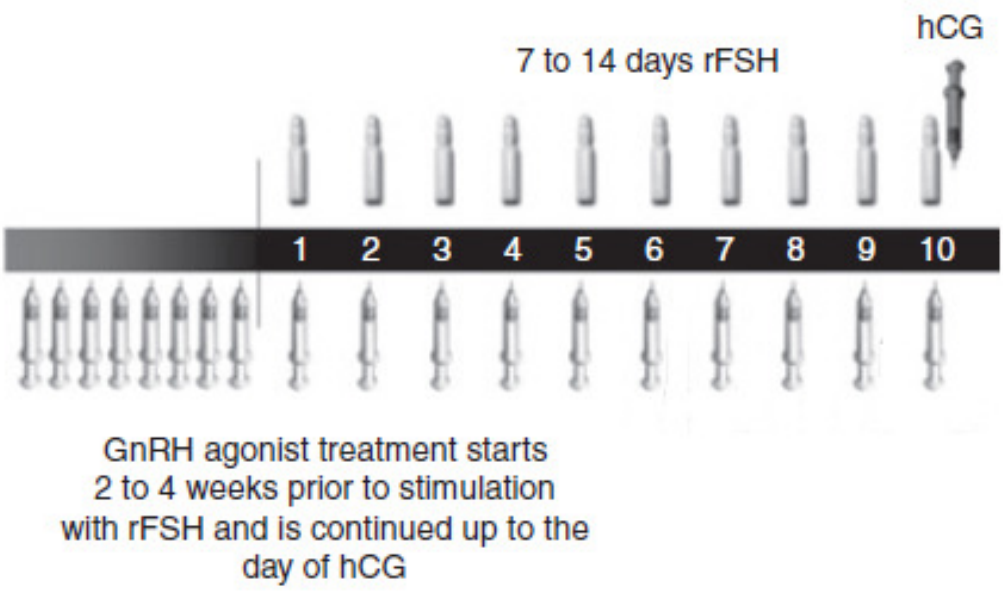


Figure 2. Schematic representation of therapeutic interventions during ovarian stimulation with rFSH in a GnRH agonist protocol (Source:De Greef 2010)



FSH and GnRH agonist or antagonist injections are continued up to and including the day the leading follicle reaches 18 to 20 mm (Heineman 2007). On this day, 34 to 36 hours prior to the ovum pick-up, human chorionic gonadotropin (hCG) is administered by injection leading to the final maturation necessary to produce the ovulation (see Figure 1; Figure 2). Two days (34 to 36 hours) later several oocytes are ready for ovum pick-up. After the pick-up, the oocytes are fertilised by IVF or ICSI. Two to five days after the fertilisation one, two or sometimes three embryos are transferred (Kovacs 2011).

Description of the intervention

Daily injections of rFSH are required to maintain steady state levels of FSH in the blood that are above the threshold for follicular development and ongoing maturation, due to its relatively short half-life and rapid metabolic clearance. The daily subcutaneous administration and side effects of the rFSH preparations can cause discomfort and be a physical burden to the patient. Many couples withdraw prematurely from IVF or ICSI due to emotional distress, which limits their chances of pregnancy. A German study showed withdrawal of 40% of non-pregnant couples after just one cycle of IVF due to emotional distress (Schroder 2004). For this reason, a patient friendly therapy regimen should be developed.

Recombinant DNA technologies have produced a new recombinant molecule which consists of the α-subunit of human FSH and a hybrid subunit consisting of the carboxyl-terminal peptide of the β-subunit of human chorionic gonadotrophin (hCG) coupled with the FSH β-subunit. This molecule is a long-acting FSH, named corifollitropin alfa (Elonva) or FSH-CTP (Fauser 2009; Koper 2008). A single injection of long-acting FSH on the first day of the stimulation can replace the first seven daily injections of rFSH and make assisted reproduction more acceptable to patients. The administration of long-acting FSH involves one subcutaneous injection on the first day of COS. The dose of long-acting FSH should be as low as possible to avoid ovarian hyperstimulation syndrome (OHSS) but high enough to support COS over the seven days. De Greef 2010 investigated 100 µg for women weighing < 60 kg and 150 µg for women weighing > 60 kg and the doses were proven to be adequate. The optimal dose of long-acting FSH is still under investigation. From day seven, the same treatment protocol as rFSH is used (see Figure 3; Figure 4).

Figure 3. Schematic representation of therapeutic interventions during ovarian stimulation with long-acting FSH (Corifollitropin alfa) in a GnRH antagonist protocol (Source: De Greef 2010)

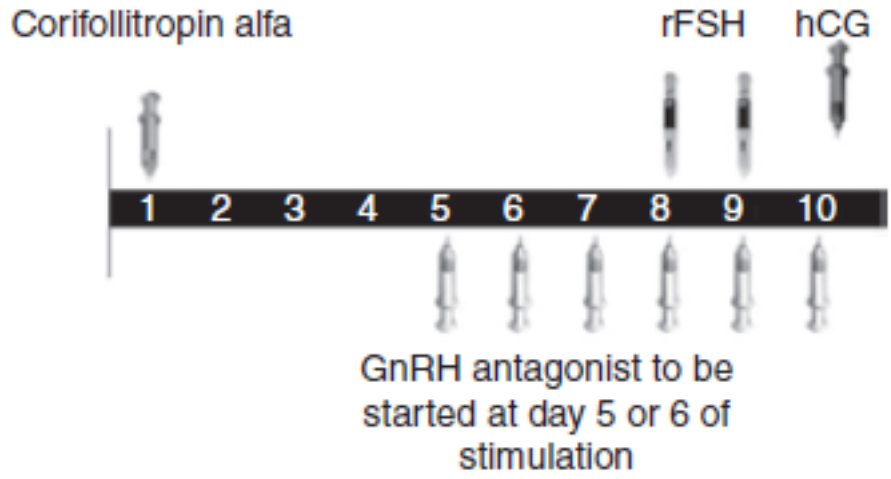
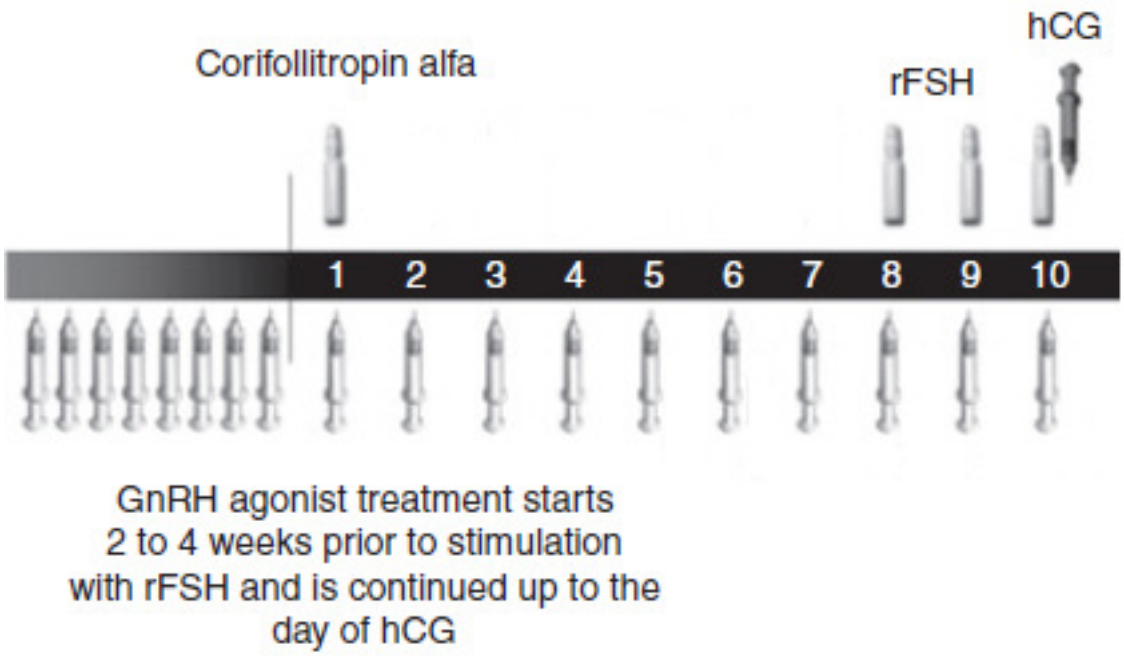


Figure 4. Schematic representation of therapeutic interventions during ovarian stimulation with long-acting FSH (Corifollitropin alfa) in a GnRH agonist protocol (Source:De Greef 2010)



How the intervention might work

Long-acting FSH has, compared with rFSH, an approximately two-fold longer elimination half-life and an almost four-fold extended time to peak serum levels (Devroey 2009; Duijkers 2002). Due to this pharmacokinetic profile, a single dose of long-acting FSH is able to keep the circulating FSH level above the threshold necessary to support multi-follicular growth for an entire week (Devroey 2009; Koper 2008). As such, a single injection of long-acting FSH can replace seven daily rFSH injections during the first week of COS.

Why it is important to do this review

The development of this new treatment regimen may provide similar or better success rates with fewer injections. It may help to reduce the treatment burden and make the therapy more patient friendly. On the other hand it could also be more costly. This review considered the evidence from randomised controlled trials for the use of long-acting FSH on pregnancy and safety outcomes.

OBJECTIVES

To compare the effectiveness of long-acting FSH versus daily FSH in terms of pregnancy and safety outcomes in women undergoing IVF or ICSI treatment cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were included in this review. Only trials that were either clearly randomised or claimed to be randomised and did not have evidence of inadequate sequence generation, such as allocation by date of birth or hospital number, were included. We planned to include cross-over trials in the review but we did not find any cross-over trials comparing long-acting FSH with daily FSH.

Types of participants

Women with subfertility and undertaking IVF or ICSI treatment cycles with a GnRH antagonist or agonist protocol were included.

Types of interventions

Trials comparing long-acting FSH versus daily FSH were eligible for inclusion. Any dose was included.

Types of outcome measures

Primary outcomes

Effectiveness

- Live birth rate per woman randomised, defined as the delivery of one or more living babies after 20 completed weeks of gestation. When there were multiple live births (e.g. twins or triplets) these were counted as one live birth event

Adverse

- Ovarian hyperstimulation syndrome (OHSS) rate per woman randomised

Secondary outcomes

Effectiveness

- Ongoing pregnancy rate per woman randomised, defined as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed by ultrasound
- Clinical pregnancy rate per woman randomised, defined as the presence of a gestational sac with or without a fetal heart beat, confirmed by ultrasound

Adverse

- Multiple pregnancy rate per woman randomised, counted as one live birth event
- Miscarriage rate per woman randomised
- Any other adverse event per woman randomised (including ectopic pregnancy, fetal abnormalities, drug side effects and infection)

Process

- Patient satisfaction with the treatment

Search methods for identification of studies

All published and unpublished RCTs studying long-acting FSH versus daily FSH were sought. We used the following search strategy, without language restriction and in consultation with the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

The following electronic databases, trial registers and websites were searched using Ovid software.

- Cochrane Central Register of Controlled Trials (CENTRAL), see Appendix 2.
- The Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials, see Appendix 3.
- MEDLINE, see Appendix 4.
- EMBASE, see Appendix 5.
- PsycINFO, see Appendix 6.
- CINAHL, see Appendix 7.

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials that appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The EMBASE search was combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).

Other electronic sources of trials included the following.

- Trial registers for ongoing and registered trials: 'Current Controlled Trials' (http://www.controlled-trials.com/); 'ClinicalTrials.gov', a service of the US National Institutes of Health (http://clinicaltrials.gov/ct2/home).
- The World Health Organization International Trials Registry Platform search portal (http://www.who.int/trialsearch/Default.aspx).
- Citation indexes (http://scientific.thomson.com/products/sci/).
- Conference abstracts in the ISI Web of Knowledge (http://isiwebofknowledge.com/), see Appendix 8.
- LILACS database, as a source of trials from the Portuguese and Spanish speaking world (htpp://regional.bvsalud.org/php/index.php?lang=en) (choose 'LILACS' in 'all sources' drop-down box).
- Clinical Study Results, for clinical trials of marketed pharmaceuticals (http://www.clinicalstudyresults.org/).
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), the random control filter for PubMed was taken from the searching chapter of the *Cochrane Handbook for Systematic Reviews of Interventions.*
- OpenSIGLE database for grey literature from Europe (http://opensigle.inist.fr/).

Searching other resources

The reference lists of articles retrieved by the search were handsearched and personal contact was made with experts in the field and with the manufacturers of long-acting FSH in order to obtain any additional, relevant data.

Data collection and analysis

Data collection and analysis was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors independently scanned the titles and abstracts of articles retrieved by the search and removed those that were very clearly irrelevant. Full texts of all potentially eligible studies were retrieved. Two review authors independently examined the full text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the review. We discussed any disagreement or doubt as to whether a study was eligible for inclusion or not with a third review author and achieved consensus. A list of the excluded studies and the reasons for exclusion are provided in the 'Characteristics of excluded studies' table.

Data extraction and management

Data were extracted from eligible studies using a data extraction form designed and pilot-tested by the authors. Where studies had multiple publications, the main trial report was used as the reference and additional details were supplemented from secondary papers. The review authors corresponded with study investigators in order to resolve any data queries, as required. Two review authors independently extracted the data. Any disagreement between these review authors was resolved by a third review author.

Assessment of risk of bias in included studies

The included studies were assessed for risk of bias using the Cochrane risk of bias assessment tool, which recommends the explicit reporting of the following domains.

1. Random sequence generation (selection bias)
    - Adequate: use of central computer randomisation, independent central randomisation office, on-site computer from which assignment could only be determined after entering patient data, random number table or serially numbered and sealed opaque envelopes
    - Inadequate: use of non-opaque envelopes or systematic methods (e.g. date of birth, medical record number, day of the week presenting)
    - Unclear: insufficient information about the process of sequence generation
2. Allocation concealment (selection bias)
    - Adequate: sequentially numbered and identical drug containers were used
    - Inadequate: use of open random allocation (e.g. date of birth, medical record number, day of the week presenting)
    - Unclear: insufficient information about the process of allocation concealment
3. Blinding of participants, researchers and care providers (performance bias)

- Adequate: blinding of the participants, researchers and the care providers, or incomplete or no blinding was used but was not likely to influence outcomes
- Inadequate: no blinding or incomplete blinding was used and likely to influence the outcomes
- Unclear: insufficient information about the process of blinding the participants, researchers and care providers

4. Blinding of the outcome assessor (detection bias)
   - Adequate: blinding of the researchers or incomplete blinding had no effect on the outcome measurement
   - Inadequate: no blinding of the researchers, or incomplete blinding had influence on the outcomes
   - Unclear: insufficient information about the process of blinding the outcome assessor
5. Incomplete outcome data (attrition bias)
   - Adequate: there were no missing data, or reasons for missing data may not influence the outcomes
   - Inadequate: reasons for missing data may influence the outcomes
   - Unclear: insufficient information about the completeness of outcome data
6. Selective outcome reporting (reporting bias)
   - Adequate: all pre-specified outcomes in the protocol have been published, or no protocol available but it was clear all pre-specified outcomes were reported
   - Inadequate: not all pre-specified outcomes in the protocol were reported
   - Unclear: insufficient information about the process of outcome reporting
7. Other potential sources of bias
   - Adequate: the study was free of other biases
   - Inadequate: other biases were present
   - Unclear: insufficient information about the other sources of bias

Two authors assessed these seven domains as 'low risk of bias' (adequate), 'high risk of bias' (inadequate), or 'unclear risk of bias' (unclear). The assessments made by the two authors were compared and any disagreements were resolved by consensus or by discussion with a third author. The conclusion is presented in the 'Risk of bias' table and was incorporated into the interpretation of review findings by means of sensitivity analyses.

Measures of treatment effect

We used the dichotomous data measures and expressed the results in the control and intervention groups of each study as Peto odds ratios (OR) with 95% confidence intervals (CI).

Unit of analysis issues

The primary analysis was per woman randomised. All included studies reported data per woman. Multiple live births (for example twins or triplets) were counted as one live birth event.

Dealing with missing data

In the case of missing data from the included studies, we contacted the original investigators to request the relevant missing data. We did not received the requested data so we made an imputation of individual values for the primary outcomes only. Live births were assumed not to have occurred in participants without a reported outcome. For other outcomes, only the available data were analysed.

We analysed all data on an intention-to-treat (ITT) basis.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. We used the I^2 statistic to assess the impact of the heterogeneity on the meta-analysis. We interpret the result of the I^2 statistic as follows:

- 0% to 40%, might not be important;
- 30% to 60%, may represent moderate heterogeneity;
- 50% to 90%, may represent substantial heterogeneity;
- 75% to 100%, considerable heterogeneity (Higgins 2011).

We did not find an I^2 statistic measurement greater than 50%, which means that there was no substantial heterogeneity (Higgins 2011). For this reason, we did not carry out any sensitivity analyses.

Assessment of reporting biases

We have taken care to search for within trial selective reporting, such as trials failing to report obvious outcomes or reporting them in insufficient detail to allow inclusion. We sought published protocols to look for any pre-planned outcomes that may not have been reported and compared the outcomes between the protocol and the final published study.

We planned to undertake informal assessment if included studies failed to report the primary outcome of live birth, but all studies reported live birth.

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise the potential impact by ensuring a comprehensive search for eligible studies.We were alert for duplication of data. To investigate the potential for publication bias, we planned to use a funnel plot if there were 10 or more studies in an analysis but due to the small number of studies per subgroup this was not possible.

Data synthesis

We carried out the statistical analysis using Review Manager version 5.1. We used a fixed-effect model to combine the data from primary studies. We planned to perform a random-effects meta-analysis in the case of substantial heterogeneity, but this was not necessary.

Subgroup analysis and investigation of heterogeneity

Data were analysed in the following subgroups.
Dose of long-acting FSH:

1. low dose (60 to 120 μg);
2. medium dose (150 to 180 μg);
3. high dose (240 μg).

We planned to do subgroup analyses on: women's age; weight; body mass index (BMI); day of starting GnRH antagonist; and poor responders to ovarian stimulation. However, we were not able to perform these subgroup analyses due to insufficient information.

Sensitivity analysis

We planned to conduct sensitivity analyses for the primary outcomes to determine whether the conclusions were robust regarding the eligibility and analysis of studies. Because we did not find substantial heterogeneity, we did not carry out the sensitivity analyses.

RESULTS

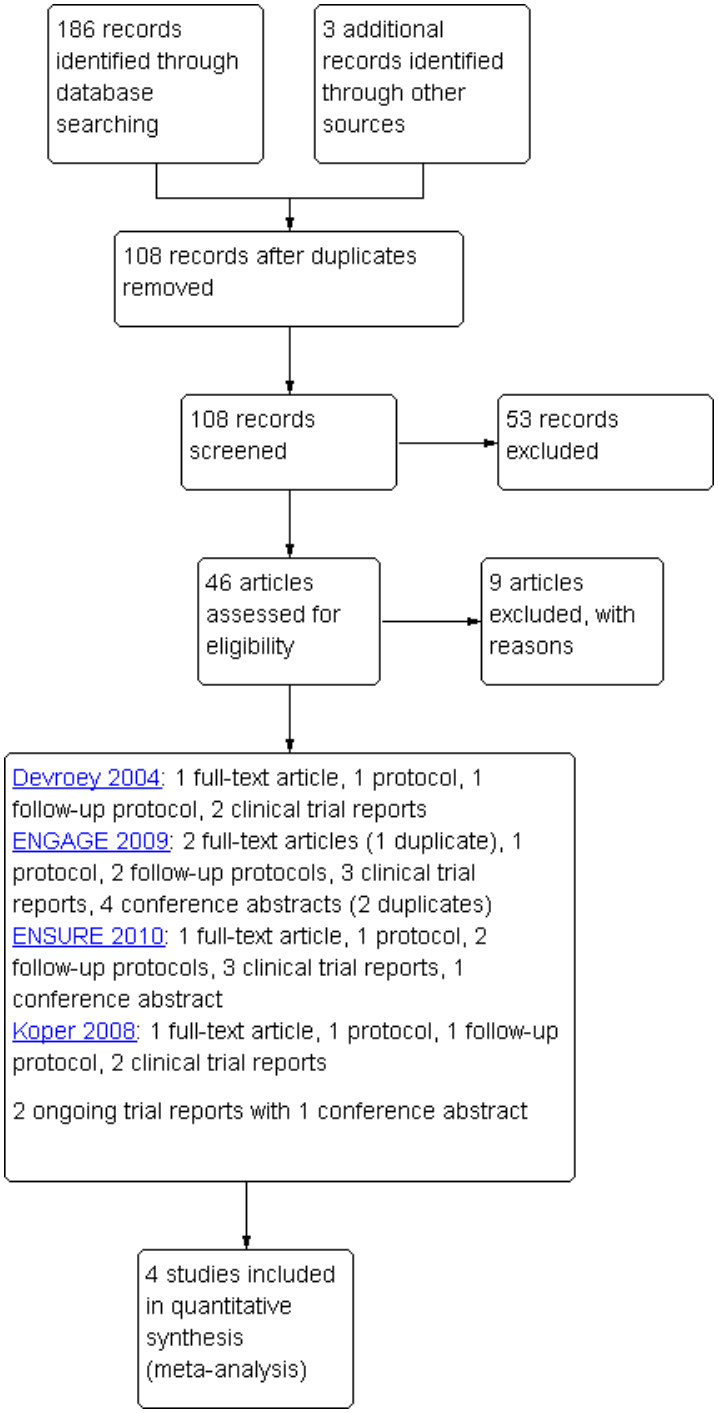
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See: Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies

Results of the search

See: study flow diagram Figure 5

Figure 5. Study flow diagram



The search was done on 10 October 2011 (for our search strategy see Methods). The search strings as stated in Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8 retrieved 107 articles. We also searched LILICS, *meta*Register of Controlled Trials-active registers, WHO International Trials Registry Platform, clinicaltrials.gov, clinicalstudyresults.org, OpenSIGLE and PubMed (MeSH terms used) using the keywords *'corifollitropin', 'corifollitropin alfa', 'corifollitropin alpha', 'ORG 36286', 'Elonva', 'FSH-CTP', 'long-acting FSH', 'long acting FSH'*. This search retrieved 79 reports, another three reports were found by using other methods such as handsearching. After removal of duplicates, 108 articles were screened, 53 records were found to be clearly irrelevant. The remaining 55 studies were retrieved in full-text or were conference abstracts, protocols or clinical study results. The reports that did not appear to meet our inclusion criteria were excluded (nine reports). Five trials met our inclusion criteria, and one study was a duplicate (Fauser 2010). We also found two ongoing trials and one conference abstract with preliminary results (Siristatidis 2011), for details see Characteristics of ongoing studies.

We found on clinicaltrials.gov the protocols of the four included studies and six protocols of follow up studies of the original included studies. Clinical study reports of all protocols were found on clinicalstudyresults.org. We included four trials and the data of four conference abstracts, six protocols and six reports of clinical study results in our meta-analyses. Overall, we included four trials.

Included studies

Study design and setting

Four randomised controlled trials were included in the review. All were multi-center trials, conducted in Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Norway, Poland, Spain, Sweden, The Netherlands, UK), North America (Canada, USA) and Asia (Korea, Taiwan). We included two four-arm trials (Devroey 2004; Koper 2008) and two two-arm trials (ENGAGE 2009; ENSURE 2010). As there were studies with four arms, three dosage arms and one control group, it was necessary to divide the control group by three. If the study did not report live births per dosage subgroup it was necessary to divide the intervention group by three. Where this number was even, then we made an arbitrary decision to increase or reduce the number of cases by one in one of the three groups.

Participants

A total of 2335 women participated in the included studies, 1348 women in the intervention groups and 987 women in the control groups. The age of the included participants ranged from 18 to 39 years, and the range of BMI was 17 to 32 kg/m^2.

The inclusion criteria differed slightly between the studies in age, BMI and weight. ENSURE 2010 included women with a body weight $\leq$ 60 kg and BMI of 18 to 32 kg/m^2, ENGAGE 2009 included women weighing > 60 kg and $\leq$ 90 kg with BMI 18 to 32 kg/m^2. The two other studies included women weighing 50 to 90 kg (Devroey 2004; Koper 2008).

There were differences for the inclusion and exclusion criteria between the protocols and the published articles. Koper 2008 reported an inclusion age range of 20 to 39 years in the article while they stated 18 to 39 years in the protocol. Devroey 2004 reported none of the exclusion criteria as stated in the protocol. All studies excluded poor responders, patients with a history of OHSS or polycystic ovary syndrome (PCOS) (hyper-responders) and women with explained subfertility.

A summary can be found in Table 1; for detail see table Characteristics of included studies.

Interventions

All included studies compared long-acting FSH with daily FSH and followed by a GnRH antagonist protocol. The studies varied in initial dose of long-acting FSH administered: 454 women received a low dose (60 to 120 μg) (Devroey 2004; ENSURE 2010; Koper 2008), 869 women received a medium dose (150 to 180 μg) (Devroey 2004; ENGAGE 2009; Koper 2008) and 25 women received a high dose (240 μg) (Devroey 2004). All studies used rFSH for the control group: three studies used 150 IU rFSH (Devroey 2004; ENSURE 2010; Koper 2008) and ENGAGE 2009 used 200 IU rFSH. ENSURE 2010 and ENGAGE 2009 used a bodyweight adjusted dose of long-acting and daily FSH.

GnRH antagonist was administered subcutaneously. Devroey 2004 started on the day the leading follicle reached 14 mm, the three other studies (ENGAGE 2009; ENSURE 2010; Koper 2008) started on day 5. None of the studies used GnRH agonists.

The number of transferred embryos varied from one or two embryos (ENGAGE 2009; ENSURE 2010) to three or fewer embryos (Devroey 2004; Koper 2008), see Table 1.

Outcomes

Primary outcomes

Effectiveness

Live birth rate was reported in four clinical trial reports with additional data obtained by follow-up studies of the original trial.

Adverse

Ovarian hyperstimulation syndrome (OHSS) was reported in all four included studies. We reported the total number of OHSS cases, including mild, moderate and severe cases.

Secondary outcomes

Effectiveness

Clinical pregnancy rate was reported in three studies (ENGAGE 2009; ENSURE 2010; Koper 2008). These three studies reported both the number of clinical pregnancies (defined as presence of gestational sac confirmed by ultrasound) and the number of vital pregnancies (defined as gestational sac and heartbeat confirmed by ultrasound). We decided to report the vital pregnancy rate per women randomised. Ongoing pregnancy rate was reported by all four studies. If results after both fresh and frozen embryo transfer were reported, we made the decision to report the ongoing pregnancy rate after fresh embryo transfer.

Adverse

Multiple pregnancy rate was reported in all four studies. Devroey 2004 reported three sets of twins in the intervention groups; we assumed that one twin pregnancy occurred in each intervention group. Miscarriage rate was reported in two studies (ENGAGE 2009; ENSURE 2010). Three studies reported ectopic pregnancy rate as an adverse event (Devroey 2004; ENGAGE 2009; ENSURE 2010). We had insufficient data to report any other adverse events.

Process

None of the included studies reported patient satisfaction with the treatment.

Excluded studies

Eleven studies were excluded from the review. Two studies (Boostanfar 2011; Fauser 2010) were duplicates of ENGAGE 2009. Nine studies did not meet our inclusion criteria, three studies were reviews (Croxtall 2011; Ledger 2009; Seyhan 2011), five studies (De Lartigue 2011; Fatemi 2010; Loutradis 2010; Norman 2011; Prados 2011) were not randomised controlled trials (RCTs) and one study (Balen 2004) was excluded because the women did not undergo IVF or ICSI after the stimulation.
See table of Characteristics of excluded studies for details.

Risk of bias in included studies

The risk of bias was assessed for each included trial in the 'Risk of bias' table, see Characteristics of included studies. We summarised our findings in the 'Risk of bias' summary (see Figure 6) and in the 'Risk of bias' graph (see Figure 7).

Figure 6. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

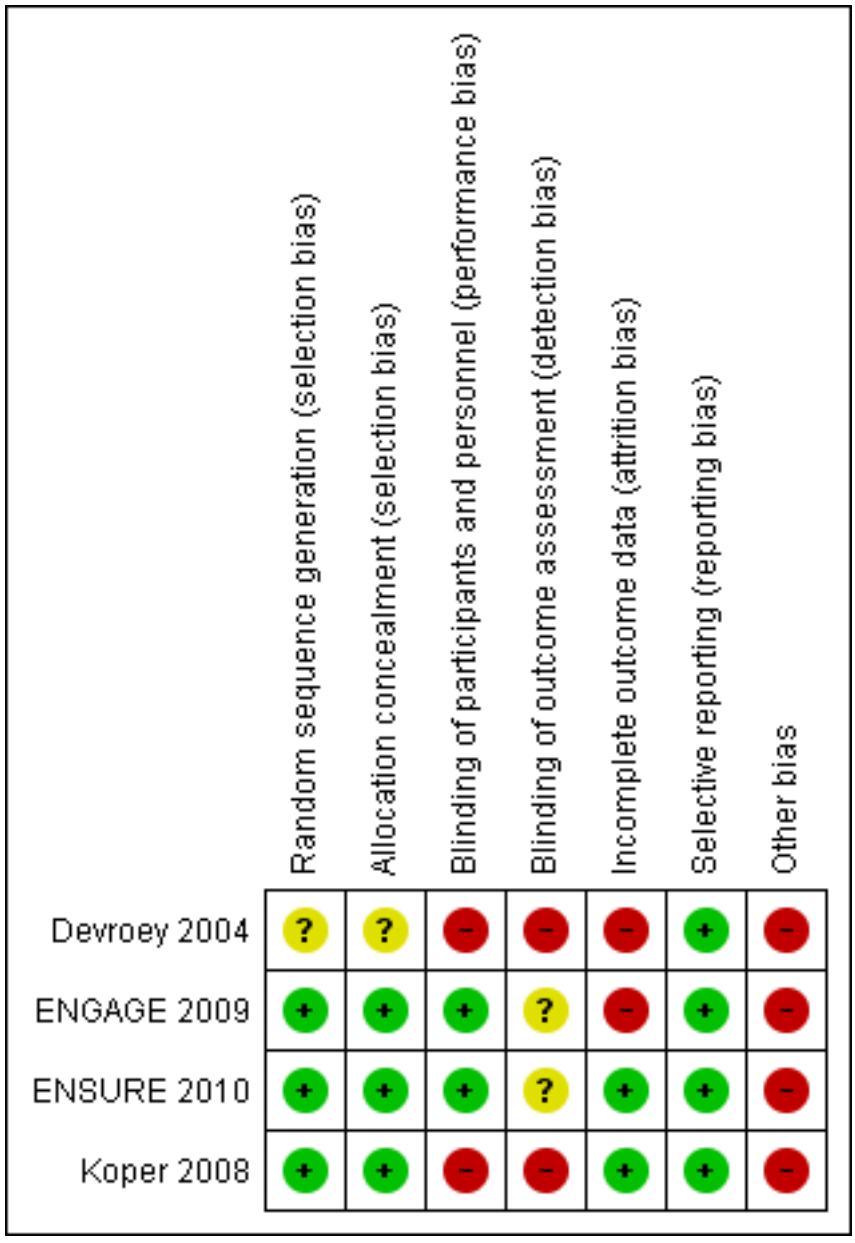
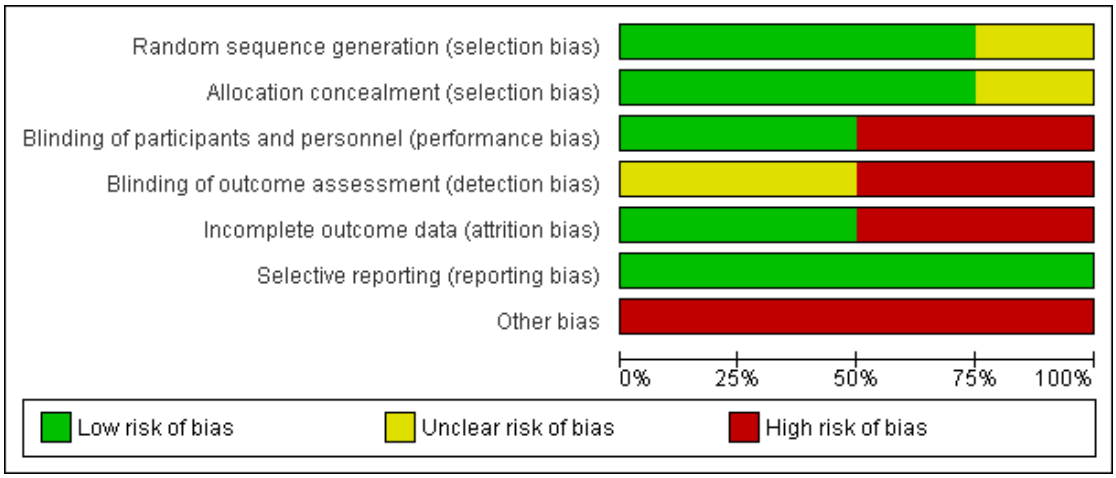


Figure 7. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



We contacted the authors for supplementary information. All included studies had the same contact author; we did not receive the requested data.

Allocation

Random sequence generation

All four included studies were randomised. We judged three studies at low risk of selection bias as they used randomly permutated blocks with an undisclosed fixed block size (ENGAGE 2009; ENSURE 2010; Koper 2008). We judged one study at unclear risk of selection bias related to random sequence generation because the authors did not report the method of randomisation used (Devroey 2004).

Allocation concealment

The allocation was concealed by using central remote allocation in three studies and we judged the method to be at low risk of bias (ENGAGE 2009; ENSURE 2010; Koper 2008). One study did not describe the method of allocation concealment and we judged this to be unclear risk of bias (Devroey 2004).

Blinding

Blinding of participants and personnel

All four studies reported their method of blinding. Two studies were open-label trials (Devroey 2004; Koper 2008) and were judged at high risk of bias. Two studies were double-blind and described use of a double-dummy placebo and were thus we deemed them to be at low risk of performance bias (ENGAGE 2009; ENSURE 2010).

Blinding of outcome assessment

Two of the studies did not report the blinding of outcome assessors and we judged them to be at unclear risk of bias (ENGAGE 2009; ENSURE 2010). The other two studies were open-label trials and for this reason we judged them to be at high risk of detection bias (Devroey 2004; Koper 2008)

Incomplete outcome data

Two studies were found to be at high risk of attrition bias. Devroey 2004 did not report reasons for all withdrawals. They reported in their protocol six participants treated with long-acting FSH during this trial; these treated participants were not analysed in their publication. We decided to analyse 105 participants (99 participants analysed in the published paper and six participants treated as stated in the protocol) in our meta-analysis.

We found ENGAGE 2009 to be at high risk of bias because the trial had a high unexplained drop-out rate. Two studies were judged to be at low risk of bias because they reported all numbers and reasons for withdrawals (ENSURE 2010; Koper 2008). Across all studies, a total of 12.7% of participants in the intervention groups and 7.5% in the control groups withdrew during the treatment before embryo transfer.

Selective reporting

Protocols were available for all included studies and all pre-specified outcomes were reported in either the published articles or unpublished data on clinical study reports (clinicalstudyresults.gov). We judged all four studies to be at low risk of reporting bias.

Other potential sources of bias

We judged all studies to be at high risk of other bias because the included studies were funded by Schering-Plough (NV Organon). ENGAGE 2009 also received fees and grants from: Ferring, Bessins, Serono, Merck Serono, IBSA, Wyeth, Schering, Ardana, Andromed, Pantrhei Bioscience and Preglem.

Effects of interventions

See: **Summary of findings for the main comparison** Long-acting FSH (all doses) versus daily FSH for women undergoing assisted reproduction

We did not conduct all the subgroup analyses as stated in our protocol. We had insufficient data to be able to conduct the analyses, see Table 1. We compared long-acting FSH (all doses) versus daily FSH with the following subgroups.

Dose of long-acting FSH:

1. low dose (60 to 120 μg);
2. medium dose (150 to 180 μg);
3. high dose (240 μg).

Primary outcomes

1.1 Live birth rate

All four trials reported the numbers of live births. There was no evidence of effect comparing long-acting FSH versus daily FSH. Moderate heterogeneity was detected but there was no indication of substantial heterogeneity (Peto OR 0.92; 95% CI 0.76 to 1.10, 4 RCTs, 2335 women, I^2 = 46%).

1.1.1 Low dose

There was evidence of a reduced live birth rate in women who received lower doses (60 to 120 μg) of long-acting FSH compared to daily FSH (Peto OR 0.60; 95% CI 0.40 to 0.91, 3 RCTs, 645 women, I^2 = 0%).

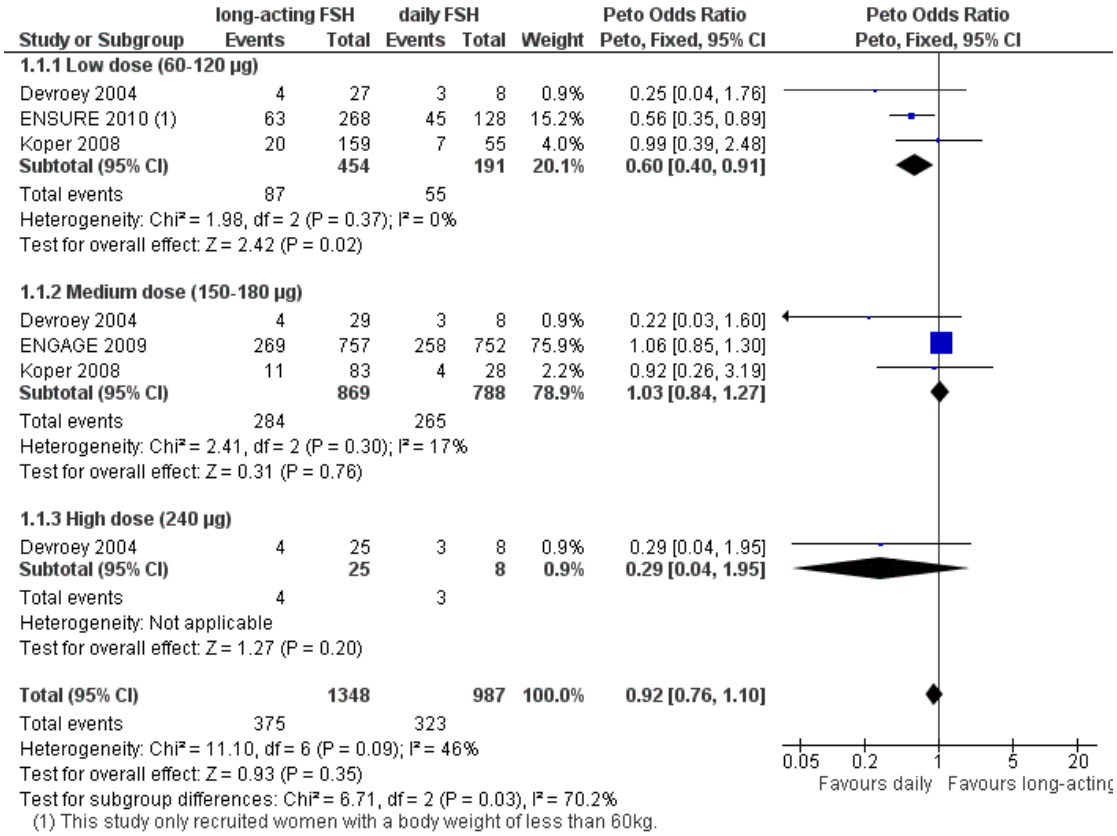
1.1.2 Medium dose

There was no evidence of difference in effect; heterogeneity was detected but there was no indication of substantial heterogeneity (Peto OR 1.03; 95% CI 0.84 to 1.27, 3 RCTs, 1647 women, I^2 = 17%).

1.1.3 High dose

No data were available to conduct high dose subgroup analysis. See Figure 8 for details.

Figure 8. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.1 Live birth rate.



1.2 Ovarian hyperstimulation syndrome (OHSS)

The primary adverse effect was reported in all four trials. There was no evidence of effect for this adverse outcome and no heterogeneity detected. (Peto OR 1.12; 95% CI 0.79 to 1.60, 4 RCTs, 2335 women, I^2 = 0%).

1.2.1 Low dose

There was no evidence of difference in effect (Peto OR 1.22; 95% CI 0.55 to 2.72, 3 RCTs, 645 women, I^2 = 0).

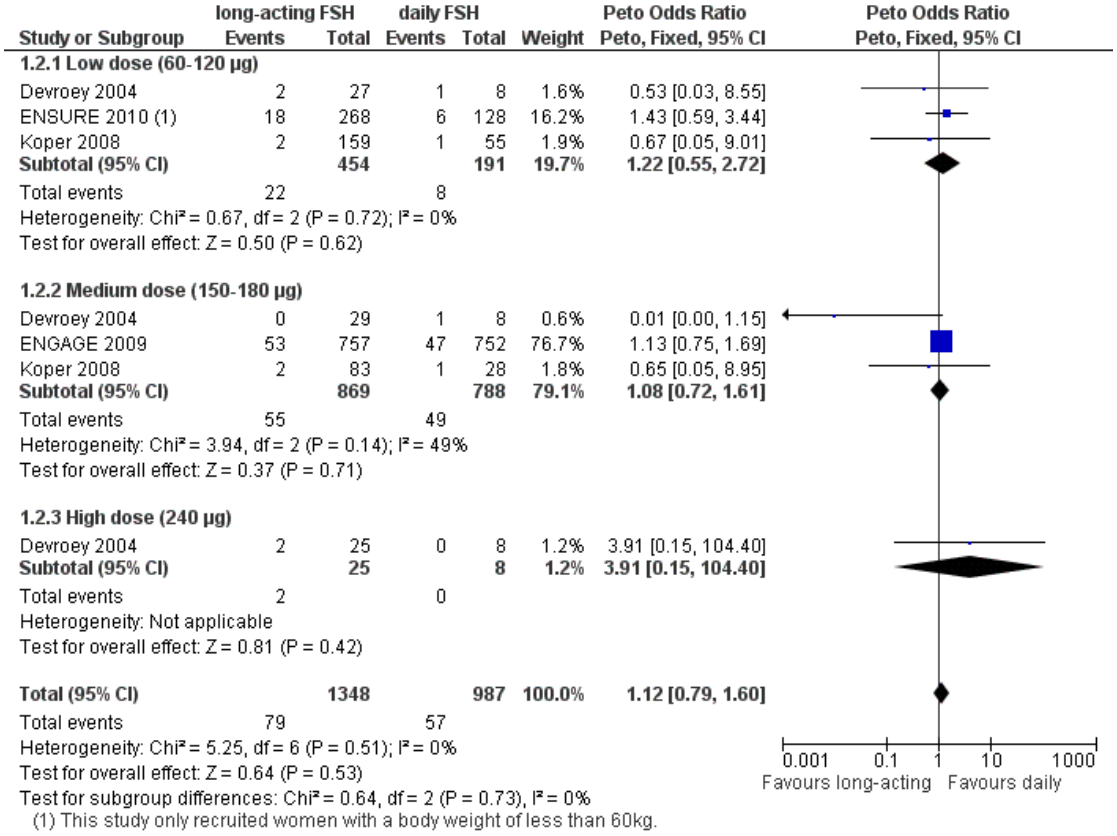
1.2.2 Medium dose

There was no evidence of difference in effect; heterogeneity was detected but there was no indication of substantial heterogeneity (Peto OR 1.08; 95% CI 0.72 to 1.61, 3 RCTs, 1657 women, I^2 = 49%).

1.2.3 High dose

There was no evidence of difference in effect (Peto OR 3.91; 95% CI 0.15 to 104.40, 1 RCT, 33 women).
See Figure 9 for details.

Figure 9. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.2 Ovarian hyperstimulation syndrome.



Secondary outcomes

1.3 Ongoing pregnancy rate

All four included studies reported ongoing pregnancy rate. There was no evidence of effect; heterogeneity was detected but no indication for substantial heterogeneity (OR 0.93; 95% CI 0.78 to 1.11, 4 RCTs, 2334 women, I^2 = 29%).

1.4.1 Low dose

There was no evidence of difference in effect; heterogeneity was detected but there was no indication of substantial heterogeneity (Peto OR 0.71; 95% CI 0.47 to 1.06, 3 RCTs, 645 women, I^2 = 26%).

1.4.2 Medium dose

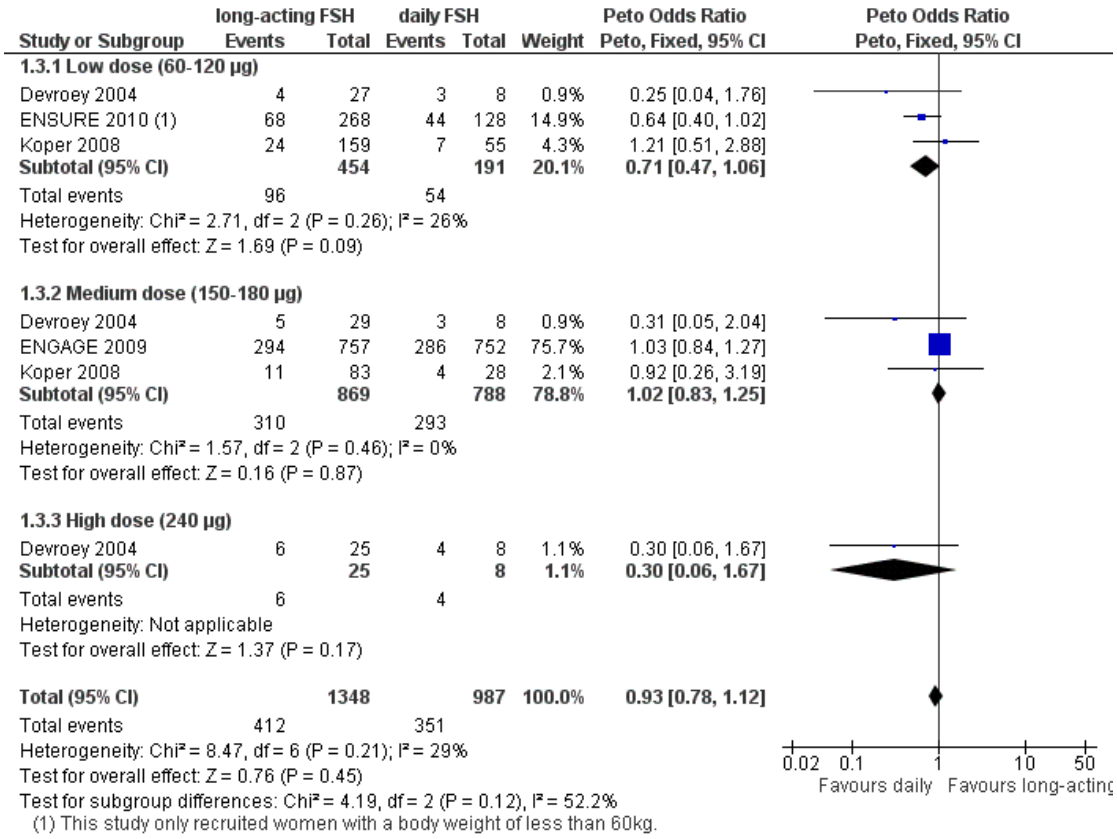
There was no evidence of difference in effect and no heterogeneity detected. (Peto OR 1.02; 95% CI 0.83 to 1.25, 3 RCTs, 1656 women, I^2 = 0%).

1.4.3 High dose

There was no evidence of difference in effect (Peto OR 0.30; 95% CI 0.06 to 1.67, 1 RCT, 33 women).

See Figure 10 for details.

Figure 10. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.3 Ongoing pregnancy rate.



1.4 Clinical pregnancy rate

Clinical pregnancy rate was reported in three trials (ENGAGE 2009; ENSURE 2010; Koper 2008). There was no evidence of effect, heterogeneity was detected but no indication for substantial heterogeneity (Peto OR 0.96; 95% CI 0.80 to 1.15, 3 RCTs, 2230 women, I^2 = 21%).

1.3.1 Low dose

There was no evidence of difference in effect and no heterogeneity detected. (Peto OR 0.71; 95% CI 0.47 to 1.06, 2 RCTs, 610 women, I^2 = 0%).

1.3.2 Medium dose

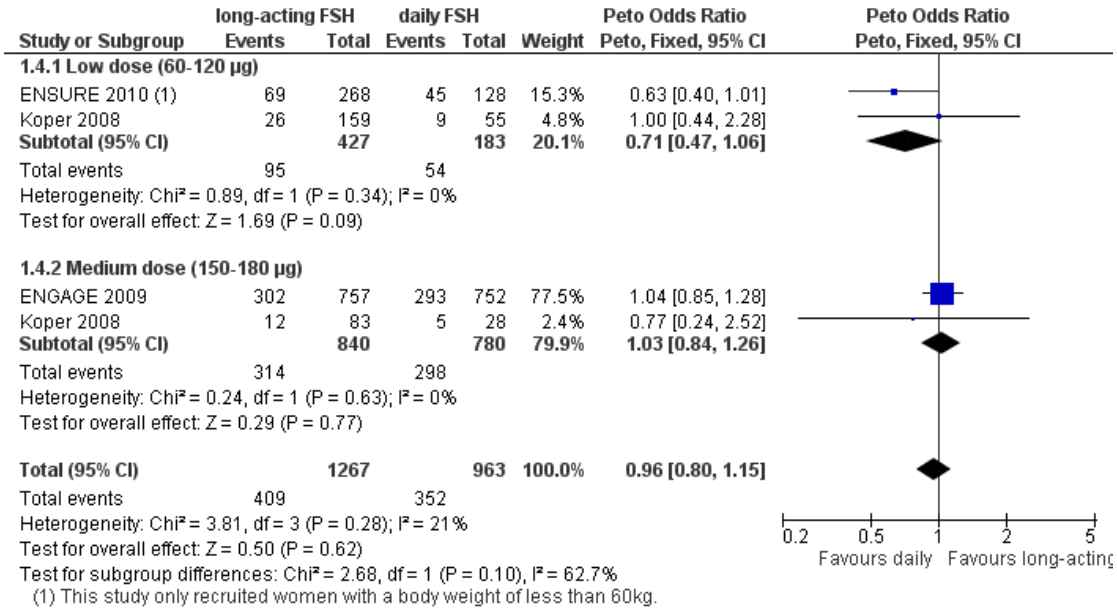
There was no evidence of difference in effect and no heterogeneity detected. (Peto OR 1.03; 95% CI 0.84 to 1.26, 2 RCTs, 1620 women, I^2 = 0%).

1.3.3 High dose

No data were available to conduct high dose subgroup analysis.

See Figure 11 for details

Figure 11. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.4 Clinical pregnancy rate.



1.5 Multiple pregnancy rate

The adverse event multiple pregnancy rate was reported in all four studies. There was no evidence of effect (Peto OR 1.24; 95% CI 0.92 to 1.68, 4 RCTs, 2335 women, I^2 = 0%).

1.5.1 Low dose

There was no evidence of difference in effect. Moderate heterogeneity detected, but no indication for substantial heterogeneity (Peto OR 1.05; 95% CI 0.51 to 2.17, 3 RCTs, 645 women, I^2 = 34%).

1.5.2 Medium dose

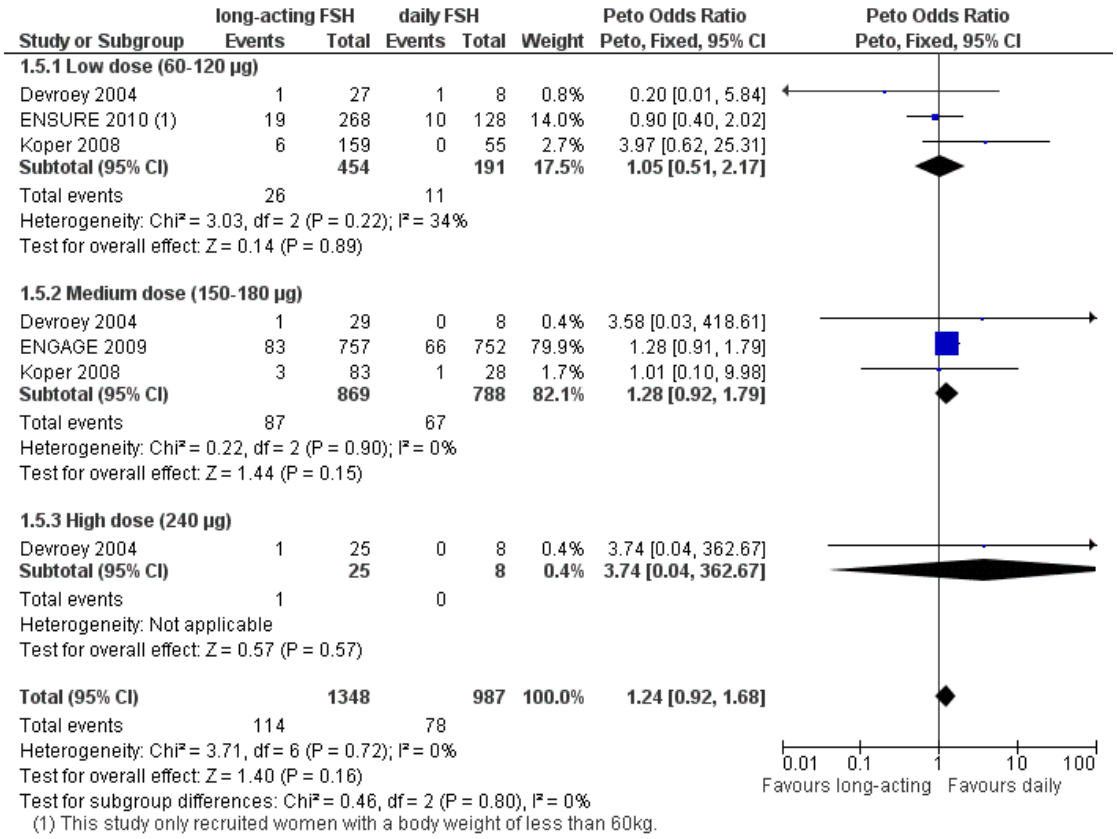
There was no evidence of difference in effect and no heterogeneity detected (Peto OR 1.28; 95% CI 0.92 to 1.79, 3 RCTs, 1657 women, I^2 = 0%).

1.5.3 High dose

There was no evidence of difference in effect (Peto OR 3.74; 95% CI 0.04 to 362.67, 1 RCT, 33 women).

See Figure 12 for details.

Figure 12. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.5 Multiple pregnancy rate.



1.6 Miscarriage rate

Two studies reported the adverse event miscarriage rate (ENGAGE 2009; ENSURE 2010). There was no evidence of effect (Peto OR 1.27; 95% CI 0.76 to 2.12, 2 RCTs, 1905 women, I^2 = 0%).

1.6.1 Low dose

There was no evidence of difference in effect (Peto OR 1.19; 95% CI 0.38 to 3.73, 1 RCT, 396 women).

1.6.2 Medium dose

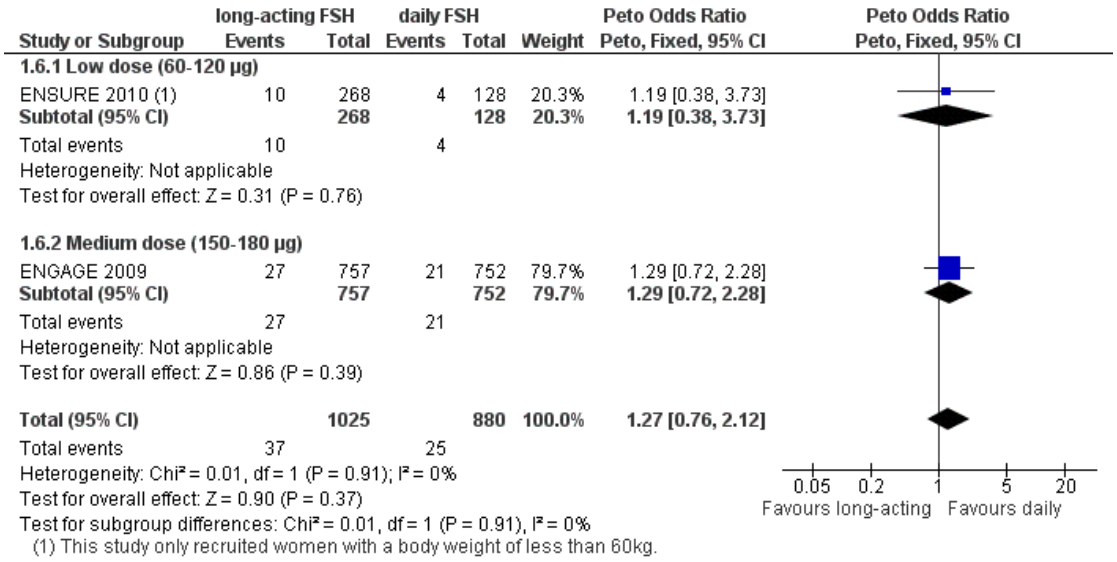
There was no evidence of difference in effect (Peto OR 1.29; 95% CI 0.72 to 2.28, 1 RCT, 1509 women).

1.6.3 High dose

Not data were available to conduct high dose subgroup analysis.

See Figure 13 for details.

Figure 13. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.6 Miscarriage rate.



1.7 Ectopic pregnancy rate

Three studies reported the adverse event ectopic pregnancy rate (Devroey 2004; ENGAGE 2009; ENSURE 2010). There was no evidence of effect and no heterogeneity was detected (Peto OR 0.91; 95% CI 0.43 to 1.92, 3 RCTs, 2004 women, I^2 = 0%).

1.7.1 Low dose

There was no evidence of effect difference and no heterogeneity was detected (Peto OR 1.05; 95% CI 0.32 to 3.42, 2 RCTs, 429 women, I^2 = 0%).

1.7.2 Medium dose

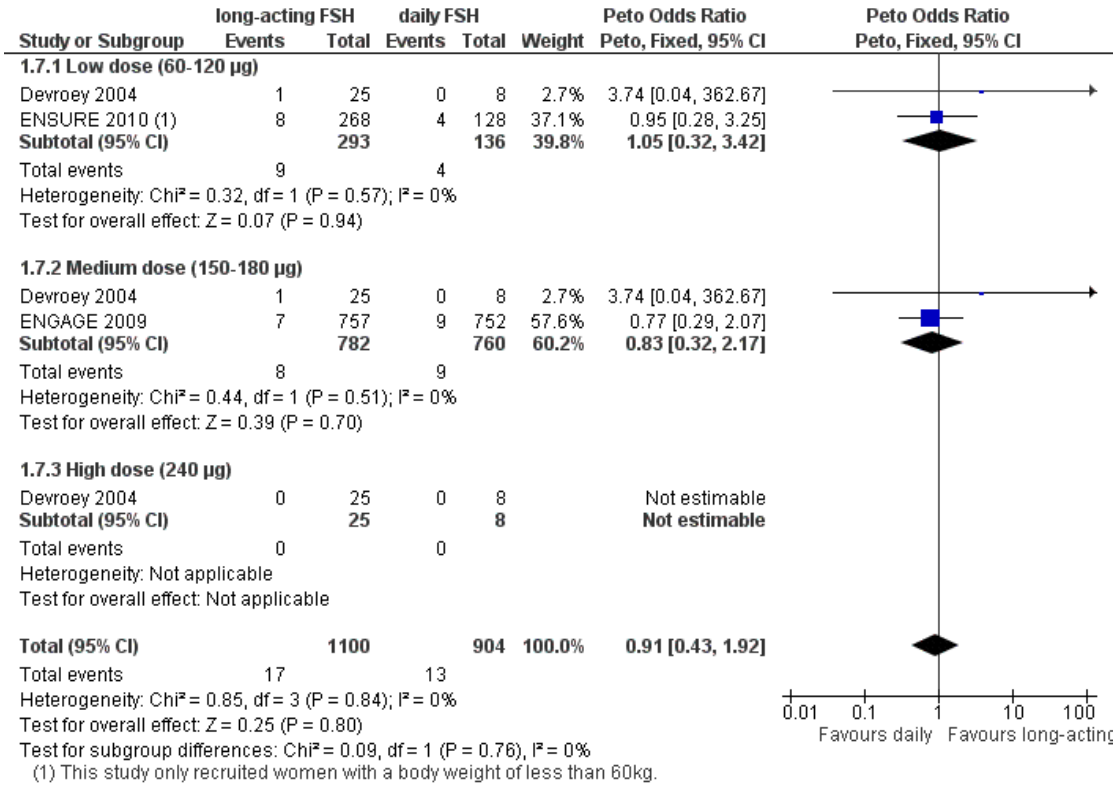
There was no evidence of difference in effect and no heterogeneity was detected (Peto OR 0.83; 95% CI 0.32 to 2.17, 2 RCTs, 1542 women, I^2 = 0%).

1.7.3 High dose

There were no events in both the intervention group and the control group.

See Figure 14 for details.

Figure 14. Forest plot of comparison: 1 Long-acting FSH (all doses) versus daily FSH, outcome: 1.7 Ectopic pregnancy rate.



DISCUSSION

Summary of main results

This review evaluated the effectiveness of long-acting FSH versus daily FSH on pregnancy and safety outcomes in women undergoing IVF or ICSI treatment cycles. There was evidence of a reduced live birth rate in women who received lower doses (60 to 120 μg) of long-acting FSH compared to daily FSH but no evidence of difference in effect on live birth rate in women receiving a medium dose (150 to 180 μg). Only one small study used a high dose (240 μg) of long-acting FSH and at present this is of no clinical value. The meta-analyses of effectiveness for the outcomes of clinical pregnancy and ongoing pregnancy did not show evidence of a difference of effect between long-acting and daily FSH. Similarly, there was no evidence of a difference in adverse events for OHSS rate, multiple pregnancy rate, miscarriage rate and ectopic pregnancy rate between long-acting and daily FSH. We can conclude that medium dose long-acting FSH is a safe treatment option, with no difference in benefits or harm.

See Summary of findings for the main comparison for a complete overview.

Overall completeness and applicability of evidence

All randomised clinical trials comparing long-acting FSH with daily FSH were included in this review. Our primary outcomes, live birth rate and OHSS rate, were reported in all four trials. Women at high risk of OHSS (hyper-responders) were excluded; this provides an explanation for the poor effect of long-acting FSH on the OHSS rate and the low number of OHSS cases in both treatment groups. Also, poor responders were excluded in all trials. For this reason, trials did not provide outcome data on the use of long-acting FSH in poor responders.

All studies excluded women with explained subfertility. Therefore,

our meta-analyses were based on women with unexplained subfertility. Our outcomes do not apply to long-acting FSH in women with explained subfertility.

Quality of the evidence

We included four studies with a total of 2335 participants in our meta-analyses. The number of participants in each study varied between 99 and 1509. Both two-arm (one intervention and one control group) and four-arm (three intervention groups and one control group) studies were included. All studies reported their outcomes per woman. Only one study performed an intention-to-treat analysis but we had sufficient data to perform intention-to-treat analyses. We found differences between the inclusion and exclusion criteria as stated in the protocol and those published in the article, see Characteristics of included studies for details. These differences were minor and did not tend to be relevant.

The included studies differ in the dose of long-acting FSH. ENGAGE 2009 and ENSURE 2010 used a dose adjusted for participant body weight. ENGAGE 2009 only included women with a body weight above 60 kg and they used a medium dose of long-acting FSH. ENSURE 2010 recruited women weighing less than 60 kg and used a low dose of long-acting FSH for these women. Both Devroey 2004 and Koper 2008 also used a low dose but they included women weighing 50 to 90 kg. This may influence the overall effect in the low dose, long-acting FSH subgroup in favour of long-acting FSH.

Only one trial (Devroey 2004) studied a high dose of long-acting FSH and this treatment subgroup contained only 25 participants. This information is insufficient to make accurate conclusions about the treatment with high dose, long-acting FSH.

None of the studies reported patient satisfaction for long-acting FSH versus daily FSH treatment so we are not able to determine if long-acting FSH treatment is more patient friendly than daily FSH.

All included trials were sponsored by the same pharmaceutical company and have the same contact author, from the company. This may have introduced a bias in favour of long-acting FSH treatment.

Two studies (Devroey 2004; Koper 2008) did not blind the participants, personnel and outcome assessment and this caused a high risk of bias. Two studies (Devroey 2004; ENGAGE 2009) did not report all the reasons for withdrawals and Devroey 2004 did not report six treated participants in their published article, constituting a high risk of bias. We detected some moderate heterogeneity between the studies and subgroups. This can be explained by differences between the inclusion and exclusion criteria for participants, participant characteristics and the small differences between the treatment after the first seven days of COS. There was no indication for substantial heterogeneity, therefore we did not perform sensitivity analyses.

Potential biases in the review process

We stated in our protocol that we would perform different subgroup analyses. Due to insufficient data, we performed only the subgroup analysis for dose of long-acting FSH. We included a small number of studies and for this reason we did not construct a funnel plot. Therefore, we were not able to estimate the existence of publication or other reporting biases.

The method we adopted to deal with data from four-arm studies (discussed in detail in Included studies) may have introduced bias. All data were extracted by two review authors (AWP and CF). AWP compared the extracted data and discussed disagreements and doubts with CF. AWP entered the data into RevMan and wrote the review. These authors' methods may have introduced bias.

Agreements and disagreements with other studies or reviews

Our results are in agreement with both previous reviews (Croxtall 2011; Seyhan 2011).

AUTHORS' CONCLUSIONS

Implications for practice

The use of a medium dose of long-acting FSH is a safe treatment option and equally effective compared to daily FSH.

Implications for research

All current trials excluded poor- and hyper-responders to ovarian stimulation and women with explained subfertility. Therefore, further research is needed to determine if long-acting FSH can be used in all women with subfertility. There is one ongoing trial about long-acting FSH in combination with a GnRH agonist treatment. More research is needed to determine the pregnancy and safety outcomes in this treatment combination. There are no studies about patient satisfaction with the treatment and further research should examine this to determine whether the new treatment is more patient friendly than the daily injections regimen.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Devroey 2004

Methods	Randomised controlled trial, open-label four-arm trial Academic multi-center trial; Belgium and The Netherlands Timing: July 2001 to October 2002 (15 months) Ethical approval and informed consent obtained Power calculation carried out (dose of FSH-CTP) No intention-to-treat analysis performed
Participants	Number of participants as stated in their protocol (unpublished data): 104 (6 subjects treated during stage I part of this trial) Number of participants as stated in published article: 99 (75 intervention, 24 control treated during phase II part of the trial) All treated subjects (104) during the trial (phase I and II) are analysed in the follow-up study. We decided to analyse 105 subjects (99 subjects analysed in the published paper and 6 subjects treated stated in the protocol) **Inclusion criteria as stated in the article** Women between 18 and 39 years of age and a regular menstrual cycle (24-35 d) and normal body weight (BMI 18-29 kg/m^2) **Inclusion criteria as stated in the protocol** Women of couples with an indication for COH before IVF or ICSI, between 18 and 39 years, regular menstrual cycle (24-35d), BMI 18-29 kg/m^2, couples have availability of ejaculatory sperm, willing and able to sign informed consent **Exclusion criteria as stated in the article** Not reported **Exclusion criteria as stated in the protocol** History of/or current endocrine abnormality such as PCOS, or polycystic ovaries according to USS, (treated) hyper-prolactinemia or evidence of ovarian dysfunction, > 3 unsuccessful COH cycles for IVF since last established ongoing pregnancy, history of non- or low ovarian response to FSH/hMG treatment, any clinically relevant hormone value outside the reference range during the early follicular phase as measured by the local laboratory (FSH, LH, E2, P, total T, TSH and prolactin), any clinically relevant abnormal laboratory value, any ovarian and/or abdominal abnormality interfering with ultrasound examination, contraindications for the use of gonadotropins, epilepsy, diabetes, cardiovascular, gastro-intestinal, hepatic, renal, pulmonary, or abdominal disease, history of alcohol or drug abuse within 12 months prior to signing informed consent, hypersensitivity to Orgalutran® or any of its compounds, administration of investigational drugs within three months prior to screening, use of hormonal preparations within one month prior to the start of Org 36286 with the exception of thyroid medication *Mean age (years) and SD* intervention 120 μg: 30.4 ± 3.8 intervention 180 μg: 31.5 ± 3.8 intervention 240 μg: 33.4 ± 4.1 control: 32.1 ± 4.3 *Mean weight (kg) and SD*: not reported *Mean BMI (kg/m^2) and SD*

	intervention 120 μg: 23.2 ± 2.8 intervention 180 μg: 22.9 ± 3.5 intervention 240 μg: 22.6 ± 2.7 control: 23.4 ± 2.8 *Mean duration of subfertility (years) and SD* intervention 120 μg: 4.2 ± 3.1 intervention 180 μg: 4.9 ± 3.6 intervention 240 μg: 5.6 ± 4.3 control: 4.6 ± 3.2 **Withdrawals** *Intervention* Total 16% of participants in intervention groups withdrawn before embryo transfer 120 μg: two subjects who received hCG did not continue with oocyte pick-up, because absence of sperm and too few pre-ovulatory follicles 180 μg: one randomised subject dropped-out before the treatment started, no reason reported. One subject did not received hCG because an excessive response. Before oocyte pick-up one subject discontinued because too few preovulatory follicles 240 μg: two subjects did not received hCG because an excessive response or a too-low response Six subjects in the intervention groups who had oocyte retrieval did not proceed with embryo transfer because of fertilisation failure or the recovery of too few or no embryos *Control* Total 4.2% of participants in control group withdrawn before embryo transfer One subject in the control group did not received hCG because a too-low response
Interventions	Intervention: 120 μg, 180 μg or 240 μg long-acting FSH Control: 150 IU rFSH GnRH antagonist was administered sc starting on the day the leading follicle reached 14 mm, until at least 3 follicles $\geq$ 17 mm No more than 3 embryos were transferred
Outcomes	**Primary** Live birth rate OHSS **Secondary** Ongoing pregnancy rate Multiple pregnancy rate Adverse events: ectopic pregnancy
Notes	They report in their protocol six subjects treated with long-acting FSH during the phase I stage of this trial. Two subjects are treated with 120 μg and four subjects are treated with 180 μg of long-acting FSH. These six subjects are not reported in their published article. We made the decision to analyse all participants of this trial instead of the 99 as reported in their article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Devroey 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Randomised" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	"Randomised" No reference to allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for one withdrawal not reported, other numbers and reasons reported, for details see Characteristics of included studies
Selective reporting (reporting bias)	Low risk	All planned protocol outcomes reported
Other bias	High risk	Funded by pharmaceutical

ENGAGE 2009

Methods	Randomised controlled trial, double-blind two-arm trial Multicenter trial; 14 centres in North America (USA, Canada), 20 centres in Europe (Spain, UK, Belgium, Czech Republic, Finland, France, Norway, Sweden, Denmark, The Netherlands) Timing June 2006 to January 2008 (20 months) Ethical approval and informed consent obtained Power calculation carried out (total no. of participants) No intention-to-treat analysis performed
Participants	Number of participants: 1509 (757 intervention, 752 control) **Inclusion criteria as stated in the article** Women aged 18-36 years with a body weight > 60kg and ≤ 90 kg, a BMI 18-32 kg/m2, a menstrual cycle 24-35 d, access to ejaculatory sperm and an indication for COS before IVF or ICSI **Inclusion criteria as stated in the protocol** Women of a couple with an indication for COS before IVF or ICSI, between 18 and 36 years with a regular menstrual cycle (24-35d), body weight > 60 kg an ≤ 90 kg, BMI 18-32 kg/m^2 , couples have availability of ejaculatory sperm (donated and/or cryopreserved sperm is allowed), willing and able to sign informed consent **Exclusion criteria as stated in the article** Patients who had a (history of) an endocrine abnormality, an abnormal outcome of blood biochemistry or hematology, an abnormal cervical smear, a chronic disease, relevant ovarian, tubal or uterine pathology that could interfere with the COS treatment (e.g.

	endometrioma >0 mm or fibroids ≥ 5 cm), embryo implantation or pregnancy were not to be included in the trial. Patients who had a history of ovarian hyperresponse (more than 30 follicles ≥ 11 mm) or OHSS, PCOS or a basal antral follicle count of more than 20 on ultrasound (<11 mm, both ovaries combined). Other exclusion criteria included a previously low ovarian response to FSH or hMG treatment (i.e. cycle cancelled due to insufficient ovarian response or less than four oocytes obtained), an FSH or LH over 12 IU/L in the early follicular phase, more than three consecutive unsuccessful IVF cycles since the last ongoing pregnancy, a history of recurrent miscarriage (three or more), or currently smoking more than five cigarettes per day **Exclusion criteria as stated in the protocol** History of/or any current (treated) endocrine abnormality, history of ovarian hyperresponse or ovarian hyperstimulation syndrome (OHSS), history of/or current polycystic ovary syndrome (PCOS), more than 20 basal antral follicles <11 mm (both ovaries combined) as measured on USS in the early follicular phase (menstrual cycle day 2-5) , less than 2 ovaries or any other ovarian abnormality (including endometrioma > 10 mm; visible on USS), presence of unilateral or bilateral hydrosalphinx (visible on USS) , presence of any clinically relevant pathology affecting the uterine cavity or fibroids ≥ 5 cm, more than three unsuccessful IVF cycles since the last established ongoing pregnancy (if applicable), history of non- or low ovarian response to FSH/hMG treatment, history of recurrent miscarriage (3 or more, even when unexplained), FSH > 12 IU/L or LH > 12 IU/L as measured by the local laboratory (sample taken during the early follicular phase: menstrual cycle day 2-5), any clinically relevant abnormal laboratory value based on a sample taken during the screening phase, contraindications for the use of gonadotropins (e.g. tumors, pregnancy/lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts), recent history of/or current epilepsy, HIV infection, diabetes, cardiovascular, gastro-intestinal, hepatic, renal or pulmonary disease, abnormal karyotyping of the patient or her partner (if karyotyping is performed), smoking more than 5 cigarettes per day, history or presence of alcohol or drug abuse within 12 months prior to signing informed consent, previous use of Org 36286, use of hormonal preparations within 1 month prior to randomisation, hypersensitivity to any of the concomitant medication prescribed as part of the treatment regimen in this protocol, administration of investigational drugs within three months prior to signing informed consent *Mean age (years) and SD* intervention: 31.5 ± 3.3 control: 31.5 ± 3.2 *Mean weight (kg) and SD* intervention: 68.8 ± 7.6 control: 68.4 ± 7.3 *Mean BMI (kg/m2) and SD* intervention: 24.8 ± 2.8 control: 24.8 ± 2.7 *Mean duration of subfertility (years) and SD* intervention: 3.3 ± 2.4 control: 3.2 ± 2.2 **Withdrawals** Total intervention group: 11.2% withdrew before embryo transfer Total control group: 6.4% withdrew before embryo transfer A total of 187 patients failed screening or dropped out due to personal reasons prior to

ENGAGE 2009 (*Continued*)

	treatment allocation. Three patients (one in the intervention and two in the comparison group) were discontinued prior to the start of treatment (one for personal reasons and two were found to violate entry criteria after randomisation but before commencing treatment). During the treatment, but before the embryo transfer, a total of 130 patients (84 interventional, 46 control) discontinued the treatment, no reason reported
Interventions	Intervention: 150 μg FSH-CTP Control: 200 IU rFSH GnRH antagonist was administered sc starting on day 5 up to and including the day of hCG (at least 3 follicles $\geq$ 17 mm) One ore two embryos were transferred Drugs provided by patient itself, partner or medical staff
Outcomes	**Primary** Live birth rate OHSS **Secondary** Clinical (vital) pregnancy rate Ongoing pregnancy rate Multiple pregnancy rate Miscarriage rate Adverse event: ectopic pregnancy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation to one of the two arms (1:1 ratio) was done per centre and stratified by age (<32 or $\geq$ 32 years) by using randomly permutated blocks with a 'undisclosed' fixed block size of four."
Allocation concealment (selection bias)	Low risk	Quote: "central remote allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (subject, investigator) Quote: "The double-dummy approach guaranteed the blinding of medication during the trial and prevented any bias in terms of treatment decisions"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	High unexplained drop out rate, for details see Characteristics of included studies

ENGAGE 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	All planned protocol outcomes reported
Other bias	High risk	Funded by pharmaceuticals

ENSURE 2010

Methods	Randomised controlled trial, double-blind two-arm trial Multicentre trial; 14 centres in Europe (Austria, Czech republic, France, Spain, Poland, Sweden, Denmark) and 5 centres in Asia (Korea, Taiwan) Timing: January 2007 to December 2007 (12 months) Ethical approval and informed consent obtained Power calculation carried out (total no. participants) Intention-to-treat analysis performed
Participants	Number of participants: 396 (268 intervention, 128 control) **Inclusion criteria as stated in the article** Women aged 18-36 years, weighing $\leq$ 60 kg and BMI 18-32 kg/m^2, normal menstrual cycle (25-34d), have an indication for ovarian stimulation before IVF or ICSI, access to ejaculatory spermatozoa **Inclusion criteria as stated in the protocol** Women aged 18-36 years, weighing $\leq$ 60 kg and BMI 18-32 kg/m^2, normal menstrual cycle (25-34d) and have an indication for IVF or ICSI, couples have availability of ejaculatory sperm (donated and/or cryopreserved sperm allowed), willing and able to sign informed consent **Exlusion criteria as stated in the article** Same as those reported in Devroey 2009; History of ovarian hyperresponse to ovarian stimulation (more than 30 follicles >11 mm) or OHSS, PCOS or more than 20 basal antral follicles on ultrasound (<11 mm, both ovaries combined), history of no or low ovarian response (i.e. cycle cancelled due to insufficient response of less than four oocytes obtained) or more than three unsuccessful ovarian stimulation cycles since the last established ongoing pregnancy **Exclusion criteria as stated in the protocol** History of/or any current (treated) endocrine abnormality, history of ovarian hyper-response or OHSS, history of/or current PCOS, more than 20 basal antral follicles <11 mm (both ovaries combined) as measured on USS in the early follicular phase (menstrual cycle day 2-5), less than 2 ovaries or any other ovarian abnormality (including endometrioma > 10 mm; visible on USS), presence of unilateral or bilateral hydrosalphinx (visible on USS), presence of any clinically relevant pathology affecting the uterine cavity or fibroids >= 5 cm, more than three unsuccessful IVF cycles since the last established ongoing pregnancy (if applicable), history of non- or low ovarian response to FSH/hMG treatment, history of recurrent miscarriage (3 or more, even when unexplained), FSH > 12 IU/L or LH > 12 IU/L as measured by the local laboratory (sample taken during the early follicular phase: menstrual cycle day 2-5), any clinically relevant abnormal laboratory value based on a sample taken during the screening phase, contraindications for the use of gonadotropins (e.g. tumors, pregnancy/lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts), recent history of/or current epilepsy, HIV infection, diabetes, cardiovascular, gastro-intestinal, hepatic, renal or pulmonary disease, abnormal

	karyotyping of the patient or her partner (if karyotyping is performed), smoking more than 5 cigarettes per day, history or presence of alcohol or drug abuse within 12 months prior to signing informed consent, previous use of Org 36286, use of hormonal preparations within 1 month prior to randomisation, hypersensitivity to any of the concomitant medication prescribed as part of the treatment regimen in this protocol, administration of investigational drugs within three months prior to signing informed consent *Mean age (years) and SD* intervention: 30.9 ± 3.2 control: 31.1 ± 3.0 *Mean weight (kg) and SD* intervention: 54.1 ± 4.2 control: 54.4 ± 4.2 *Mean BMI (kg/m^2) and SD* intervention: 20.5 ± 1.5 control: 20.6 ± 1.6 *Mean duration of subfertility (years) and SD* intervention: 3.2 ± 2.2 control: 3.3 ± 2.1 **Withdrawals** *Intervention* Total 8.2% of participants in intervention group All the randomised patients started stimulation, two subjects cancelled the treatment before hCG because of insufficient ovarian response and a patients decision. All hCG treated patients underwent oocyte retrieval, twenty subjects cancelled before embryo transfer, one because the risk of OHSS, one suspicious for tuberculosis, too high ovarian response (5 subjects), no/too few/bad quality oocytes retrieved (2 subjects), no or abnormal fertilisation (4 subjects), no/too few/bad quality embryos for transfer (7 subjects) *Control* Total 6.3% of participants in control group All the randomised subjects started stimulation, one cancelled before the hCG treatment because too high ovarian response. All hCG treated patients underwent oocyte retrieval, a total of seven subjects discontinued before embryo transfer. The reasons are: no/too few/bad oocytes retrieved (2 subjects), one subject because of too high ovarian response, in one subject no fertilisation was possible, one had no/too few/bad quality embryos, no or abnormal fertilisation (2 subjects)
Interventions	Intervention: 100 μg long-acting FSH Control: 150 IU rFSH GnRH antagonist was administered sc starting on day 5 up to and including the day of hCG (at least 3 follicles $\geq$ 17 mm) One ore two embryos were transferred
Outcomes	**Primary** Live birth rate Cumulative live birth rate OHSS **Secondary** Clinical pregnancy rate Ongoing pregnancy rate

ENSURE 2010 (*Continued*)

	Multiple pregnancy rate Miscarriage rate	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation to one of the two treatment groups in a 2:1 ratio (investigational:reference group) was performed at each centre and stratified by age (<32 or ≥ 32 years) and planned fertilisation procedure (IVF or ICSI) by central remote allocation using randomly permutated blocks with an 'undisclosed' fixed block size of three."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation by central remote allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind "To conceal the allocation all patients also started daily sc injection of rFSH or placebo on the same day, daily active or placebo rFSH injections were continued through the first seven days of stimulation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported, for details see Characteristics of included studies
Selective reporting (reporting bias)	Low risk	All planned protocol outcomes reported
Other bias	High risk	Funded by pharmaceutical

Koper 2008

Methods	Randomised controlled trial, open-label four-arm trial Multicentre trial; 14 centres in Europe Timing: May 2003 to May 2004 (12 months) Ethical approval and informed consent obtained Power calculation carried out (no. participants per group) No intention-to-treat analyses performed
Participants	Number of participants: 325 (242 intervention, 83 control) **Inclusion criteria as stated in the article** Women aged 20-39 years with a normal menstrual cycle (24-35d) and a BMI 17-31 kg/m^2 with an indication for COS before IVFor ICSI **Inclusion criteria as stated in the protocol** Women of couples with an indication for COH and IVF or ICSI, aged 18-39 years, normal menstrual cycle (24-35d), BMI 17-31 kg/m^2, with an indication for IVF or ICSI, couples have availability of ejaculatory sperm (donated or frozen sperm is allowed) , able and willing to sign informed consent **Exclusion criteria as stated in the article** Women with a history of OHSS, PCOS, any endocrine abnormality, previous poor response to FSH or hCG, more than three unsuccessful COS cycles since last ongoing pregnancy, fewer than two ovaries, abnormal hormone levels during days 2-7 of the menstrual cycle, use of hormonal preparations within 1 month before treatment or previous use of Corifollitropin alfa, were excluded **Exclusion criteria as stated in the protocol** History of/or any current (treated) endocrine abnormality, history of ovarian hyperstimulation syndrome (OHSS), history of/or current polycystic ovary syndrome (PCOS) or current polycystic ovaries according to USS (at least 10 follicles of 2-8 mm in each ovary) , more than three unsuccessful COH cycles since the last established ongoing pregnancy (if applicable), history of non- or low ovarian response to FSH/hMG treatment, any clinically relevant hormone value outside the reference range during the early follicular phase (menstrual cycle day 2-7) as measured by the local laboratory (FSH, LH, E2, P, total T, TSH and prolactin), any clinically relevant abnormal laboratory value, less than 2 ovaries, any ovarian and/or abdominal abnormality interfering with ultrasound examination, contraindications for the use of gonadotropins (e.g. tumors, pregnancy/lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts), epilepsy, diabetes, cardiovascular, gastro-intestinal, hepatic, renal, pulmonary, or abdominal disease, history of presence of alcohol or drug abuse within 12 months prior to signing informed consent, previous use of Org 36286, use of hormonal preparations within 1 month prior to randomisation, hypersensitivity to Org 32489 (Puregon®) and/or Org 37462 (Orgalutran®) and/or Pregnyl® or any of their components, administration of investigational drugs within three months prior to signing informed consent *Mean age (years) and SD* intervention 60 μg: 32.0 ± 3.5 intervention 120 μg: 32.0 ± 4.1 intervention 180 μg: 32.4 ± 3.5 control rFSH: 32.1 ± 3.8 *Mean weight (kg) and SD* intervention 60 μg: 63.8 ± 9.0 intervention 120 μg: 64.8 ± 8.8 intervention 180 μg: 64.0 ± 9.3

	control rFSH: 65.2 ± 9.3 *Mean BMI (kg/m2) and SD* intervention 60 μg: 22.7 ± 3.2 intervention 120 μg: 23.5 ± 3.2 intervention 180 μg: 22.7 ± 2.6 control rFSH: 23.1 ± 3.0 *Mean duration of subfertility (years) and SD* intervention 60 μg: 3.2 ± 1.8 intervention 120 μg: 3.3 ± 1.9 intervention 180 μg: 3.1 ± 2.5 control rFSH: 3.1 ± 2.2 **Withdrawals** 58 subject are excluded before randomisation, reasons not reported *Interventions* Total 21.1% of participants in intervention groups withdrew before embryo transfer 60 μg: One subject excluded before stimulation because PCOS. 23 Subjects did not received hCG because insufficient ovarian response (22 subjects) and one (serious) adverse event. Five subjects are excluded before oocyte retrieval, two because insufficient ovarian response, and two inadequate oocytes retrieved (none, too few or poor quality). Before embryo transfer six subjects withdrew because no fertilisation (2 subjects, inadequate embryos (3 subjects) and one because ICSI not possible (dead sperm) 120 μg: Three subjects excluded before start stimulation because personal reasons, five did not underwent hCG treatment because insufficient ovarian response (2 subjects), risk of hyperstimulation (2 subjects) and one for personal reasons. After oocyte retrieval two excluded before transfer because no fertilisation or inadequate embryos 180 μg: Before the start of treatment four subjects are excluded because spontaneous pregnancy (2 subjects) and personal reasons (2 subjects). After oocyte retrieval 4 subjects did not underwent embryo transfer because risk of hyperstimulation, no fertilisation and inadequate embryos (2 subjects) *Control* Total of 20.5% in control group withdrawn before embryo transfer Two Subjects did not started stimulation because a menstrual disorder and personal reasons, six subjects discontinued before the hCG treatment because insufficient ovarian response (5 subjects) and one because personal reasons. Two subjects are excluded before oocyte retrieval because an insufficient ovarian response and inadequate oocytes retrieved. After oocyte retrieval seven subjects dropped-out because inadequate oocytes retrieved (5 subjects) and in two subjects no fertilisation take place
Interventions	Intervention: 60 μg, 120 μg or 180 μg long-acting FSH Control: 150 IU rFSH GnRH antagonist was administered sc starting on day 5 up to and including the day of hCG (at least 3 follicles $\geq$ 17 mm) No more than 3 embryos were transferred
Outcomes	**Primary** Live birth rate OHSS **Secondary** Clinical (vital) pregnancy rate

Koper 2008 (*Continued*)

	Ongoing pregnancy rate Multiple pregnancy rate	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation to one of the four arms (1:1:1:1) was stratified by age (<32 or ≥ 32 years) and by centre using a fixed block size of four and a minimization algorithm combined with randomly permutated blocks."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation by using a central remote allocation procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and most reasons for withdrawals reported, for details see Characteristics of included studies
Selective reporting (reporting bias)	Low risk	All planned protocol outcomes reported
Other bias	High risk	Funded by pharmaceutical

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

Study	Reason for exclusion
Balen 2004	This trial is excluded because no IVF or ICSI performed after stimulation
Croxtall 2011	Not a RCT (review)
De Lartigue 2011	Not a RCT
Fatemi 2010	Not a RCT

(*Continued*)

Ledger 2009	Not a RCT (review)
Loutradis 2010	Not a RCT
Norman 2011	Not a RCT
Prados 2011	Not a RCT
Seyhan 2011	Not a RCT (review)

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

Pursue 2010

Trial name or title	Efficacy and safety of a single injection of SCH 900962 versus daily recFSH injections in women undergoing controlled ovarian stimulation (Study P06029)
Methods	Randomised controlled trial, double-blind (Subject, Caregiver, Investigator, Outcomes Assessor), double-dummy, two-arm trial
Participants	Estimated enrolment: 1400 participants **Inclusion criteria** Willing and able to provide written informed consent for trial P06029 as well as for the Frozen-Thawed Embryo Transfer (FTET) follow-up trial P06031, and for the pharmacogenetic analysis (if applicable), female and ≥35 to ≤42 years of age with indication for COS and IVF/ICSI, body weight ≥50.0 kg, BMI ≥18.0 to ≤32.0 kg/m^2, regular spontaneous menstrual cycle with variation not outside the 24-35 days, ejaculatory sperm must be available (donated and/or cryopreserved sperm is allowed), results of clinical laboratory tests, cervical smear, physical examination within normal limits or clinically acceptable to the investigator, adhere to trial schedule **Exclusion criteria** A recent history of/or any current endocrine abnormality, a history of ovarian hyper-response or ovarian hyperstimulation syndrome, a history of/or current polycystic ovary syndrome, more than 20 basal antral follicles <11 mm (both ovaries combined) in the early follicular phase, less than 2 ovaries or any other ovarian abnormality, unilateral or bilateral hydrosalpinx, intrauterine fibroids ≥5 cm or any clinically relevant pathology, which could impair embryo implantation or pregnancy continuation, more than three unsuccessful COS cycles for IVF/ICSI since the last established ongoing pregnancy (if applicable), a history of non- or low ovarian response to FSH/hMG treatment, a history of recurrent miscarriage, FSH >15.0 IU/L or LH >12. 0 IU/L during the early follicular phase, positive for HIV or Hepatitis B, contraindications for the use of gonadotropins or GnRH antagonists, a recent history of/or current epilepsy, thrombophilia, diabetes, cardiovascular, gastro-intestinal, hepatic, renal or pulmonary or auto-immune disease requiring regular treatment, smoking or recently stopped smoking (ie, within the last 3 months prior to signing informed consent), a recent history or presence of alcohol or drug abuse, the subject or the sperm donor has known gene defects, genetic abnormalities, or abnormal karyotyping, relevant for the current indication or for the health of the offspring, prior or concomitant medications disallowed by protocol
Interventions	Intervention: corifollitropin alfa, 100 μg for women weighing ≤60 kg, and 150 μg for women weighing >60 kg

Pursue 2010 (*Continued*)

	Control: recombinant FSH 150-300 IU daily until > 2 follicles are >18 mm
Outcomes	**Primary:** Vital pregnancy (assessed by ultrasound at least 35 days after embryo transfer **Secondary:** Number of oocytes retrieved Live birth rate
Starting date	June 2010
Contact information	No contacts provided
Notes	Estimated study completion date: September 2012

Siristatidis 2011

Trial name or title	Corifollitropin alfa versus recombinant follicle stimulating hormone (FSH) in ovarian stimulation of women undergoing in vitro fertilisation
Methods	Randomised controlled trial Single-blind (participant), two-arm trial One-centre trial
Participants	Estimated enrolment: 100 **Includion criteria** Women aged 18-36 years old with a body weight of more than 60 kg up to 90 kg, BMI of 18-32 kg/m^2, menstrual cycle length of 23-35 days, an indication for controlled ovarian stimulation for IVF or ICSI **Exclusion Criteria** History of an endocrine abnormality, abnormal outcome of blood biochemistry or hematology, abnormal cervical smear, chronic disease, uterine pathology that interfering with the COS treatment (e.g. fibroids $\geq$ 5 cm)
Interventions	Intervention: corifollitropin alfa 150 μg Control: recombinant FSH 300 IU Both GnRH agonists (long) and antagonists protocols will be used. Final oocyte maturation will be induced by the administration of hCG on the day that 2 follicles >18 mm were recognized on the transvaginal ultrasound scan One or two embryos will be transferred
Outcomes	**Primary**: Ongoing pregnancy rate, defined as the presence of fetal heart at ultrasound after 12 gestational weeks **Secondary:** Clinical pregnancy rate, defined as the presence of fetal heart at transvaginal ultrasound at 6+2 gestational weeks Cancellation rate Miscarriage rate Ectopic pregnancy rate

Siristatidis 2011 (*Continued*)

Starting date	January 2011
Contact information	Siristatidis CS, MD, PhD; harrysiri@yahoo.gr, 6932294994 ext 0030
Notes	Estimated completion date: January 2013

DATA AND ANALYSES

Comparison 1. Long-acting FSH (all doses) versus daily FSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	4	2335	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.76, 1.10]
1.1 Low dose (60-120 μg)	3	645	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.40, 0.91]
1.2 Medium dose (150-180 μg)	3	1657	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.84, 1.27]
1.3 High dose (240 μg)	1	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.04, 1.95]
2 Ovarian hyperstimulation syndrome	4	2335	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.79, 1.60]
2.1 Low dose (60-120 μg)	3	645	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.55, 2.72]
2.2 Medium dose (150-180 μg)	3	1657	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.72, 1.61]
2.3 High dose (240 μg)	1	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.91 [0.15, 104.40]
3 Ongoing pregnancy rate	4	2335	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.78, 1.12]
3.1 Low dose (60-120 μg)	3	645	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.47, 1.06]
3.2 Medium dose (150-180 μg)	3	1657	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.83, 1.25]
3.3 High dose (240 μg)	1	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.06, 1.67]
4 Clinical pregnancy rate	3	2230	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.80, 1.15]
4.1 Low dose (60-120 μg)	2	610	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.47, 1.06]
4.2 Medium dose (150-180 μg)	2	1620	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.84, 1.26]
5 Multiple pregnancy rate	4	2335	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.92, 1.68]
5.1 Low dose (60-120 μg)	3	645	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.51, 2.17]
5.2 Medium dose (150-180 μg)	3	1657	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.92, 1.79]
5.3 High dose (240 μg)	1	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.74 [0.04, 362.67]
6 Miscarriage rate	2	1905	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.76, 2.12]
6.1 Low dose (60-120 μg)	1	396	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.38, 3.73]
6.2 Medium dose (150-180 μg)	1	1509	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.72, 2.28]
7 Ectopic pregnancy rate	3	2004	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.43, 1.92]
7.1 Low dose (60-120 μg)	2	429	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.32, 3.42]
7.2 Medium dose (150-180 μg)	2	1542	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.32, 2.17]
7.3 High dose (240 μg)	1	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

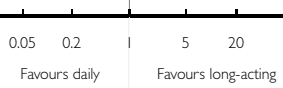
Analysis 1.1. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 1 Live birth rate.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 1 Live birth rate

Study or subgroup	long-acting FSH n/N	daily FSH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose (60-120 g)					
Devroey 2004	4/27	3/8		0.9 %	0.25 [0.04, 1.76]
ENSURE 2010 (1)	63/268	45/128		15.2 %	0.56 [0.35, 0.89]
Koper 2008	20/159	7/55		4.0 %	0.99 [0.39, 2.48]
Subtotal (95% CI)	**454**	**191**		**20.1 %**	**0.60 [0.40, 0.91]**
Total events: 87 (long-acting FSH), 55 (daily FSH)					
Heterogeneity: Chi^2 = 1.98, df = 2 (P = 0.37); I^2 =0.0%					
Test for overall effect: Z = 2.42 (P = 0.015)					
2 Medium dose (150-180 g)					
Devroey 2004	4/29	3/8		0.9 %	0.22 [0.03, 1.60]
ENGAGE 2009	269/757	258/752		75.9 %	1.06 [0.85, 1.30]
Koper 2008	11/83	4/28		2.2 %	0.92 [0.26, 3.19]
Subtotal (95% CI)	**869**	**788**		**78.9 %**	**1.03 [0.84, 1.27]**
Total events: 284 (long-acting FSH), 265 (daily FSH)					
Heterogeneity: Chi^2 = 2.41, df = 2 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 0.31 (P = 0.76)					
3 High dose (240 g)					
Devroey 2004	4/25	3/8		0.9 %	0.29 [0.04, 1.95]
Subtotal (95% CI)	**25**	**8**		**0.9 %**	**0.29 [0.04, 1.95]**
Total events: 4 (long-acting FSH), 3 (daily FSH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.20)					
Total (95% CI)	**1348**	**987**		**100.0 %**	**0.92 [0.76, 1.10]**
Total events: 375 (long-acting FSH), 323 (daily FSH)					
Heterogeneity: Chi^2 = 11.10, df = 6 (P = 0.09); I^2 =46%					
Test for overall effect: Z = 0.93 (P = 0.35)					
Test for subgroup differences: Chi^2 = 6.71, df = 2 (P = 0.03), I^2 =70%					



(1) This study only recruited women with a body weight of less than 60kg.

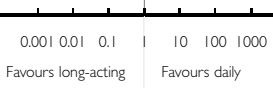
Analysis 1.2. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 2 Ovarian hyperstimulation syndrome.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 2 Ovarian hyperstimulation syndrome

Study or subgroup	long-acting FSH n/N	daily FSH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose (60-120 g)					
Devroey 2004	2/27	1/8		1.6 %	0.53 [0.03, 8.55]
ENSURE 2010 (1)	18/268	6/128		16.2 %	1.43 [0.59, 3.44]
Koper 2008	2/159	1/55		1.9 %	0.67 [0.05, 9.01]
Subtotal (95% CI)	**454**	**191**		**19.7 %**	**1.22 [0.55, 2.72]**
Total events: 22 (long-acting FSH), 8 (daily FSH)					
Heterogeneity: Chi^2 = 0.67, df = 2 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.50 (P = 0.62)					
2 Medium dose (150-180 g)					
Devroey 2004	0/29	1/8		0.6 %	0.01 [0.00, 1.15]
ENGAGE 2009	53/757	47/752		76.7 %	1.13 [0.75, 1.69]
Koper 2008	2/83	1/28		1.8 %	0.65 [0.05, 8.95]
Subtotal (95% CI)	**869**	**788**		**79.1 %**	**1.08 [0.72, 1.61]**
Total events: 55 (long-acting FSH), 49 (daily FSH)					
Heterogeneity: Chi^2 = 3.94, df = 2 (P = 0.14); I^2 =49%					
Test for overall effect: Z = 0.37 (P = 0.71)					
3 High dose (240 g)					
Devroey 2004	2/25	0/8		1.2 %	3.91 [0.15, 104.40]
Subtotal (95% CI)	**25**	**8**		**1.2 %**	**3.91 [0.15, 104.40]**
Total events: 2 (long-acting FSH), 0 (daily FSH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.81 (P = 0.42)					
Total (95% CI)	**1348**	**987**		**100.0 %**	**1.12 [0.79, 1.60]**
Total events: 79 (long-acting FSH), 57 (daily FSH)					
Heterogeneity: Chi^2 = 5.25, df = 6 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.53)					
Test for subgroup differences: Chi^2 = 0.64, df = 2 (P = 0.73), I^2 =0.0%					



(1) This study only recruited women with a body weight of less than 60kg.

Analysis 1.3. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 3 Ongoing pregnancy rate.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 3 Ongoing pregnancy rate

Study or subgroup	long-acting FSH n/N	daily FSH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose (60-120 g)					
Devroey 2004	4/27	3/8		0.9 %	0.25 [0.04, 1.76]
ENSURE 2010 (1)	68/268	44/128		14.9 %	0.64 [0.40, 1.02]
Koper 2008	24/159	7/55		4.3 %	1.21 [0.51, 2.88]
Subtotal (95% CI)	**454**	**191**		**20.1 %**	**0.71 [0.47, 1.06]**
Total events: 96 (long-acting FSH), 54 (daily FSH)					
Heterogeneity: Chi^2 = 2.71, df = 2 (P = 0.26); I^2 =26%					
Test for overall effect: Z = 1.69 (P = 0.091)					
2 Medium dose (150-180 g)					
Devroey 2004	5/29	3/8		0.9 %	0.31 [0.05, 2.04]
ENGAGE 2009	294/757	286/752		75.7 %	1.03 [0.84, 1.27]
Koper 2008	11/83	4/28		2.1 %	0.92 [0.26, 3.19]
Subtotal (95% CI)	**869**	**788**		**78.8 %**	**1.02 [0.83, 1.25]**
Total events: 310 (long-acting FSH), 293 (daily FSH)					
Heterogeneity: Chi^2 = 1.57, df = 2 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 0.16 (P = 0.87)					
3 High dose (240 g)					
Devroey 2004	6/25	4/8		1.1 %	0.30 [0.06, 1.67]
Subtotal (95% CI)	**25**	**8**		**1.1 %**	**0.30 [0.06, 1.67]**
Total events: 6 (long-acting FSH), 4 (daily FSH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Total (95% CI)	**1348**	**987**		**100.0 %**	**0.93 [0.78, 1.12]**
Total events: 412 (long-acting FSH), 351 (daily FSH)					
Heterogeneity: Chi^2 = 8.47, df = 6 (P = 0.21); I^2 =29%					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Chi^2 = 4.19, df = 2 (P = 0.12), I^2 =52%					

(1) This study only recruited women with a body weight of less than 60kg.

Analysis 1.4. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 4 Clinical pregnancy rate.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 4 Clinical pregnancy rate

Study or subgroup	long-acting FSH n/N	daily FSH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose (60-120 g)					
ENSURE 2010 (1)	69/268	45/128		15.3 %	0.63 [0.40, 1.01]
Koper 2008	26/159	9/55		4.8 %	1.00 [0.44, 2.28]
Subtotal (95% CI)	**427**	**183**		**20.1 %**	**0.71 [0.47, 1.06]**
Total events: 95 (long-acting FSH), 54 (daily FSH)					
Heterogeneity: Chi^2 = 0.89, df = 1 (P = 0.34); I^2 =0.0%					
Test for overall effect: Z = 1.69 (P = 0.092)					
2 Medium dose (150-180 g)					
ENGAGE 2009	302/757	293/752		77.5 %	1.04 [0.85, 1.28]
Koper 2008	12/83	5/28		2.4 %	0.77 [0.24, 2.52]
Subtotal (95% CI)	**840**	**780**		**79.9 %**	**1.03 [0.84, 1.26]**
Total events: 314 (long-acting FSH), 298 (daily FSH)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
Total (95% CI)	**1267**	**963**		**100.0 %**	**0.96 [0.80, 1.15]**
Total events: 409 (long-acting FSH), 352 (daily FSH)					
Heterogeneity: Chi^2 = 3.81, df = 3 (P = 0.28); I^2 =21%					
Test for overall effect: Z = 0.50 (P = 0.62)					
Test for subgroup differences: Chi^2 = 2.68, df = 1 (P = 0.10), I^2 =63%					

(1) This study only recruited women with a body weight of less than 60kg.

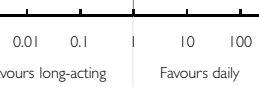
Analysis 1.5. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 5 Multiple pregnancy rate.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 5 Multiple pregnancy rate

Study or subgroup	long-acting FSH n/N	daily FSH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose (60-120 g)					
Devroey 2004	1/27	1/8		0.8 %	0.20 [0.01, 5.84]
ENSURE 2010 (1)	19/268	10/128		14.0 %	0.90 [0.40, 2.02]
Koper 2008	6/159	0/55		2.7 %	3.97 [0.62, 25.31]
Subtotal (95% CI)	**454**	**191**		**17.5 %**	**1.05 [0.51, 2.17]**
Total events: 26 (long-acting FSH), 11 (daily FSH)					
Heterogeneity: Chi² = 3.03, df = 2 (P = 0.22); I² =34%					
Test for overall effect: Z = 0.14 (P = 0.89)					
2 Medium dose (150-180 g)					
Devroey 2004	1/29	0/8		0.4 %	3.58 [0.03, 418.61]
ENGAGE 2009	83/757	66/752		79.9 %	1.28 [0.91, 1.79]
Koper 2008	3/83	1/28		1.7 %	1.01 [0.10, 9.98]
Subtotal (95% CI)	**869**	**788**		**82.1 %**	**1.28 [0.92, 1.79]**
Total events: 87 (long-acting FSH), 67 (daily FSH)					
Heterogeneity: Chi² = 0.22, df = 2 (P = 0.90); I² =0.0%					
Test for overall effect: Z = 1.44 (P = 0.15)					
3 High dose (240 g)					
Devroey 2004	1/25	0/8		0.4 %	3.74 [0.04, 362.67]
Subtotal (95% CI)	**25**	**8**		**0.4 %**	**3.74 [0.04, 362.67]**
Total events: 1 (long-acting FSH), 0 (daily FSH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Total (95% CI)	**1348**	**987**		**100.0 %**	**1.24 [0.92, 1.68]**
Total events: 114 (long-acting FSH), 78 (daily FSH)					
Heterogeneity: Chi² = 3.71, df = 6 (P = 0.72); I² =0.0%					
Test for overall effect: Z = 1.40 (P = 0.16)					
Test for subgroup differences: Chi² = 0.46, df = 2 (P = 0.80), I² =0.0%					



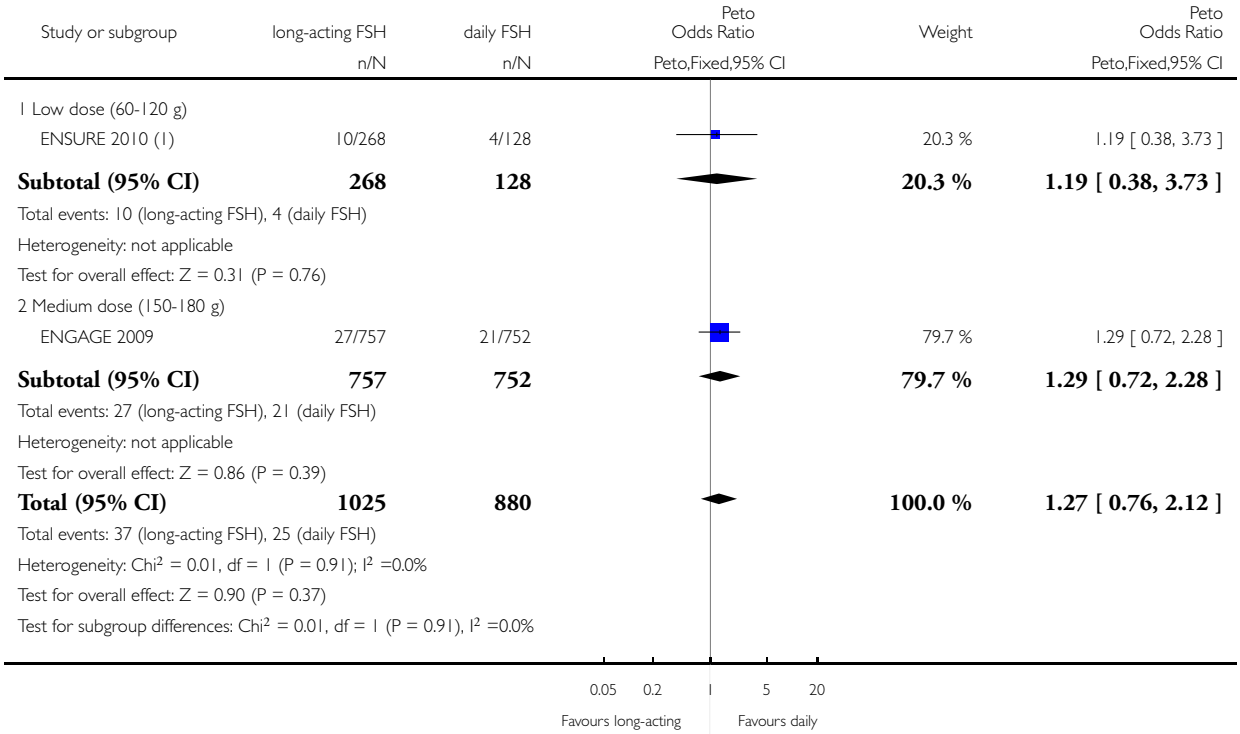
(1) This study only recruited women with a body weight of less than 60kg.

Analysis 1.6. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 6 Miscarriage rate.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 6 Miscarriage rate



(1) This study only recruited women with a body weight of less than 60kg.

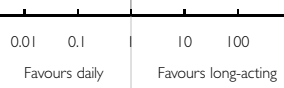
Analysis 1.7. Comparison 1 Long-acting FSH (all doses) versus daily FSH, Outcome 7 Ectopic pregnancy rate.

Review: Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Comparison: 1 Long-acting FSH (all doses) versus daily FSH

Outcome: 7 Ectopic pregnancy rate

Study or subgroup	long-acting FSH n/N	daily FSH n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose (60-120 g)				
Devroey 2004	1/25	0/8		3.74 [0.04, 362.67]
ENSURE 2010 (1)	8/268	4/128		0.95 [0.28, 3.25]
Subtotal (95% CI)	**293**	**136**		**1.05 [0.32, 3.42]**
Total events: 9 (long-acting FSH), 4 (daily FSH)				
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%				
Test for overall effect: Z = 0.07 (P = 0.94)				
2 Medium dose (150-180 g)				
Devroey 2004	1/25	0/8		3.74 [0.04, 362.67]
ENGAGE 2009	7/757	9/752		0.77 [0.29, 2.07]
Subtotal (95% CI)	**782**	**760**		**0.83 [0.32, 2.17]**
Total events: 8 (long-acting FSH), 9 (daily FSH)				
Heterogeneity: Chi^2 = 0.44, df = 1 (P = 0.51); I^2 =0.0%				
Test for overall effect: Z = 0.39 (P = 0.70)				
3 High dose (240 g)				
Devroey 2004	0/25	0/8		0.0 [0.0, 0.0]
Subtotal (95% CI)	**25**	**8**		**0.0 [0.0, 0.0]**
Total events: 0 (long-acting FSH), 0 (daily FSH)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**1100**	**904**		**0.91 [0.43, 1.92]**
Total events: 17 (long-acting FSH), 13 (daily FSH)				
Heterogeneity: Chi^2 = 0.85, df = 3 (P = 0.84); I^2 =0.0%				
Test for overall effect: Z = 0.25 (P = 0.80)				
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 =0.0%				



(1) This study only recruited women with a body weight of less than 60kg.

ADDITIONAL TABLES

Table 1. Summary of characteristics of included studies

Study ID	Participant age (years)	Participant BMI (kg/m2)	Participant weight (kg)	Start GnRH antagonist	No. of embryos transferred	Poor responders
Devroey 2004	18-39	18-29	50-90	leading follicle >/ = 14mm	</=3	Excluded
ENGAGE 2009	18-36	18-32	>60 and </=90	Day 5	1 or 2	Excluded
ENSURE 2010	18-36	18-32	<60	Day 5	1 or 2	Excluded
Koper 2008	20-39 Protocol:18-39	17-31	50-90	Day 5	</=3	Excluded

APPENDICES

Appendix 1. Glossary

Assisted reproductive technology (ART)

All treatments or procedures that include the in vitro handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization and transcervical embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor.

Cancelled cycle

an ART cycle in which ovarian stimulation or monitoring has been carried out with the intent of undergoing ART but which did not proceed to follicular aspiration or, in the case of a thawed embryo, to transfer.

Clinical pregnancy

Evidence of pregnancy by clinical or ultrasound parameters (ultrasound visualization of a gestational sac). It includes ectopic pregnancy. Multiple gestational sacs in one patient are counted as one clinical pregnancy.

Controlled ovarian stimulation (COS)

Medical treatment to induce the development of multiple ovarian follicles to obtain multiple oocytes at follicular aspiration

Cryopreservation or cryostorage

Freezing and storage of gametes, zygotes, or embryos.

Ectopic pregnancy

A pregnancy that occurs outside of the uterus.

Embryo

Product of conception from the time of fertilization to the end of the embryonic stage eight weeks after fertilization (the term pre-embryo or dividing conceptus, has been replaced by embryo).

Embryo transfer (ET)

Procedure in which embryos are placed in the uterus or fallopian tube.

Fertilisation

The penetration of the ovum by the spermatozoon and fusion of genetic materials resulting in the development of a zygote.

Fetus

The product of conception starting from completion of embryonic development (at eight completed weeks after fertilisation) until birth or abortion.

Follicle

The sac in which an egg develops in the ovary.

Follicle-stimulating hormone (FSH)

A hormone produced and released from the pituitary gland. In women it stimulates the production of oestrogen and follicles in the ovary ready for ovulation. In men it stimulates the production of sperm.

Gestational age

Age of an embryo or foetus calculated by adding 14 days (2 weeks) to the number of completed weeks since fertilisation.

Gestational sac

A fluid-filled structure containing an embryo that develops early in pregnancy usually within the uterus.

Gonadotrophin releasing hormone (GnRH)

A substance produced by the hypothalamus (part of the brain) to enable the pituitary gland to secrete LH and FSH.

Gonadotropins

Pituitary hormones FSH and LH which stimulate the testes and ovaries.

Human chorionic gonadotrophin (hCG)

A hormone produced by placental tissue that can be measured in the blood and urine of pregnant women.

Hyper-responder

A women who produce a large number of oocytes (women with PCOS, see polycystic ovary syndrome, or a history of OHSS, see ovarian hyperstimulation syndrome).

Implantation

The attachment and subsequent penetration by the zona-free blastocyst (usually in the endometrium) which starts five to seven days following fertilization.

Intracytoplasmic sperm injection (ICSI)

When an egg is surgically removed from a woman and injected with a single spermatozoon is injected through the zona pellucida into the oocyte . If fertilisation is successful the embryo is placed into the woman's uterus. This technique is used when a male partner has a low sperm count or other sperm related problem.

Intrauterine

Inside the uterus.

In vitro fertilization (IVF)

An ART procedure which involves extracorporeal fertilization.

Live birth

A birth in which a fetus is delivered with signs of life after complete expulsion or extraction from its mother, beyond 20 completed weeks of gestational age. Live births are counted as birth events (e.g., a twin or triplet live birth is counted as one birth event).

Luteinising hormone (LH)

A hormone produced and released by the pituitary gland. In women it is responsible for ovulation and progesterone production. In men it stimulates the production of testosterone and is involved with the production of sperm cells.

Miscarriage

Spontaneous end of a pregnancy at prior to 20 weeks of gestation.

Oocyte

The egg from a woman's ovary.

Ova

A woman's reproductive cell, also known as egg or oocyte.

Ovarian hyperstimulation syndrome (OHSS)

A condition that occurs from fertility drugs when a large number of follicles in the ovary are stimulated to develop and ovulate. This stimulation causes an enlargement of the ovaries.

Ovulation

The release of an egg/ova from an ovarian follicle.

Ovulation Induction

Medical treatment to produce ovulation.

Ovulatory hCG (human chorionic gonadotrophin)

Hormone given to trigger ovulation in assisted reproduction.

Polycystic ovary syndrome (PCOS)

When a woman has enlarged ovaries with multiple cysts and the surface of the ovary is thickened. The woman may ovulate infrequently or not at all.

Poor responder

A women who require large doses of medication to stimulate the ovary but produce less than an optimal number of oocytes.

Premature LH-surge

In a normal menstrual cycle an increase in LH-levels (LH-surge) is needed to start ovulation. In IVF/ICSI cycles it is important that the ovulation does not start before the oocytes are mature enough to be retrieved. A LH-surge that occurs too early is called premature and is an unwanted event in IVF/ICSI cycles.

Recombinant (as in recombinant FSH)

Is a naturally occurring hormone which has been made in the laboratory with the use of DNA technology. Recombinant technology examines the DNA sequence of a hormone. The sequence is then placed inside certain bacteria (bacterial factories), which produce a protein from the DNA sequence. This protein is then taken from the bacteria and packaged as a hormone.

Semen

A thick white fluid produced in the reproductive organs of men that usually contains the sperm cells produced in the testicles.

Spermatozoa/sperm

Male reproductive cells found in semen.

Subfertility

Failure to achieve pregnancy after at least one year of unprotected coitus.

Subcutaneous

Under the skin

Ultrasound

Radiology sounds waves of a high frequency used to examine the inside of the body. Ultrasound is also used to visualise the developing foetus in the uterus to check size, growth and the presence of abnormalities.
Most of the definitions were achieved from the glossary of the MDSG module 2008.

Appendix 2. CENTRAL search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials (CENTRAL)
Date of search: 10-10-2011
1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (1533)
2 embryo transfer$.tw. (853)
3 in vitro fertili?ation.tw. (1282)
4 ivf-et.tw. (244)
5 (ivf or et).tw. (5804)
6 icsi.tw. (626)
7 intracytoplasmic sperm injection$.tw. (389)
8 (blastocyst adj2 transfer$).tw. (63)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (2133)
10 assisted reproduct$.tw. (373)
11 artificial insemination.tw. (53)
12 iui.tw. (270)
13 intrauterine insemination$.tw. (373)
14 ovulation induc$.tw. (414)
15 ovarian hyperstimulation.tw. (524)
16 COH.tw. (117)
17 (ovari$ adj2 stimulat$).tw. (702)
18 superovulat$.tw. (127)
19 infertil$.tw. (1688)
20 subfertil$.tw. (127)
21 (ovari$ adj2 induction).tw. (25)
22 or/1-21 (8905)
23 corifollitropin alfa.tw. (12)
24 corifollitropin alpha.tw. (1)
25 org 36286.tw. (2)
26 org36286.tw. (0)
27 FSH carboxy terminal peptide.tw. (1)
28 FSH-CTP.tw. (5)
29 FSH CTP.tw. (5)
30 long acting follitropin.tw. (0)
31 Elonva$.tw. (0)
32 sustained follicle stimulat$.tw. (0)
33 long acting fsh.tw. (3)
34 long acting follicle stimulating hormone.tw. (0)
35 or/23-34 (14)
36 22 and 35 (7)

Appendix 3. MDSG search strategy

Date of search: 10-10-2011
Keywords CONTAINS “IVF”or“ICSI” or “subfertility” or “in vitro fertilisation” or “in vitro fertilization” or “intracytoplasmic sperm injection” or “assisted conception” or “assisted reproduction” or “ART” or “infertility” or “IUI” or “Intrauterine Insemination” or “artificial insemination” or “ovarian hyperstimulation” or “ovarian stimulation” or “ovulation induction”or“COH” or “controlled ovarian ” or “insemination” or “insemination-intrauterine” or Title CONTAINS “IVF”or“ICSI” or “subfertility” or “in vitro fertilisation” or “in vitro fertilization” or “intracytoplasmic sperm injection” or “assisted conception” or “assisted reproduction” or “ART” or “infertility” or “IUI” or “Intrauterine Insemination” or “artificial insemination” or “ovarian hyperstimulation” or “ovarian stimulation” or “ovulation induction”or“COH” or “controlled ovarian ” or “insemination” or “insemination-intrauterine”
AND
Keywords CONTAINS “corifollitropin alfa” or Title CONTAINS “corifollitropin alfa”

Appendix 4. MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE (1948 to present)
Date of search: 10-10-2011
1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (29168)
2 embryo transfer$.tw. (7138)
3 in vitro fertili?ation.tw. (14924)
4 ivf-et.tw. (1669)
5 (ivf or et).tw. (154947)
6 icsi.tw. (4487)
7 intracytoplasmic sperm injection$.tw. (4173)
8 (blastocyst adj2 transfer$).tw. (424)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (47003)
10 assisted reproduct$.tw. (7212)
11 artificial insemination.tw. (4355)
12 iui.tw. (1012)
13 intrauterine insemination$.tw. (1571)
14 ovulation induc$.tw. (3109)
15 ovarian hyperstimulation.tw. (3292)
16 COH.tw. (894)
17 (ovari$ adj2 stimulat$).tw. (4178)
18 superovulat$.tw. (2718)
19 infertil$.tw. (36915)
20 subfertil$.tw. (2981)
21 (ovari$ adj2 induction).tw. (200)
22 or/1-21 (227905)
23 corifollitropin alfa.tw. (22)
24 corifollitropin alpha.tw. (1)
25 org 36286.tw. (4)
26 org36286.tw. (0)
27 FSH carboxy terminal peptide.tw. (2)
28 FSH-CTP.tw. (7)
29 FSH CTP.tw. (7)
30 long acting follitropin.tw. (1)
31 Elonva$.tw. (3)
32 sustained follicle stimulat$.tw. (5)
33 long acting fsh.tw. (13)
34 long acting follicle stimulating hormone.tw. (5)
35 or/23-34 (40)
36 22 and 35 (28)
37 randomized controlled trial.pt. (319965)
38 controlled clinical trial.pt. (83743)
39 randomized.ab. (234955)
40 placebo.tw. (137303)
41 clinical trials as topic.sh. (158838)
42 randomly.ab. (172143)
43 trial.ti. (100880)
44 (crossover or cross-over or cross over).tw. (52403)
45 or/37-44 (783234)
46 exp animals/ not humans.sh. (3701210)
47 45 not 46 (723312)
48 36 and 47 (11)

Appendix 5. EMBASE search strategy

Embase.com (1980 to current)
Date of search: 10-10-2011
1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (42896)
2 embryo$ transfer$.tw. (9711)
3 in vitro fertili?ation.tw. (17136)
4 ivf-et.tw. (2023)
5 icsi.tw. (6900)
6 intracytoplasmic sperm injection$.tw. (5013)
7 (blastocyst adj2 transfer$).tw. (667)
8 (ivf or et).tw. (299448)
9 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (63983)
10 artificial insemination.tw. (4135)
11 intrauterine insemination.tw. (1904)
12 assisted reproduct$.tw. (9674)
13 iui.tw. (1423)
14 ovulation induc$.tw. (3738)
15 (ovari$ adj2 stimulat$).tw. (5358)
16 ovarian hyperstimulation.tw. (4173)
17 COH.tw. (1095)
18 superovulat$.tw. (2637)
19 infertil$.tw. (43284)
20 subfertil$.tw. (3494)
21 (ovari$ adj2 induction).tw. (236)
22 or/1-21 (385118)
23 exp corifollitropin alfa/ (35)
24 corifollitropin alfa.tw. (46)
25 corifollitropin alpha.tw. (5)
26 FSH carboxy terminal peptide.tw. (1)
27 FSH-CTP.tw. (12)
28 FSH CTP.tw. (12)
29 long acting follitropin.tw. (1)
30 Elonva$.tw. (23)
31 sustained follicle stimulat$.tw. (9)
32 long acting fsh.tw. (16)
33 long acting follicle stimulating hormone.tw. (5)
34 org 36286.tw. (16)
35 org36286.tw. (0)
36 or/23-35 (82)
37 Clinical Trial/ (819367)
38 Randomized Controlled Trial/ (290224)
39 exp randomization/ (54690)
40 Single Blind Procedure/ (14260)
41 Double Blind Procedure/ (100996)
42 Crossover Procedure/ (30907)
43 Placebo/ (185441)
44 Randomi?ed controlled trial$.tw. (64940)
45 Rct.tw. (7766)
46 random allocation.tw. (1056)
47 randomly allocated.tw. (15613)
48 allocated randomly.tw. (1708)
49 (allocated adj2 random).tw. (688)

50 Single blind$.tw. (11114)
51 Double blind$.tw. (118240)
52 ((treble or triple) adj blind$).tw. (247)
53 placebo$.tw. (159940)
54 prospective study/ (173744)
55 or/37-54 (1147610)
56 case study/ (13429)
57 case report.tw. (208273)
58 abstract report/ or letter/ (795123)
59 or/56-58 (1012785)
60 55 not 59 (1114252)
61 22 and 36 and 60 (35)
62 (2010$ or 2011$).em. (2228857)
63 61 and 62 (24)

Appendix 6. PsycINFO search strategy

PsycINFO (1980 to current)
Date of search: 10-10-2011
1 exp reproductive technology/ (1093)
2 in vitro fertili?ation.tw. (433)
3 ivf-et.tw. (16)
4 (ivf or et).tw. (78691)
5 icsi.tw. (37)
6 intracytoplasmic sperm injection$.tw. (30)
7 (blastocyst adj2 transfer$).tw. (2)
8 assisted reproduct$.tw. (379)
9 artificial insemination.tw. (202)
10 iui.tw. (17)
11 intrauterine insemination$.tw. (12)
12 ovulation induc$.tw. (13)
13 (ovari$ adj2 stimulat$).tw. (42)
14 superovulat$.tw. (5)
15 ovarian hyperstimulation.tw. (8)
16 COH.tw. (44)
17 infertil$.tw. (2154)
18 subfertil$.tw. (50)
19 (ovari$ adj2 induction).tw. (4)
20 or/1-19 (81563)
21 corifollitropin alfa.tw. (0)
22 corifollitropin alpha.tw. (0)
23 org 36286.tw. (0)
24 org36286.tw. (0)
25 FSH carboxy terminal peptide.tw. (0)
26 FSH-CTP.tw. (0)
27 FSH CTP.tw. (0)
28 long acting follitropin.tw. (0)
29 Elonva$.tw. (0)
30 sustained follicle stimulat$.tw. (0)
31 long acting fsh.tw. (0)
32 long acting follicle stimulating hormone.tw. (0)
33 exp Follicle Stimulating Hormone/ (71)

34 Follicle Stimulating Hormone$.tw. (406)
35 FSH.tw. (329)
36 rFSH.tw. (0)
37 or/21-36 (520)
38 20 and 37 (27)
39 random.tw. (33464)
40 control.tw. (261118)
41 double-blind.tw. (15184)
42 clinical trials/ (5432)
43 placebo/ (2981)
44 exp Treatment/ (495944)
45 or/39-44 (748851)
46 38 and 45 (12)

Appendix 7. CINAHL search strategy

Date of search: 10-10-2011		
#	**Results**	**Query**
S30	24	S17 and S29
S29	1036	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28
S28	0	"ovarial hyperstimulation"
S27	216	"ovarian hyperstimulation"
S26	17	"controlled ovarian stimulation"
S25	103	"COS"
S24	31	"COH"
S23	298	"assisted reproduction"
S22	9	"assisted reproductive technique"
S21	157	"ICSI"
S20	8	"Intracytoplasmatic sperm injection"
S19	20	(MH "Fertilization in Vitro")
S18	328	(MH "Embryo Transfer")
S17	68	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16

(*Continued*)

S16	12	"recombinant FSH"
S15	7	"rFSH"
S14	53	(MH "Follicle-Stimulating Hormone")
S13	0	"long-acting follicle stimulating hormone"
S12	0	"long acting follicle stimulating hormone"
S11	0	"FSH carboxy terminal peptide"
S10	0	"long acting FSH"
S9	0	"long-acting FSH"
S8	0	"FSH-CTP"
S7	0	"FSH CTP"
S6	0	"ORG36386"
S5	0	"ORG 36286"
S4	2	"Corifollitropin"
S3	0	"Elonva"
S2	0	"Corifollitropin alpha"
S1	2	"Corifollitropin alfa"

Appendix 8. ISI Web of Knowledge search strategy

Date of search: 10-10-2011		
Set	**Results**	**Search**
#6	15	#4 AND #3 Refined by: Document Type=(MEETING) *Timespan=All Years*
#5	96	#4 AND #3 *Timespan=All Years*

(*Continued*)

#4	798	#2 AND #1 *Timespan=All Years*
#3	232,390	Topic=(embryo transfer) OR Topic=(in vitro fertilisation) OR Topic=(in vitro fertilization) OR Topic=(ivf) OR Topic=(icsi) OR Topic=(intracytoplasmatic sperm injections) OR Topic=(artificial insemination) OR Topic=(intrauterine insemination) OR Topic=(ovulation induction) OR Topic=(COS) OR Topic=(COH) OR Topic=(hyperstimulation) OR Topic=(assisted reproduction) OR Topic=(assited reproduction technique) *Timespan=All Years*
#2	60,600	Topic=(rFSH) OR Topic=(recombinant FSH) OR Topic=(recombinant follicle stimulating hormone) OR Topic=(FSH) *Timespan=All Years*
#1	674	Topic=(Corifollitropin) OR Topic=(Corifollitropin alfa) OR Topic=(Corifollitropin alpha) OR Topic=(Elonva) OR Topic=(ORG36286) OR Topic=(ORG 36286) OR Topic=(FSH-CTP) OR Topic=(FSH CTP) OR Topic=(long-acting FSH) OR Topic=(long acting FSH) OR Topic=(FSH carboxy terminal peptide) OR Topic=(long acting follicle stimulating hormone) OR Topic=(long-acting follicle stimulating hormone) *Timespan=All Years*

HISTORY

Protocol first published: Issue 1, 2012

Review first published: Issue 6, 2012

CONTRIBUTIONS OF AUTHORS

AWP and CF extracted data. AWP entered data and wrote the review. CF helped to draft the review, acted as a clinical expert and commented on the review. JK acted as a clinical expert and commented on the review.

DECLARATIONS OF INTEREST

No declarations of interest

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