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Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles (Review)

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Journal:

The Cochrane Collaboration 2011

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[Intervention Review]

Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles

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Editorial group: Cochrane Menstrual Disorders and Subfertility Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2011.
Review content assessed as up-to-date: 19 October 2010.

Citation: van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F, Al-Inany HG. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No.: CD005354. DOI: 10.1002/14651858.CD005354.pub2.

ABSTRACT

Background

Several systematic reviews compared recombinant gonadotrophin with urinary gonadotrophins (HMG, purified FSH, highly purified FSH) for ovarian hyperstimulation in IVF and ICSI cycles and these reported conflicting results. Each of these reviews used different inclusion and exclusion criteria for trials. Our aim in producing this review is to bring together all randomised studies in this field under common inclusion criteria with consistent and valid statistical methods.

Objectives

To compare the effectiveness of recombinant gonadotrophin (rFSH) with the three main types of urinary gonadotrophins (i.e. HMG, FSH-P and FSH-HP) for ovarian stimulation in women undergoing IVF or ICSI treatment cycles.

Search methods

An extended search was done according to Cochrane guidelines including the Menstrual Disorders & Subfertility Group's Specialised Register of controlled trials (up to May 2010), The Cochrane Central Register of Controlled Trials (up to May 2010), MEDLINE (1966 to May 2010), EMBASE (1980 to May 2010), CINAHL (1982 to May 2010), National Research Register, and Current Controlled Trials (up to May 2010).

Selection criteria

All randomised controlled trials reporting data comparing clinical outcomes for women undergoing IVF/ICSI cycles and using recombinant FSH in comparison with HMG or highly purified HMG, purified urinary FSH (FSH-P), and highly purified urinary FSH (FSH-HP) for ovarian hyperstimulation in IVF or ICSI cycles were included.

Data collection and analysis

Data selected by three reviewers (MvW, IK, and AV). Data extraction and risk assessment done by four reviewers (MvW, IK, AB and AV). Primary outcome measure was live birth rate and OHSS per randomised woman. Binary outcomes were analysed using odds ratios and also reported in absolute terms. Grouped analyses were carried out for all outcomes to explore whether relative effects differed due to key features of the trials.

Main results

We included 42 trials with a total of 9606 couples. Comparing rFSH to any of the other gonadotrophins irrespective of the down-regulation protocol used, did not result in any evidence of a statistically significant difference in live birth rate (28 trials, 7339 couples, odds ratio 0.97, 95% CI 0.87 to 1.08). This suggests that for a group with a 25% live birth rate using urinary gonadotrophins the rate would be between 22.5% and 26.5% using rFSH. There was also no evidence of a difference in the OHSS rate (32 trials, 7740 couples, OR 1.18, 95% CI 0.86 to 1.61). This means that for a group with 2% risk of OHSS using urinary gonadotrophins, the risk would be between 1.7% and 3.2% using rFSH.

Authors' conclusions

Clinical choice of gonadotrophin should depend on availability, convenience and costs. Further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.

PLAIN LANGUAGE SUMMARY

Recombinant FSH versus urinary gonadotrophins (HMG, purified FSH, highly purified FSH) for ovarian hyperstimulation in IVF and ICSI cycles

Several systematic reviews compared recombinant FSH with urinary gonadotrophins (HMG, purified FSH, highly purified FSH) for ovarian hyperstimulation in IVF and ICSI cycles and these reported conflicting results. We included 42 trials with in total 9606 couples. Comparing rFSH with urinary gonadotrophins overall did not result in any difference in live birth rate, OHSS or any of the other outcomes. Comparing rFSH with HMG/HP-HMG resulted in a significantly lower live birth rate in the rFSH group though differences were small. There was no proof of a difference in live birth when comparing rFSH with FSH-P or with FSH-HP. We may conclude that all these gonadotrophins are equally effective and safe, and that further trials are unwarranted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

rFSH versus urinary gonadotrophins: primary analyses for ovarian stimulation in assisted reproductive technology cycles

Patient or population: patients with ovarian stimulation in assisted reproductive technology cycles
Settings:
Intervention: rFSH versus urinary gonadotrophins: primary analyses

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	RFSH versus urinary gonadotrophins: primary analyses				
Live birth (or ongoing pregnancy) by urinary gonadotrophin	Study population		OR 0.97 (0.87 to 1.08)	7339 (28 studies)	⊕⊕⊕⊕ high	
	245 per 1000	239 per 1000 (220 to 260)				
	Medium risk population					
	237 per 1000	232 per 1000 (213 to 251)				
Live birth (or ongoing pregnancy) by urinary gonadotrophin - rFSH versus HMG/HMG-HP	Study population		OR 0.84 (0.72 to 0.99)	3197 (11 studies)	⊕⊕⊕⊕ high	
	255 per 1000	223 per 1000 (198 to 253)				
	Medium risk population					
	237 per 1000	207 per 1000 (183 to 235)				

Live birth (or ongoing pregnancy) by urinary gonadotrophin - rFSH versus FSH-P	**Study population**		**OR 1.26** (0.96 to 1.64)	1430 (5 studies)	⊕⊕⊕⊕ **high**
	170 per 1000	**205 per 1000** (164 to 251)			
	Medium risk population				
	154 per 1000	**187 per 1000** (149 to 230)			
Live birth (or ongoing pregnancy) by urinary gonadotrophin - rFSH versus FSH-HP	**Study population**		**OR 1.03** (0.86 to 1.22)	2712 (13 studies)	⊕⊕⊕⊕ **high**
	267 per 1000	**273 per 1000** (239 to 308)			
	Medium risk population				
	267 per 1000	**273 per 1000** (239 to 308)			
OHSS by urinary gonadotrophin	**Study population**		**OR 1.18** (0.86 to 1.61)	7740 (32 studies)	⊕⊕⊕⊕ **high**
	19 per 1000	**22 per 1000** (16 to 30)			
	Medium risk population				
	17 per 1000	**20 per 1000** (15 to 27)			

*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.

BACKGROUND

Description of the condition

The first phase of vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI) consists of ovarian hyperstimulation to produce multiple follicles for follicle aspiration. The strategy of stimulating the ovaries with gonadotrophins is well established. This review addresses the use of gonadotrophins for ovarian induction in IVF and ICSI cycles. Couples that have an indication for IVF or ICSI after ovarian stimulation with gonadotropins are couples that have a low chance to conceive naturally. The most prevalent indications for IVF or ICSI are a tubal factor, a male factor and or unexplained subfertility.

Description of the intervention

The first generation of gonadotrophins, used in the 1970's, was human menopausal gonadotrophin, produced from the urine of menopausal women (HMG, a combination of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in a 1:1 ratio). Since the 1980's, a variety of urinary gonadotrophins have been produced, such as purified FSH (FSH-P) which contains less than one international unit (IU) of LH per 75 IU of FSH. The third generation of urinary gonadotrophins was highly purified FSH (FSH-HP) with less than 0.1 IU of LH per 75 IU of FSH. An early systematic review (Daya 1995) reported a higher clinical pregnancy rate per cycle with FSH-P and FSH-HP when compared with HMG, but a later review (Agrawal 2000) reported no difference between these urinary gonadotrophin products.

The fourth generation of gonadotrophins was produced using recombinant DNA technology (recombinant FSH, rFSH), which is free from LH activity. The production of rFSH is independent of urine collection, thus guaranteeing a high availability of a bio chemically pure FSH preparation that is free from urinary protein contaminants. The production process also yields FSH with minimal batch-to-batch discrepancy (Bergh 1999) and low immunogenicity which allows subcutaneous administration.

How the intervention might work

In the follicular phase of a normal menstrual cycle a cohort of 10 to 20 ovarian antral follicles develops. Of this cohort only one follicle obtains dominance over the others and shows continued growth until ovulation takes place. The aim in standard IVF or ICSI is to achieve the maturation of a much larger part of the ovarian antral follicle cohort. This is accomplished by ovarian stimulation with FSH containing gonadotrophins.

Why it is important to do this review

Several systematic reviews and one international Health Technology Assessment report compared rFSH with urinary gonadotrophins (HMG, FSH-P, FSH-HP) Daya 1998; Larizgoitia 2000;Daya 2002;Van Wely 2003;NCC-WCH 2004;Al-Inany 2003; Al-Inany 2008;Coomarisamy 2008).

These reviews addressed several comparisons. Two reviews compared rFSH to urinary FSH and found higher pregnancy rates per cycle started for rFSH (Daya 2002, updated from Daya 1998).

Three reviews compared rFSH versus urinary gonadotrophins (HMG, FSH-P, FSH-HP together) and found no evidence of a difference between these two groups (Larizgoitia 2000;Al-Inany 2003;NCC-WCH 2004).

Three reviews compared rFSH with HMG and reported evidence of a difference in live birth and clinical pregnancy rate per cycle between rFSH and HMG (Van Wely 2002;Al-Inany 2008;Coomarisamy 2008).

Apart from the different comparisons, three aspects in particular deserve attention.

Firstly, gonadotrophin-releasing hormone (GnRH) agonists and GnRH antagonist are often used in conjunction with gonadotrophins to facilitate cycle control and achieve pituitary down-regulation in ovarian stimulation during assisted reproductive treatment cycles. There is evidence of effectiveness in increased clinical pregnancy rate with the use of GnRHa when compared with no GnRHa in ovarian stimulation for IVF (Hughes 1992). Long pituitary-down GnRHa protocols were found to increase clinical pregnancy rates when compared with short or ultrashort GnRHa protocols (Daya 1998). Nowadays, GnRH antagonists are also often used for down-regulation.

Secondly many trials have been performed by pharmaceutical companies and the conflict of interest may have introduced bias.

Thirdly, it is now customary to freeze supernumerary embryos and to transfer frozen/thawed embryos if transfer of fresh embryos has failed. Hence, we will include all studies which involved fresh or frozen cycles embryo transfer, then explore any influence different settings have on the treatment differences.

The systematic reviews mentioned above reported conflicting results. Each of these reviews used different inclusion and exclusion criteria for trials (Daya 1995; Agrawal 2000; Daya 2002; Al-Inany 2003; Larizgoitia 2000;Van Wely 2003;NCC-WCH 2004;Al-Inany 2008; Coomarisamy 2008). Some based their conclusion on rates per cycle that had been invalidly analysed as if each woman contributed a single cycle. Legitimate but different choices of meta-analytic model (fixed or random effects, odds ratio or risk ratio) complicate comparison further. Our aim in producing this review is to bring together all randomised studies in this field under common inclusion criteria with consistent and valid statistical methods.

OBJECTIVES

To compare the effectiveness of recombinant gonadotrophin (rFSH) with the three main types of urinary gonadotrophins (i.e. HMG, FSH-P and FSH-HP) for ovarian stimulation in women undergoing IVF or ICSI treatment cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials only. Quasi-randomised controlled trials, in which allocation was, for example, by alternation or reference to case record number or to dates of birth, were excluded. Crossover trials were excluded since the design was not appropriate in this context (Vail 2003).
Trials in which fresh and frozen embryos are transferred were included.

Types of participants

Normogonadotrophic (defined as having normal serum concentration of FSH and LH) women undergoing fresh and/or frozen-thawed IVF or ICSI treatment cycles.

Types of interventions

Ovarian stimulation with recombinant gonadotrophin (rFSH) versus HMG, FSH-P or FSH-HP, with or without the use of a GnRH down-regulation protocol in women undergoing IVF and ICSI cycles.

Types of outcome measures

Primary outcomes

Effectiveness:
One or more live birth(s) per woman or, if not reported, one or more pregnancy ongoing beyond 20 weeks per woman
Adverse:
Rate of ovarian hyperstimulation syndrome per woman

Secondary outcomes

Effectiveness:
Cumulative live birth/ongoing pregnancy per woman including the result of frozen-thawed embryo transfers
Clinical pregnancy rate per woman (as confirmed by the presence of foetal heart rate)
Patient acceptability/satisfaction
Number of oocytes produced per cycle

Adverse:
Multiple pregnancy rate per woman and per pregnancy
Miscarriage rate per woman
Process outcomes:
Amount of gonadotrophins used per woman per cycle (total dose in IU [international units])
Duration of ovarian stimulation per woman per cycle

Search methods for identification of studies

We searched the Menstrual Disorders & Subfertility Group's Specialised Register of controlled trials (until May 2010), The Cochrane Central Register of Controlled Trials (CENTRAL) on the latest issue of the Cochrane Library (until May 2010), MEDLINE (1966 to May 2010), EMBASE (1980 to May 2010), CINAHL (1982 to May 2010), National Research Register, and web-based trials databases such as Current Controlled Trials. There was no language restriction. Additionally all references in the published reviews, identified trials and background papers were checked and authors were contacted if necessary. The search strategy was developed by Marian Showell, the trial search coordinator of the Cochrane Menstrual Disorders & Subfertility Group (MDSG). The search strategy is shown in Appendix 1. Furthermore, trial registries were searched for additional (ongoing) trials. We also contacted pharmaceutical companies for any published, unpublished or ongoing studies not identified with our search strategy.

Data collection and analysis

Selection of studies

Three reviewers (MvW, IK, and AV) independently examined the electronic search results for reports of possibly relevant trials and these reports were retrieved in full. All reviewers applied the selection criteria independently to the trial reports, rechecking trial eligibility and resolving disagreements by discussion with the other reviewers (HI, AB, FV and JT).

Data extraction and management

Four reviewers (MvW, IK, AB and AV) independently extracted the outcomes data and information on funding, location, clinical and design details and participants. Any differences were resolved by discussion among reviewers. Details of the studies were entered into the Table of Included Studies. Studies that appeared to meet

the inclusion criteria but were excluded from the review are presented in the Table of Excluded Studies, briefly stating the reason for exclusion but giving no further information.

Assessment of risk of bias in included studies

Four reviewers (MvW, IK, AB and AV) extracted information regarding the risk of bias (threats to internal validity) under six domains (also see :Table 1).

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

Missing details were sought from the authors. All details are presented in the Risk of bias table following each included study. Any differences were resolved by discussion.

Measures of treatment effect

All binary outcomes were summarised using the odds ratio (OR) with 95% confidence intervals (CI).

Ordinal scales used in patient acceptability, amount of gonadotrophin used and duration of ovarian stimulation were treated as continuous outcomes. Means and standard deviations were abstracted, calculated or requested.

Unit of analysis issues

All outcomes were expressed per woman randomised. Where only data 'per cycle' were available, and participants had contributed multiple cycles, data were omitted from meta-analysis.

The secondary outcome multiple pregnancy, was also expressed per clinical pregnancy.

Dealing with missing data

Where there was insufficient information in the published report, we attempted to contact the authors for clarification. If missing data became available, they were included in the analysis. It was anticipated that trials conducted over 10 years ago might not have data on live birth rates of the study participants. Data extracted from the trials were analysed on an intention to treat basis. Where randomised cases were missing from outcome assessment, we first contacted the authors for additional data. If further data were not available, we assumed that missing participants had failed to achieve pregnancy and had not suffered reported adverse events.

Assessment of heterogeneity

Presence of statistical heterogeneity of treatment effect among trials was determined using the I^2 statistic. We adopted the following broad interpretation: 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 present (Higgins 2008).

Assessment of reporting biases

We assessed the methods section for relevant determined outcomes. When data was measured but not reported in the paper this was considered internal reporting bias.

To evaluate external reporting bias funnel plots for primary outcomes and for clinical pregnancy rate are presented. When there was evidence of small-study effects, publication bias was considered as only one of a number of possible explanations. We also informally compared results for clinical pregnancy rates between those reporting ongoing pregnancy or live birth and those that did not.

Data synthesis

Review Manager software was used to perform the meta-analyses using a fixed effect model. For binary outcomes, we used the Peto approach. For reporting purposes, primary outcomes were translated to absolute risks. Results for continuous outcomes were combined using mean difference. If studies had reported acceptability scores using different scales, the standardised mean difference would have been used.

Prospectively it was planned to undertake four different stratifications of the primary outcomes:

- different urinary gonadotrophins (HMG, FSH-P and FSH-HP)
- different GnRH protocols (antagonist, long GnRHa, short/ultrashort GnRHa protocol, and no GnRHa)
- use of fresh or frozen-thawed embryos
- different sponsors (commercial, non-commercial)(Lexchin 2003)

Subgroup analysis and investigation of heterogeneity

If excessive heterogeneity existed within strata it would have been explored informally, using the clinical and design details recorded in the Table of included studies. Heterogeneity between strata was anticipated, and possible reasons discussed.

Sensitivity analysis

We assessed the influence of excluding data from reports that pooled multiple cycles per woman.
We assessed the influence of risk of bias on effect size by removing trials deemed to be at high risk.
Analyses were repeated using a random effects model to explore whether different conclusions would be reached.
All sensitivity analyses were reported for live birth, OHSS and clinical pregnancy only.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.
For details on the studies please see: Characteristics of included studies;Characteristics of excluded studies, Characteristics of studies awaiting classification.

Results of the search

The search strings identified a total of 121 references, handsearching identified another 11 papers. Most references identified by the search were excluded at the first screening step as they were clearly irrelevant. The most frequent reasons for exclusion at this level were: article was a review or a commentary or case study; the treatment was not IVF or ICSI, or study was clearly a non-randomised design.
A total 53 studies, 40 full-text papers and 13 abstracts from congress proceedings, were then formally assessed.

Included studies

Fourty-two trials described in 43 publications (including 8 abstracts from congress proceedings) met all selection criteria and were included in the review. The total number of study participants was 9606 and the total number of cycles was 9644.
PATIENTS
The studies included in this review used different inclusion criteria such that the individual studies differ in indication for treatment, female age and number of previous cycles. Detail can be found in the Characteristics of included studies table.
INTERVENTIONS
Twelve of the 42 included trials compared rFSH with HMG or HP-HMG (n=3775). The size of these trials varied from 40 to 721. In these 12 trials the following down regulation protocols were used: antagonist by one trial (Bosch 2008), long GnRH agonist by eight trials (Andersen 2006;Balasch 2003; EISG 2002; Gordon 2001; Hompes 2008; Kilani 2003;Ng 2001;Westergaard 2001), short GnRH agonist by two trials (Rashidi 2005; Strehler 2001) and no down regulation by one trial (Jansen 1998).
Seven of the 42 included trials compared rFSH with FSH-P (n= 1560). The size of these trials varied from 40 to 721. In these 7 trials the following down regulation protocols were used: long GnRH agonist by six trials (Alvino 1995;Drakakis 2002;Gordon 2001;Hedon 1995; Out 1995; RHFSHG 1995), and no down regulation by one trial (Meden-Vrtovec 2003).
Twenty-two of the 42 included trials compared rFSH with FSH-HP (n=4147). In these 23 trials the following down regulation protocols were used: long GnRH agonist by 18 trials (Abate 2009; Antoine 2007; Baker 2009; Berger 1999; Bergh 1997; Dickey 2002; Dickey 2003; Franco 2000; Frydman 2000; Gallego 2003a; Ghosh 1999; Hoomans 1999;Lenton 2000; Mohamed 2006;Nardo 2000 Schats 2000; Selman 2002; O´ Dea 1993), short GnRH agonist by two trials (Cheon 2004; Hugues 2001) and no down regulation by three trials (Ferraretti 1999; Germond 2000; Machado 1999).
One study compared HMG, FSH-P, FSH-HP and rFSH in 124 women (137 cycles) (Kornilov 1999). In this study a long GnRH agonist was used for down-regulation.
The studies included in this review varied in initial gonadotrophin dose given, primary outcome measurements and methodological quality.
Three trials studied the results of transfer of frozen-thawed embryos in addition to transfer of fresh embryos (Out 1995; Hompes 2008; Andersen 2006). In one trial, the frozen cycles resulted in an additional 22 ongoing pregnancies in the rFSH group and seven ongoing pregnancies in the FSH-P group (Out 1995). In the FIRM trial there were an extra four deliveries in the rFSH group and an extra five deliveries in the HP-HMG group following frozen-thawed cycles (Hompes 2008). The cryo-cycle results of the Merit trial (Andersen 2006) could be extracted from another publication on that trial (Ziebe 2007).
Another heterogeneity between the trials was the used fertilisation method, in 20 of the 42 trials only IVF was done, in six of the trials only ICSI was done and in 16 trials both IVF and ICSI cycles were done.
OUTCOMES
Of the included trials we were able to retrieve intention to treat data from 28 trials on live birth, 31 trials had data on OHSS and from 41 trials full data on clinical pregnancy was available.

Excluded studies

Eleven studies were excluded from the analysis. Seven studies did not meet the selection criteria (see Characteristics of excluded studies). Three studies were not truly randomised (Duijkers 1997;Manassiev 1997;Serhal 2000). One study compared two down regulation protocols besides rFSH and HMG (GnRH agonist plus HMG versus GnRH antagonist plus rFSH) in oocyte donors (Martinez 2008). One study was a duplicate of Dickey 2003a study (Dickey 2003b). One study compared rFSH with a

combination of uFSH and rFSH (Pacchiarotti 2007). One study compared rFSH plus HMG versus FSH-HP plus HMG (Raga 1999).

Five studies are awaiting classification. For two studies we were not able to obtain the abstract (Kahn 1999; Strowitzki 2007). For one study the abstract contained no usable data and author nor sponsor were able to provide more data (Olivennes F 1999). The other two studies are probably double publications (Chakravarty 2000; Righini 1998)

Risk of bias in included studies

The risk of bias per included trial was judged in the table Characteristics of included studies. Also see Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

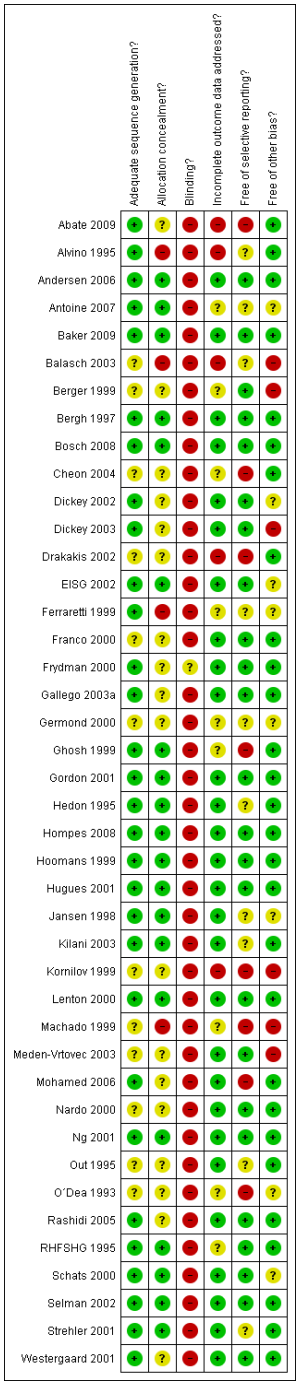
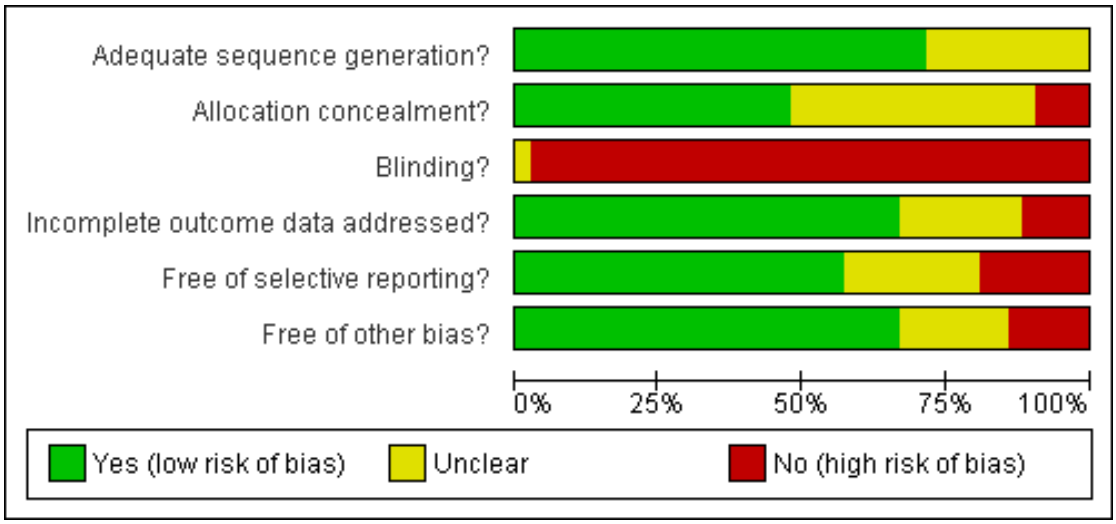


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



We received additional data on randomisation, concealment of allocation, blinding, sponsoring and/or data relevant for effect size calculation from the authors of 24 studies (Abate 2009; Antoine 2007; Baker 2009; Balasch 2003; Bergh 1997; Bosch 2008; Cheon 2004; Dickey 2002; Dickey 2003; EISG 2002; Ferraretti 1999; Gordon 2001; Hompes 2008; Hoomans 1999; Jansen 1998; Kilani 2003; Meden-Vrtovec 2003; Mohamed 2006; Ng 2001;Out 1995;Schats 2000; Selman 2002; Strehler 2001; Westergaard 2001). In 7 trials, additional information was not needed (Alvino 1995; Andersen 2006; Franco 2000; Frydman 2000; Hedon 1995;Hugues 2001; Lenton 2000 , and for 11 trials we tried but failed to contact study authors (Berger 1999;Kornilov 1999; Drakakis 2002; Gallego 2003a; Ghosh 1999; O´ Dea 1993; Germond 2000; Machado 1999 Nardo 2000; Rashidi 2005; RHFSHG 1995).

Allocation

All 42 included studies were randomised controlled trials but for five studies the method of randomisation remained unclear (O´ Dea 1993;Berger 1999;Kornilov 1999;Nardo 2000;Drakakis 2002;Cheon 2004). Allocation to the intervention or control group was adequately concealed in 28 of 42 trials (Andersen 2006; Antoine 2007; Baker 2009 Bergh 1997; Bosch 2008; Dickey 2002; Dickey 2003;EISG 2002; Frydman 2000; Germond 2000; Ghosh 1999; Gordon 2001; Hedon 1995;Hompes 2008;Hoomans 1999; Hugues 2001; Jansen 1998; Kilani 2003; Lenton 2000; Meden-Vrtovec 2003; Mohamed 2006;Ng 2001; RHFSHG 1995; Schats 2000; Selman 2002; Strehler 2001; Westergaard 2001). The allocation concealment was qualified as inadequate in six trials (Alvino 1995; Balasch 2003; Franco 2000; Ferraretti 1999; Machado 1999;Kornilov 1999) and unclear in eight trials (Abate 2009; Berger 1999; Cheon 2004; Drakakis 2002; Gallego 2003a; Nardo 2000; O´ Dea 1993 Rashidi 2005). Also see Figure 1.

Blinding

Partially blinded outcome assessment was reported in 13 of the 42 RCTs. However, we considered only double blinded trials to be adequately blinded. Therefore none of the included trials had adequate blinding.

Incomplete outcome data

For the pregnancy outcomes, data were presented according to intention to treat (ITT) or otherwise the ITT data could usually be retraced from extra information on the respective trials. For abstracts however, it was not always known whether data were ITT or not. The data from the following RCTs may not be presented according to ITT (Berger 1999, Gallego 2003a, Ghosh 1999, Machado 1999, Kornilov 1999;O´ Dea 1993). Therefore

sensitivity analyses were performed excluding these trials. Pregnancy data from one of the trials that was planned to be included in the primary analysis only could not be extracted as data were presented as a percentage per embryo transfer only and absolute pregnancy numbers could not be retrieved (Kornilov 1999).

In three trials some women underwent multiple cycles: 165 cycles in 148 couples (Berger 1999), 79 cycles in 71 women (Machado 1999), 137 cycles in 124 women (Kornilov 1999) and 241 women undergoing 254 cycles (Cheon 2004). In all other trials only one fresh IVF or ICSI cycle was offered to each couple randomised into the trial. The results of these four trials with multiple cycles were presented per cycle and not per woman randomised. Therefore sensitivity analyses were performed excluding these trials.

The sensitivity analyses were done for the outcomes live birth, OHSS and clinical pregnancy and are presented for the general outcome and grouped according to the types of urinary gonadotrophins, type of down-regulation, use of fresh/frozen protocol and sponsor.

Oocytes were usually presented per woman with oocytes or per oocyte pick-up. The number of oocytes per couple randomised could therefore not be determined. As the pooled result would be biased we did not pool the data, hence results are presented per study only. In theory this practice of not including failures in the outcome can produce massive bias, for instance in the case that one protocol would result in more cancellations. We can therefore not exclude that even the per trial results are biased.

Amount of gonadotrophin used and duration of ovarian stimulation was usually presented only for those couples that actually received gonadotrophins thus not including cancelled cycles. As the pooled result would be biased we did not pool the data, hence results are presented per study only. Amount of gonadotrophin used and duration of ovarian stimulation had more problems. Several older trials compared different starting doses of rFSH and urinary FSH, generally lower rFSH starting doses were used. Furthermore in some trials fixed dosages were used. This will have impact on the outcome amount of gonadotrophin used and duration of treatment. Thus besides the bias due to not presenting the results per woman randomised, a difference in these outcomes may also be due to the trial design. With these outcomes even the results per trial may well present biased outcomes.

Due to these serious problems with oocytes retrieved, amount of gonadotrophins used and duration of ovarian stimulation we have removed these outcomes from the analyses table. The data can be found under additional tables (Table 2, Table 3; Table 4) for oocytes retrieved, amount of gonadotrophins used and duration of ovarian stimulation respectively.

Preference of patients for rFSH or urinary gonadotrophins was a planned secondary outcome. However, there were no RCTs that compared the preference of the patients.

Selective reporting

Selective reporting can never be completely excluded, but funnel plots for live birth rate (Figure 3), OHSS (Figure 4) and clinical pregnancy (Figure 5) did not suggest presence of selective reporting.

Figure 3. Funnel plot of comparison: 1 rFSH versus urinary gonadotrophins, outcome: 1.1 Live birth (or pregnancy ongoing beyond 20 weeks).

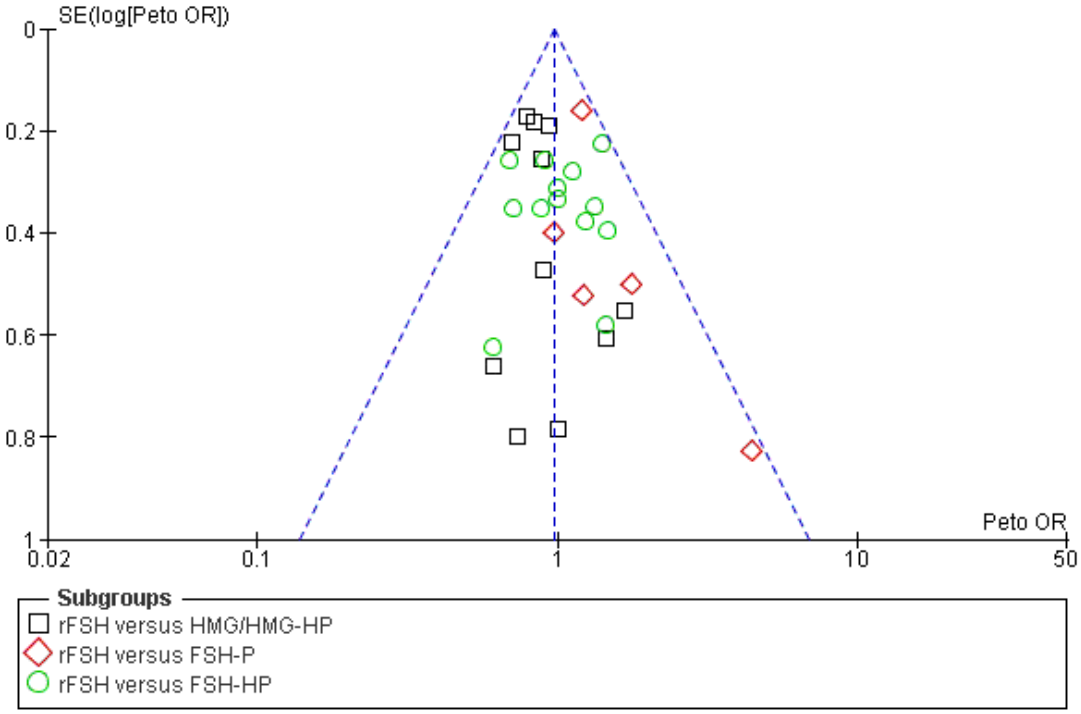


Figure 4. Funnel plot of comparison: 1 rFSH versus urinary gonadotrophins, outcome: 1.5 Ovarian Hyperstimulation Syndrome (OHSS).

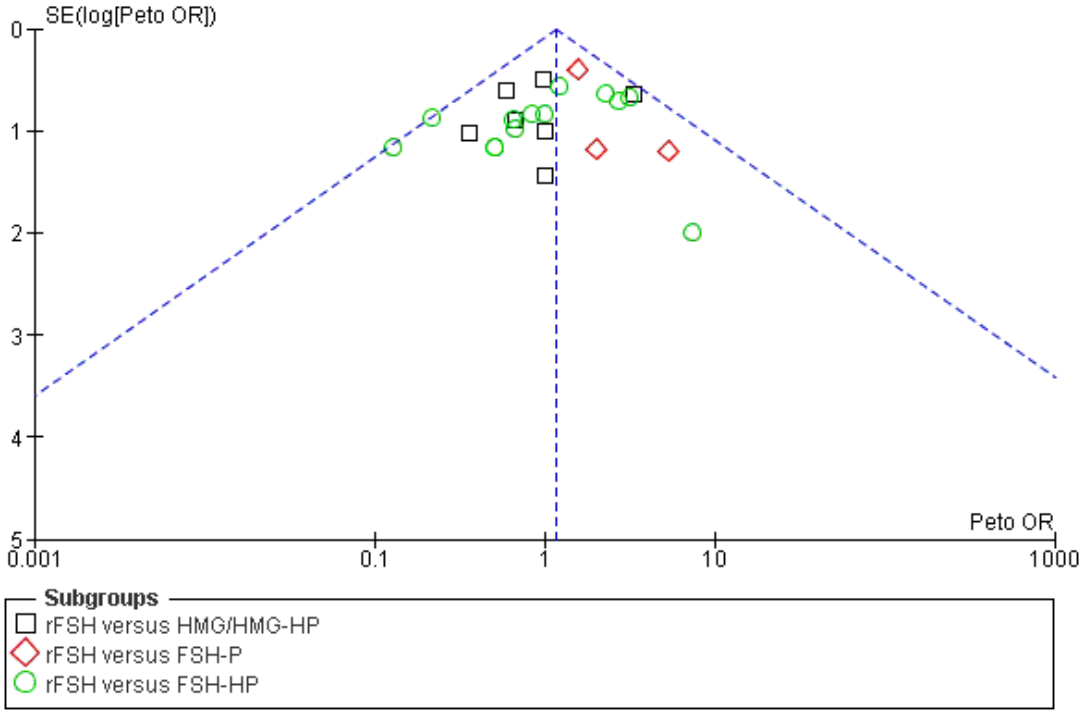
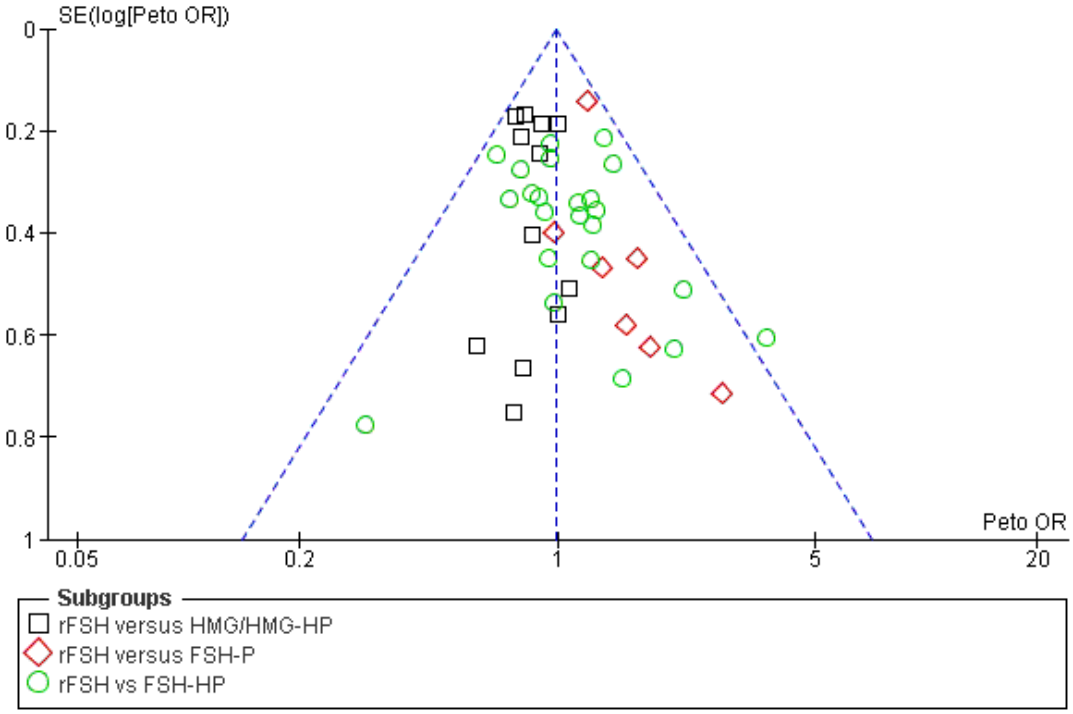


Figure 5. Funnel plot of comparison: 1 rFSH versus urinary gonadotrophins, outcome: 1.9 Clinical pregnancy.



Other potential sources of bias

Of the 42 studies 22 were industry sponsored. This is an important issue since there could be a conflict of interest. Ten studies were sponsored by Serono (Alvino 1995, Bergh 1997, Franco 2000, Frydman 2000, Hedon 1995, Lenton 2000, Machado 1999, Schats 2000, O´ Dea 1993; RHFSHG 1995

Three RCTs were sponsored by Organon (Hoomans 1999, Jansen 1998, Out 1995)

Seven RCTs were sponsored by Ferring (Kornilov 1999, Andersen 2006, Dickey 2002, Dickey 2003, EISG 2002, Hompes 2008, Westergaard 2001)

Two RCTs were sponsored by IBSA (Antoine 2007, Baker 2009).

For six RCTs the funding was unclear: (Berger 1999, Drakakis 2002, Gallego 2003a, Germond 2000, Ghosh 1999, Nardo 2000)

A further 14 trials reported having no funding or governmental funding (Abate 2009, Balasch 2003, Bosch 2008,Cheon 2004, Ferraretti 1999, Gordon 2001, Hugues 2001,Kilani 2003, Meden-Vrtovec 2003,Mohamed 2006, Ng 2001, Rashidi 2005, Selman 2002, Strehler 2001).

Miscarriages were in some studies presented per biochemical pregnancy (very early miscarriages), in some per clinical pregnancy and in others per ongoing pregnancy (late miscarriages). Similarly multiple pregnancy data was mostly presented for clinical multiple pregnancies and sometimes only for ongoing multiple pregnancies.

Effects of interventions

See: **Summary of findings for the main comparison** rFSH versus urinary gonadotrophins: primary analyses for ovarian stimulation in assisted reproductive technology cycles

Primary analysis for rFSH versus urinary gonadotrophins

Data are presented in "Data and analyses" under "1 rFSH versus urinary gonadotrophins". The outcomes live birth, OHSS and clinical pregnancy data are presented by grouping according to types of urinary gonadotrophins, type of down-regulation, fresh/frozen policy, and pharmaceutical sponsor. Also see the Summary of findings table 1.

Primary outcomes

Primary efficacy outcome: Live birth

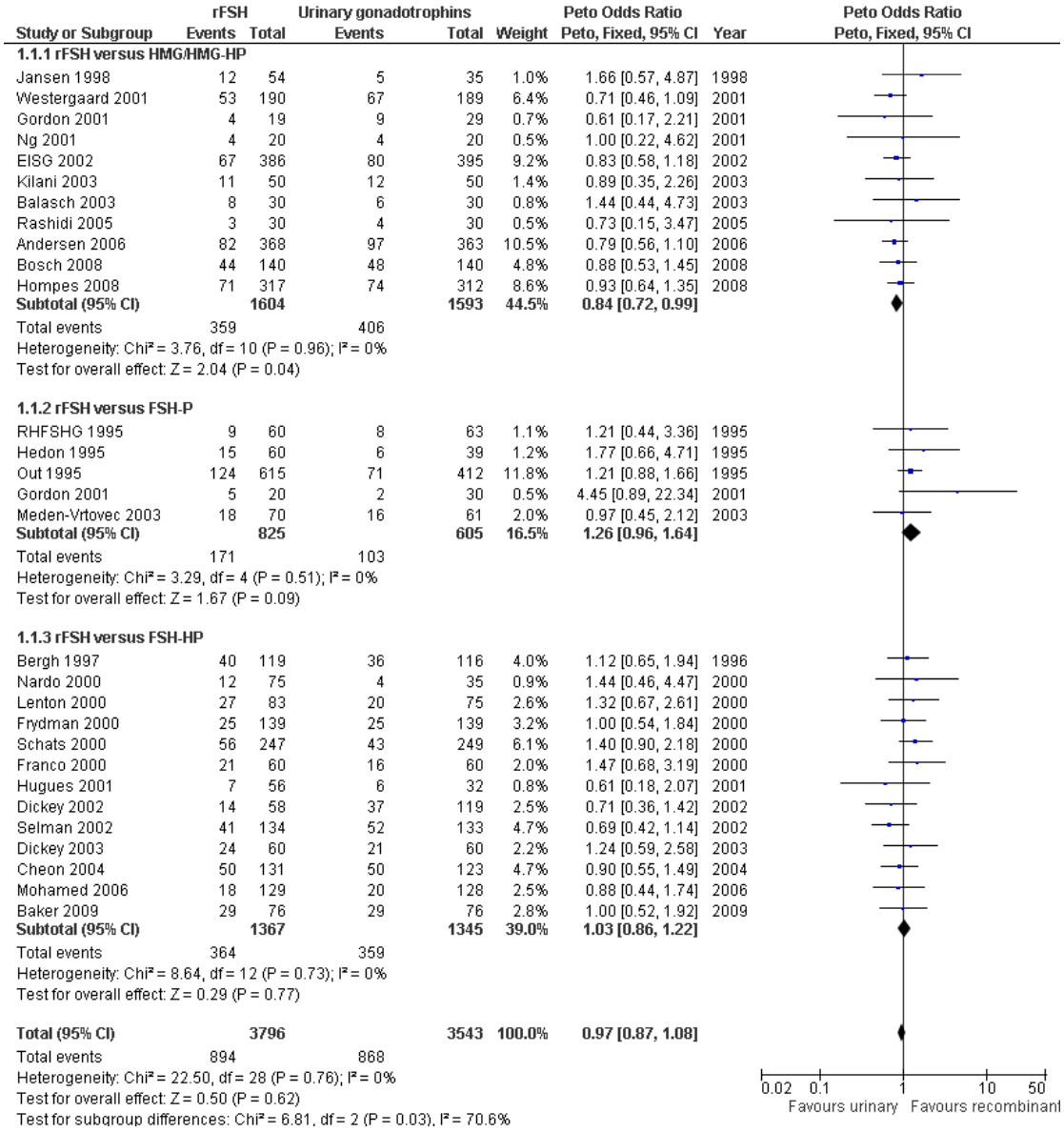
There was no evidence of a statistically significant difference in the primary outcome live births or pregnancies ongoing beyond 20 weeks (28 trials, N=7339; Analysis 1.1; OR 0.97, 95% CI 0.87 to 1.08) for rFSH versus urinary gonadotrophins. This means that of 25% live births using urinary gonadotrophins, use of rFSH instead would be expected to result in a live birth rate between 22.5% and 26.5%. There was no indication of statistical heterogeneity. Visual inspection of the forest plot showed that the OR and 95%CI of the individual trials overlapped and the I^2 was 0%.

1.1 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by the different urinary gonadotrophins

See Analysis 1.1.

Of the 28 trials with data on live births 11 trials compared rFSH versus HMG/HP-HMG, 5 trials compared rFSH with FSH-P and 13 trials compared rFSH with FSH-HP (for the corresponding forest plot see Figure 6 .

Figure 6. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.1 Live birth (or ongoing pregnancy) by urinary gonadotrophin.



There were significantly fewer live births after rFSH as compared to HMG (OR 0.84, 95% CI 0.72 to 0.99; 11 trials, N=3197; Analysis 1.1). This means that for a live birth rate of 25%, use of rFSH instead would be expected to result in a live birth rate between 19% and 25%. There was no indication of statistical heterogeneity. Visual inspection of the forest plot showed that the OR and 95%CI of the individual trials largely overlapped and the I^2 was 0%. Pooling using a random effects model resulted in the same OR.

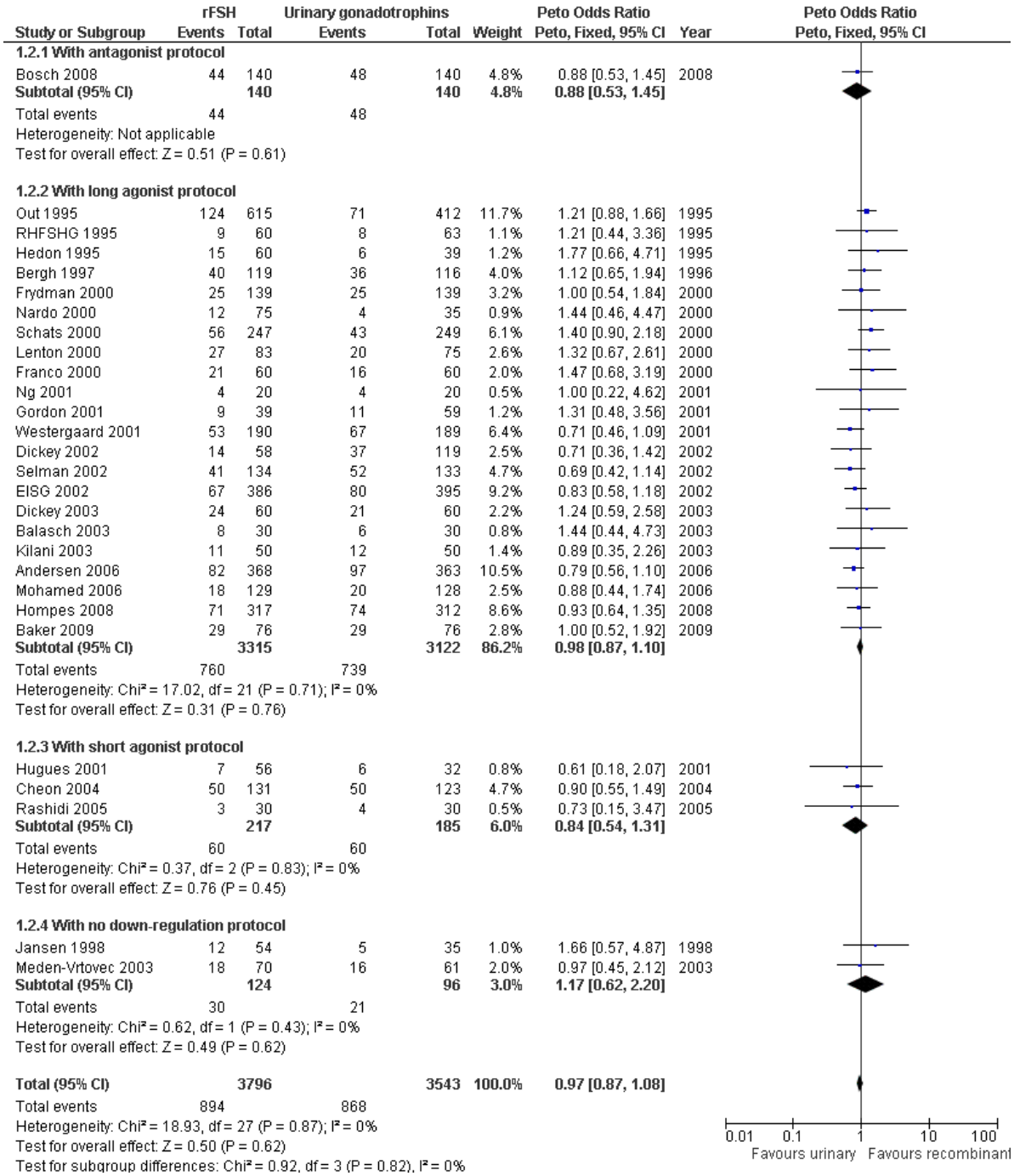
There was no evidence of a statistically significant difference in live birth between rFSH and FSH-P (5 trials, N=1430; Analysis 1.1. OR 1.26, 95% CI 0.96 to 1.64; I^2 of 0%;) and between rFSH and FSH-HP (13 trials, N=2712; Analysis 1.1. OR 1.03, 95% CI 0.86 to 1.22; I^2 of 0%).

1.2 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by down regulation protocol

See Analysis 1.2

Of the 28 trials with data on live births 1 trial used an antagonist protocol, 22 trials used a long GnRH agonist protocol, three used a short GnRH agonist protocol, and two did not use down-regulation (for the corresponding forest plot see Figure 7).

Figure 7. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.2 Live birth (or ongoing pregnancy) by down regulation protocol.



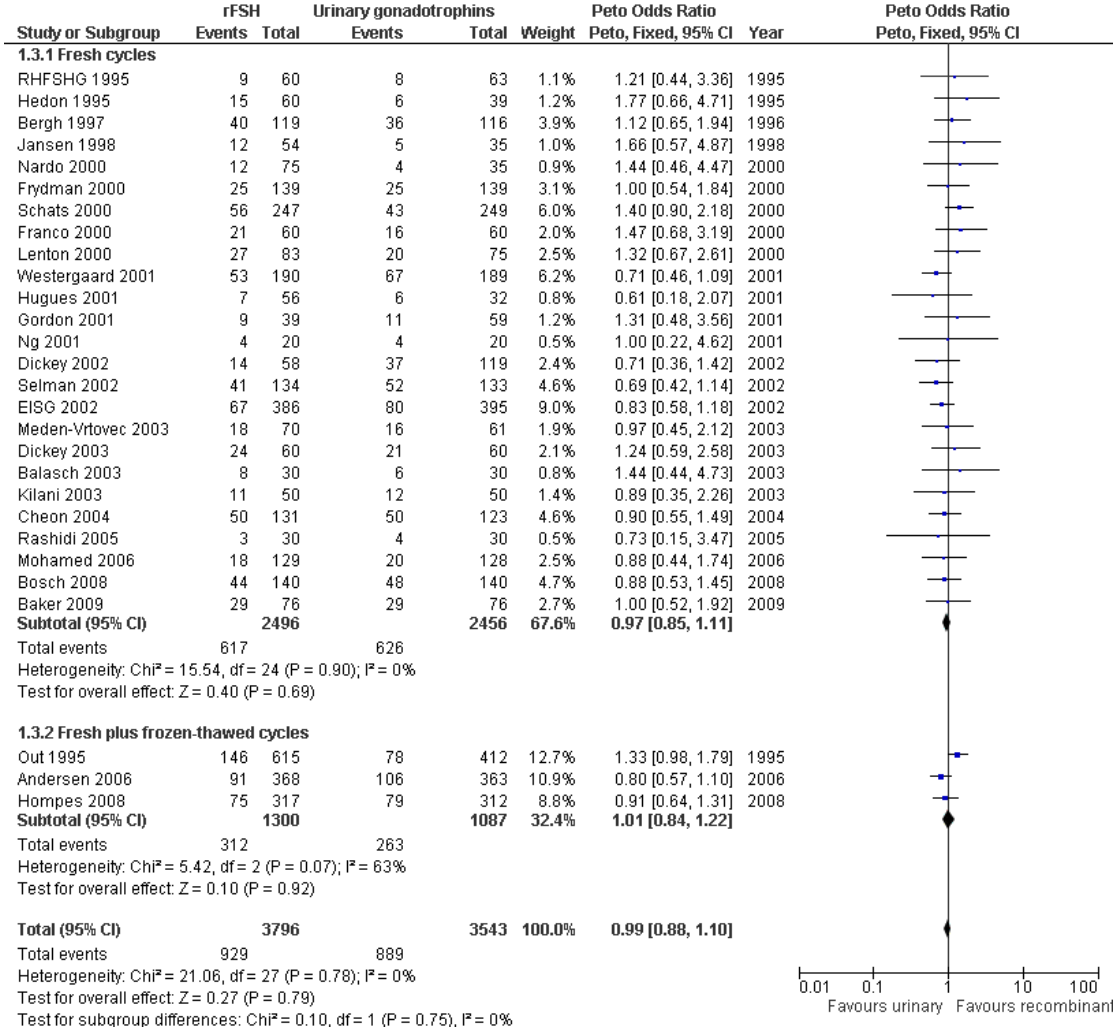
There was no evidence of a statistically significant difference in live birth between rFSH and urinary gonadotrophins for any of the down regulation protocols (antagonist protocol, 1 trial, N= 280; Analysis 1.2; OR 0.88, 95% CI 0.53 to 1.45), (long GnRHa protocol, 22 trials, N=6437; OR 0.98, 95% CI 0.87 to 1.10; Analysis 1.2), (short GnRHa protocol,3 trials, N=402; Analysis 1.2; OR 0.84, 95% CI 0.54 to 1.31), (no down regulation, 2 trials, N=220; Analysis 1.2; OR 1.17, 95% CI 0.62 to 2.20). There was no indication of statistical heterogeneity (I^2 of 0%).

1.3 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by fresh/frozen policy

See Analysis 1.3

Of the 28 trials with data on live births the outcome of frozen-thawed cycles was known for only three trials (for the corresponding forest plot see Figure 8). There was no evidence of a statistically significant difference between rFSH and urinary gonadotrophins for live births after fresh cycles (25 trials, N=4952; Analysis 1.3; OR 0.97, 95% CI 0.85 to 1.11) and for cumulative live birth rate after fresh and frozen-thawed cycles (3 trials, N=2387; Analysis 1.3; OR 1.01, 95% CI 0.84 to 1.22). There was no indication of statistical heterogeneity (I^2 of 0%).

Figure 8. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.3 Live birth (or ongoing pregnancy) by fresh/frozen policy.

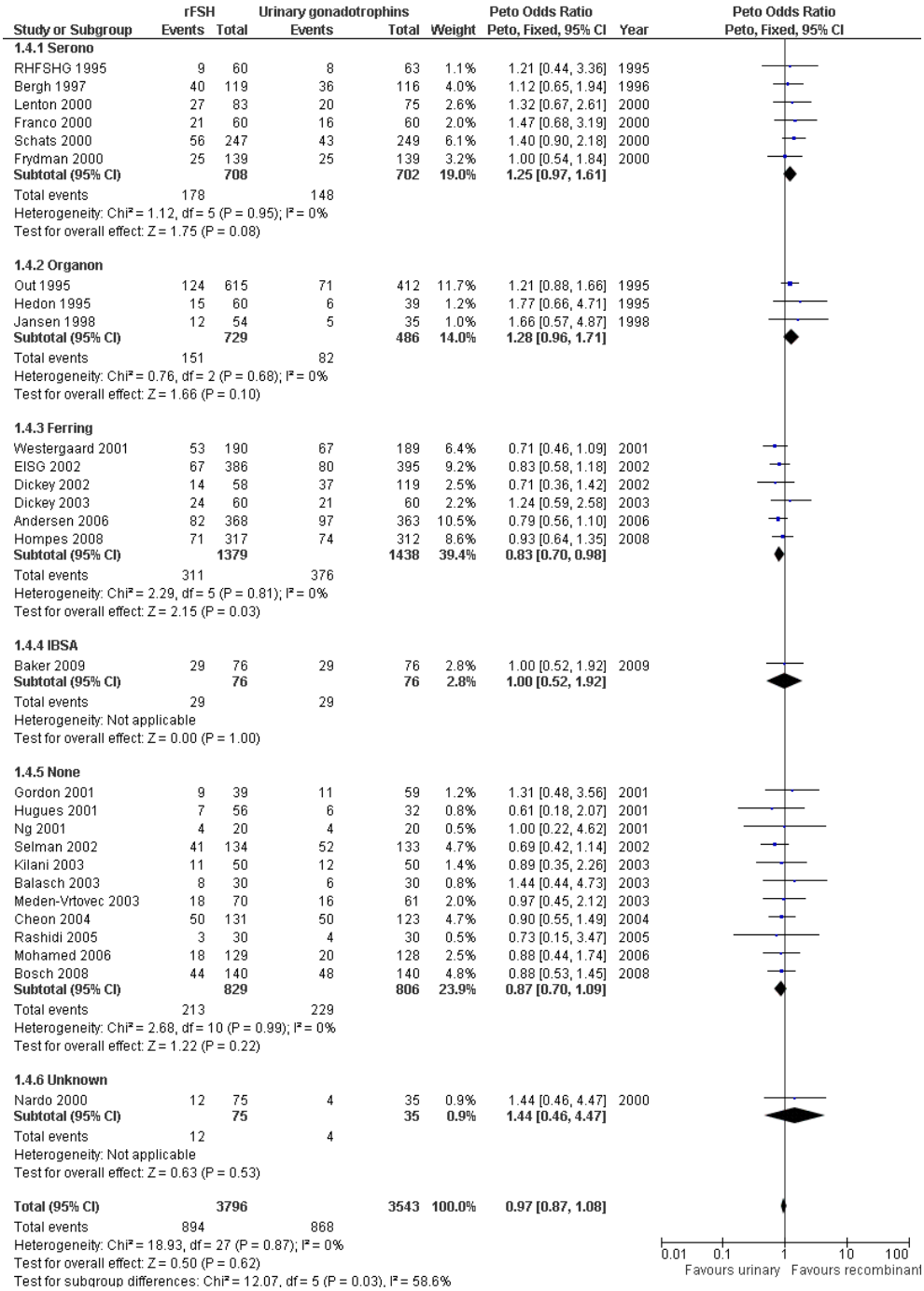


1.4 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by pharmaceutical sponsor

See Analysis 1.4

Of the 28 trials with data on live births six trials were sponsored by Serono, three trials were sponsored by Organon - now MSD, six trials were sponsored by Ferring, one trials was sponsored by IBSA, 11 trials were not sponsored by a pharmaceutical company and for one trial sponsoring was unknown (for the corresponding forest plot see Figure 9).

Figure 9. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.4 Live birth (or ongoing pregnancy) by sponsor.



There was no evidence of a statistically significant difference in live births between rFSH and urinary gonadotrophins for the trials sponsored by Serono (6 trials, N=1410; Analysis 1.4; OR 1.25, 95% CI 0.97 to 1.61), the trials sponsored by Organon (3 trials, N=1215; Analysis 1.4; OR 1.28, 95% CI 0.96 to 1.71), the trial sponsored by IBSA (1 trials N=152; Analysis 1.4; OR 1.00, 95% CI 0.52 to 1.92), and the non-sponsored trials (11 trials, N= 1635; Analysis 1.4; OR 0.87, 95% CI 0.70 to 1.09). However, there were significantly fewer live births after rFSH as compared to urinary gonadotrophins for the trials sponsored by Ferring (6 trials, N=2817; Analysis 1.4; OR 0.83, 95% CI 0.69 to 0.98). To evaluate whether this is a pharmaceutical effect or really a result from the interventions done an additional unplanned sub analysis was performed (see last results section Extra unplanned analysis). There was no indication of statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

Primary safety outcome: OHSS

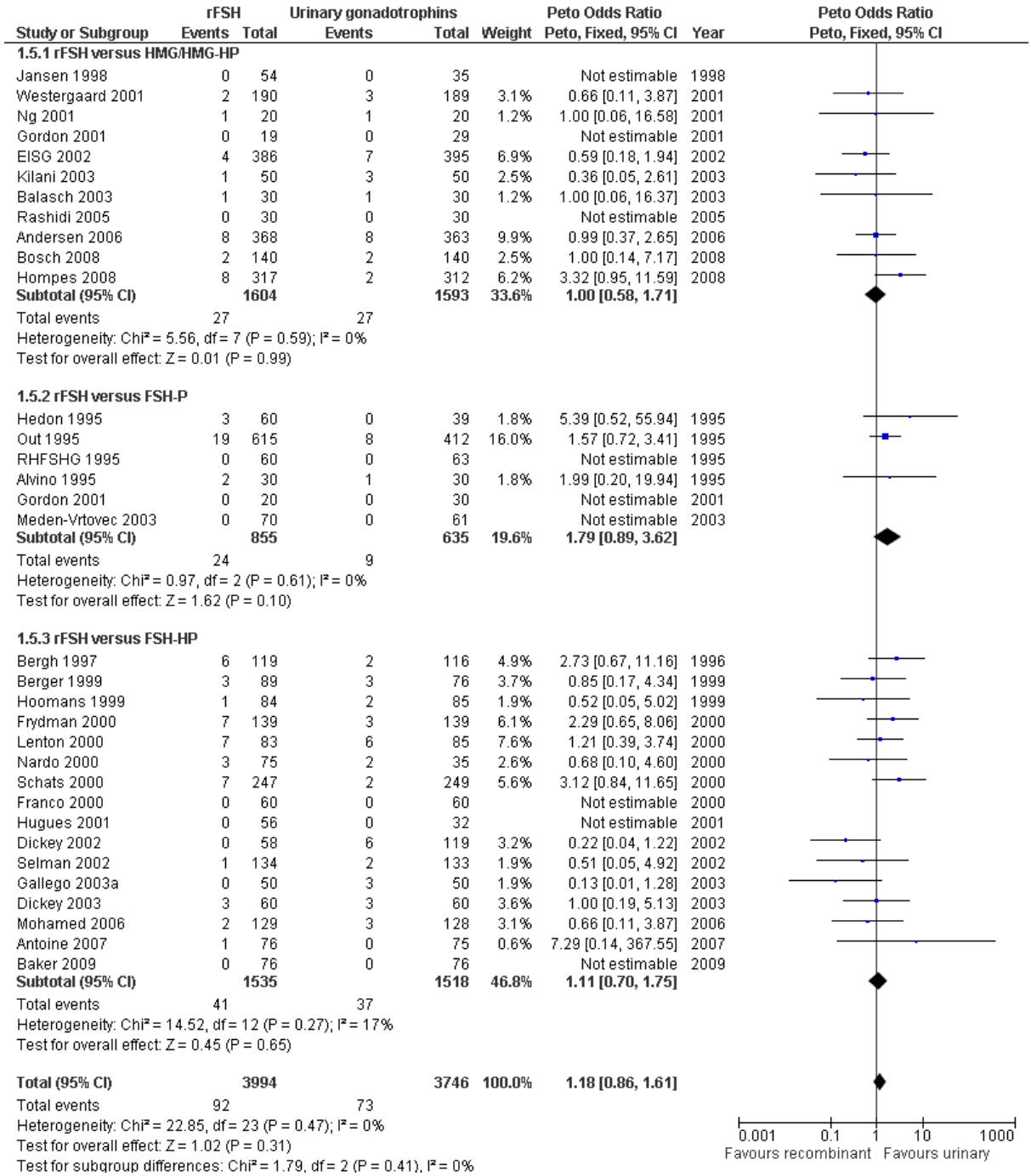
There was no evidence of a statistically significant difference in the primary safety outcome OHSS for rFSH versus urinary gonadotrophins (32 trials, N=7740; Analysis 1.5; OR 1.18, 95% CI 0.86 to 1.61; I^2 of 0%). This means that for a typical rate of 2% OHSS using urinary gonadotrophins, use of rFSH instead would be expected to result in an OHSS rate between 1.7% and 3.2% OHSS. There was no indication for statistical heterogeneity. Visual inspection of the forest plot showed that the OR and 95%CI of the individual trials overlapped and the I^2 was 0%.

1.5 OHSS grouped by the different urinary gonadotrophins

See Analysis 1.5

Of the 32 trials with data on OHSS 11 trials compared rFSH versus HMG/HP-HMG, 6 trials compared rFSH with FSH-P and 16 trials compared rFSH with FSH-HP (for the corresponding forest plot see Figure 10).

Figure 10. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.5 OHSS by urinary gonadotrophin.



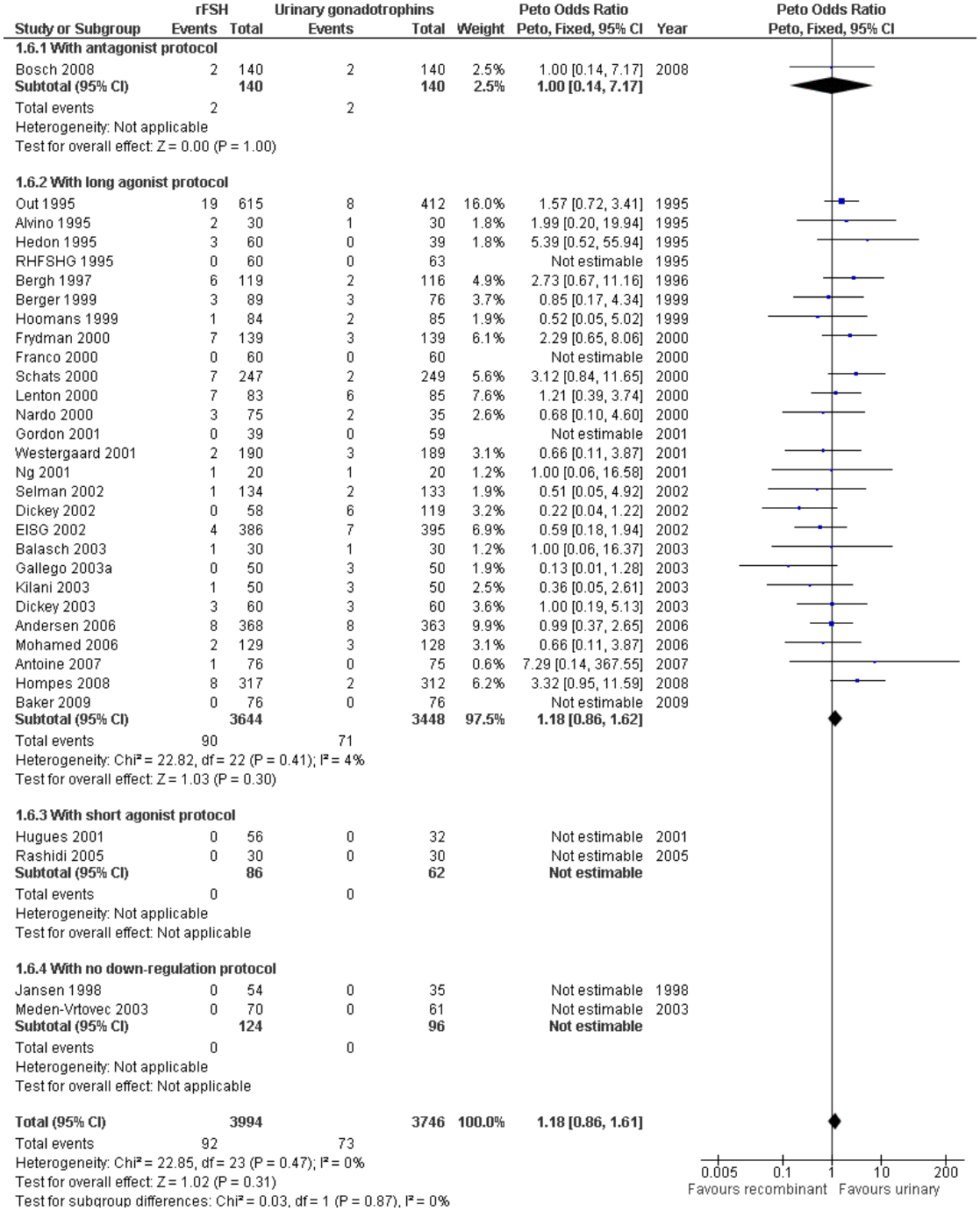
There was no evidence of a statistically significant difference in OHSS for rFSH versus HMG (11 trials, N=3197; Analysis 1.5; OR 1.00, 95% CI 0.58 to 1.71), also not for rFSH versus FSH-P (6 trials, N=1490; Analysis 1.5; OR 1.79, 95% CI 0.89 to 3.62), and for rFSH versus FSH-HP (16 trials, N=3053; Analysis 1.5; OR 1.11, 95% CI 0.70 to 1.75; I^2 was 0%). There was no indication for statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

1.6 OHSS grouped by down regulation protocol

See Analysis 1.6

Of the 32 trials with data on live birth 1 trial used an antagonist protocol, 27 trials used a long GnRH agonist protocol, two used a short GnRH agonist protocol, and two did not use down-regulation (for the corresponding forest plot see Figure 11).

Figure 11. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.6 OHSS by down regulation protocol.



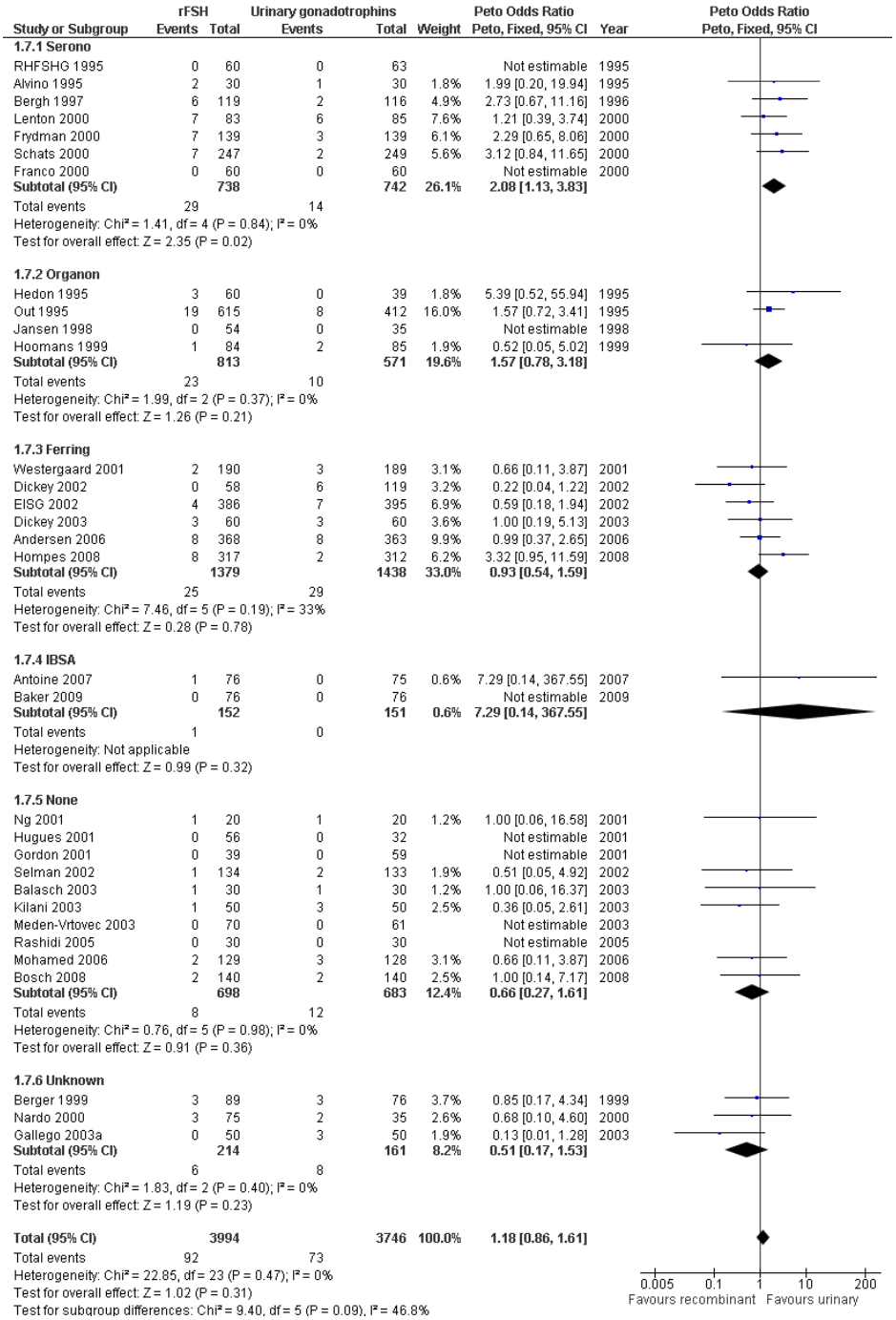
There was no evidence of a statistically significant difference in OHSS between rFSH and urinary gonadotrophins for any of the down regulation protocols (antagonist protocol, N=280; Analysis 1.6; OR 1.00, 95% CI 0.14 to 7.17), (long GnRHa protocol, N=7092; Analysis 1.6; OR 1.18, 95% CI 0.86 to 1.62), (short GnRHa protocol, N=148; Analysis 1.6; OR not estimable due to lack of OHSS cases), (no down regulation, N=220; OR not estimable due to lack of OHSS cases). There was no indication for statistical heterogeneity for any of these grouped comparisons (I^2 of 0%).

1.8 OHSS grouped by sponsor

See Analysis 1.7

Of the 32 trials with data on OHSS seven trials were sponsored by Serono, four trials were sponsored by Organon - now MSD, six trials were sponsored by Ferring, two trials were sponsored by IBSA, 10 trials were not sponsored by a pharmaceutical company and for three trials sponsoring was unknown (for the corresponding forest plot see Figure 12).

Figure 12. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.8 OHSS by sponsor.



There was more OHSS in the rFSH group as compared to urinary gonadotrophins in studies sponsored by Serono (7 trials, N= 1480; Analysis 1.7; OR 2.08, 95% CI 1.13 to 3.83). There was no evidence of a statistically significant difference in OHSS between rFSH and urinary gonadotrophins for the trials sponsored by Organon (4 trials, N=1387; Analysis 1.7; OR 1.57, 95% CI 0.78 to 3.18), the trials sponsored by Ferring (6 trials, N=2817; Analysis 1.7; OR 0.93, 95% CI 0.54 to 1.59), the trials sponsored by IBSA (2 trials N=303; Analysis 1.7; OR 7.29, 95% CI 0.14 to 368), the sponsoring unknown trials (3 trials N=375; Analysis 1.7; OR 0.51, 95% CI 0.17 to 1.53) and the non-sponsored trials (10 trials, N=1381; Analysis 1.7; OR 0.66, 95% CI 0.27 to 1.61). There was no indication for statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

Secondary outcomes

Clinical pregnancy rate

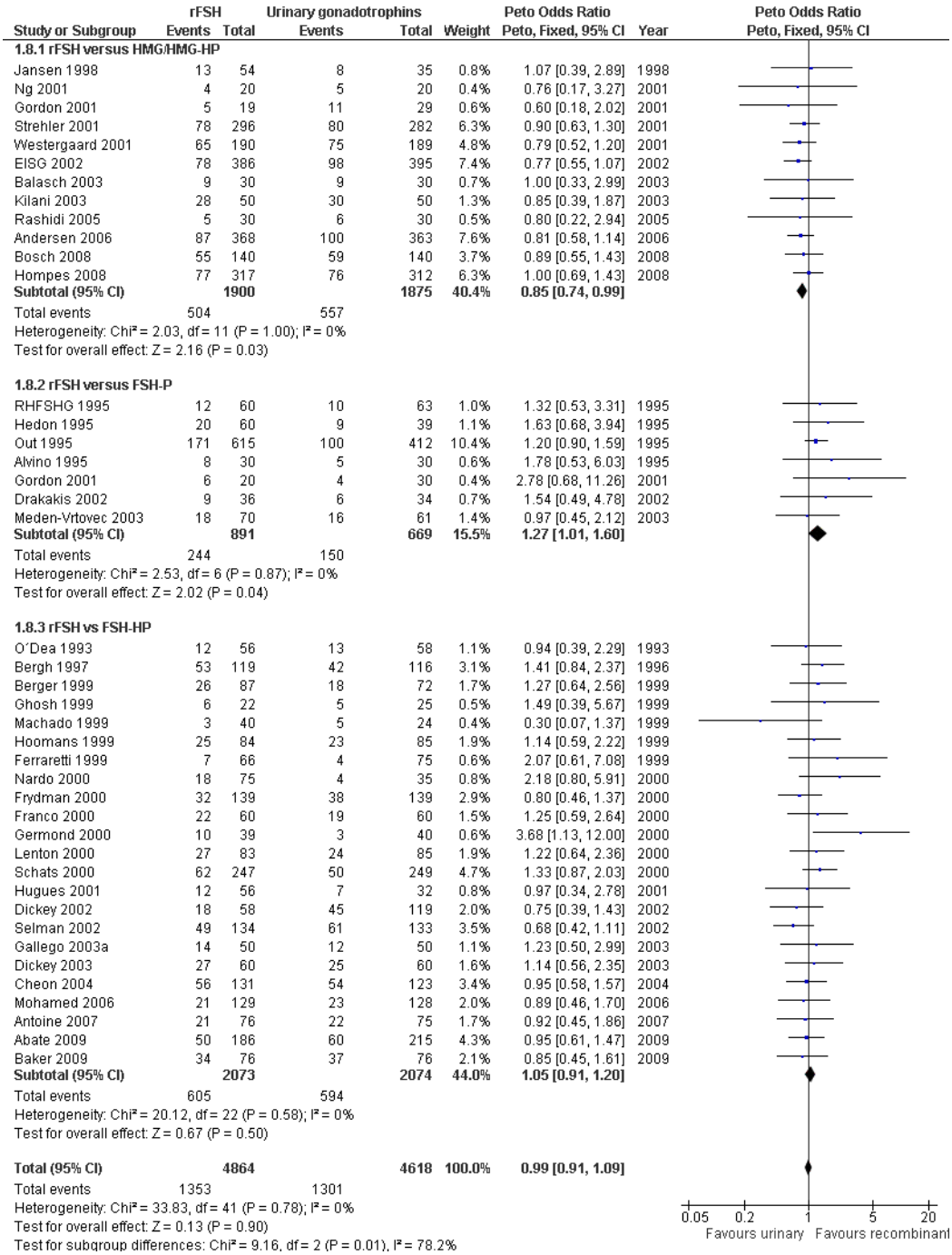
There was no evidence of a statistically significant difference in the clinical pregnancy rate (41 trials, N=9482; Analysis 1.8; OR 0.99, 95% CI 0.91 to 1.09) for rFSH versus urinary gonadotrophins. This means that for a typical clinical pregnancy rate of 28% using urinary gonadotrophins, use of rFSH instead would be expected to result in a clinical pregnancy rate between 26% and 30%. There was no indication of statistical heterogeneity. Visual inspection of the forest plot showed that the OR and 95%CI of the individual trials overlapped and the I^2 was 0%.

1.9 Clinical pregnancy rate grouped by the different urinary gonadotrophins

See Analysis 1.8

Of the 41 trials with data on clinical pregnancies 12 trials compared rFSH versus HMG/HP-HMG, seven trials compared rFSH with FSH-P and 23 trials compared rFSH with FSH-HP (for the corresponding forest plot see Figure 13).

Figure 13. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.9 Clinical pregnancy by urinary gonadotrophin.



There were significantly fewer clinical pregnancies after rFSH as compared to HMG/HP-HMG (OR 0.85, 95% CI 0.74 to 0.99; I^2 of 0%; 12 trials, N=3775; Analysis 1.8). This means that for a typical clinical pregnancy rate of 28% using HMG/HP-HMG, use of rFSH instead would be expected to result in a clinical pregnancy rate between 23% and 28%.

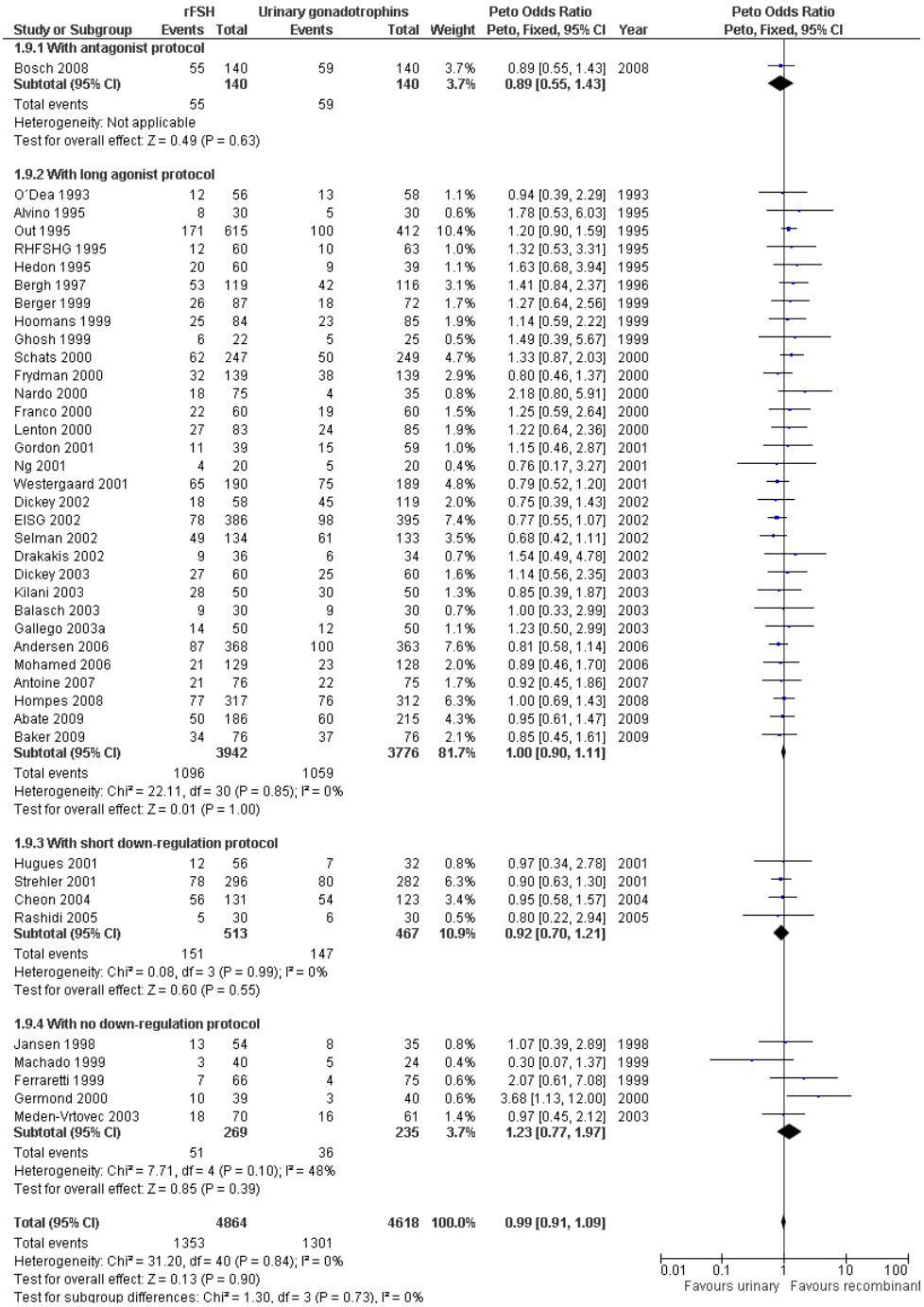
There were significantly more clinical pregnancies after rFSH as compared to FSH-P (OR 1.27, 95% CI 1.01 to 1.60; I^2 of 0%; 7 trials, N=1560; Analysis 1.8). This means that for a typical clinical pregnancy rate of 28% using FSH-P, use of rFSH instead would be expected to result in a clinical pregnancy rate between 28% and 40%.There was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and FSH-P (23 trials, N= 4147; Analysis 1.8; OR 1.05, 95% CI 0.91 to 1.20; I^2 of 0%).

1.10 Clinical pregnancy rate grouped by down regulation protocol

See Analysis 1.9

Of the 41 trials with data on clinical pregnancies one trial used an antagonist protocol, 31 trials used a long GnRH agonist protocol, four used a short GnRH agonist protocol, and five did not use down-regulation (for the corresponding forest plot see Figure 14).

Figure 14. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.10 Clinical pregnancy by down regulation protocol.



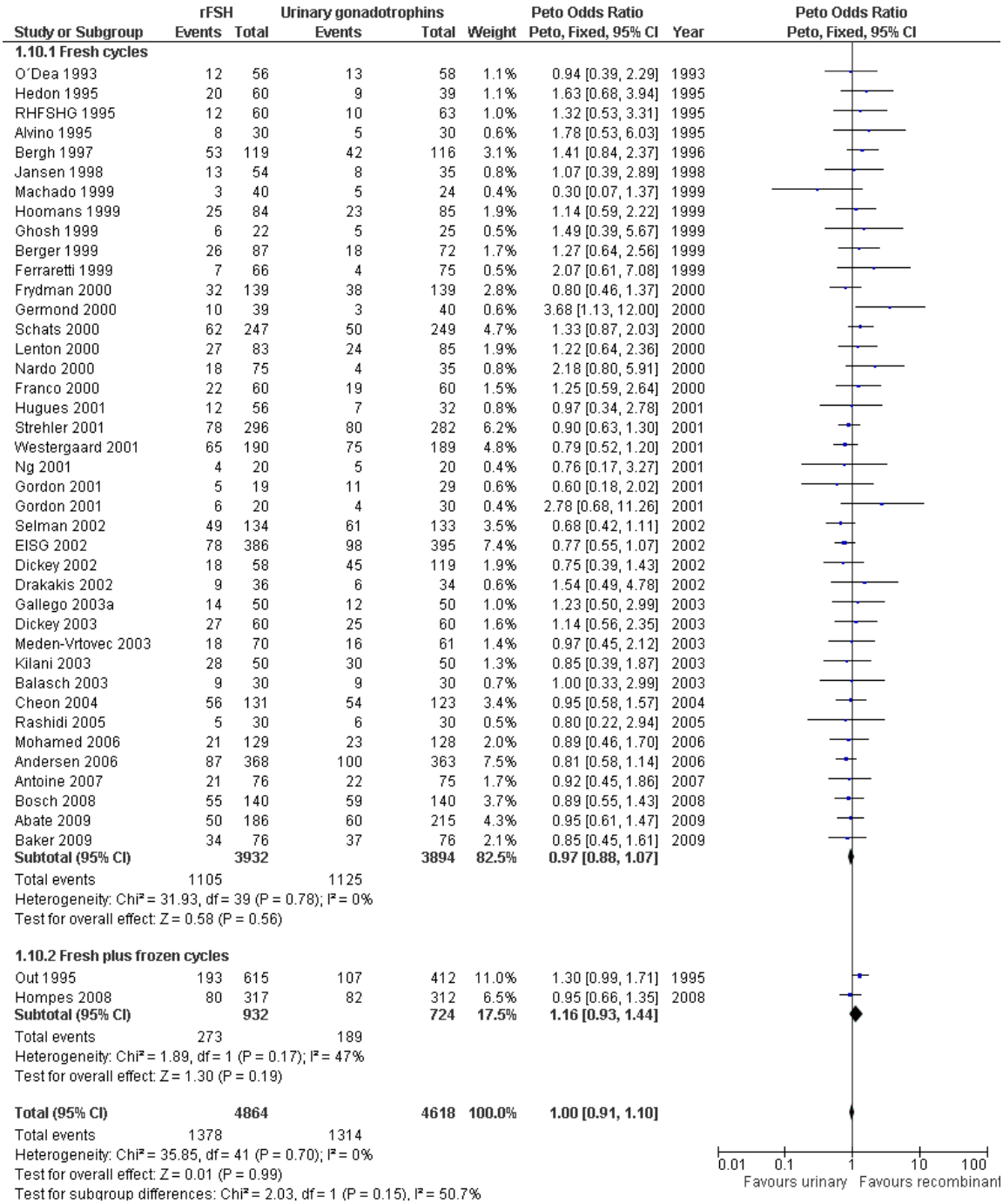
There was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and urinary gonadotrophins for any of the down regulation protocols (antagonist protocol, N= 280; Analysis 1.9; OR 0.89, 95% CI 0.55 to 1.43), (long GnRHa protocol, N=7718; Analysis 1.9; OR 1.00, 95% CI 0.90 to 1.11), (short GnRHa protocol, N=980; Analysis 1.9; OR 0.92, 95% CI 0.70 to 1.21), (no down regulation, N=504; Analysis 1.9; OR 1.23, 95% CI 0.77 to 1.97). There was no indication of any statistical heterogeneity of these grouped comparisons (I^2 was 0%).

1.11 Clinical pregnancy rate grouped by fresh/frozen policy

See Analysis 1.10

Of the 41 trials with data on clinical pregnancies the outcome of frozen-thawed cycles was known for only two trials (for the corresponding forest plot see Figure 15). There was no evidence of a statistically significant difference between rFSH and urinary gonadotrophins for clinical pregnancy rate after fresh cycles (39 trials, N=8744; Analysis 1.10; OR 0.97, 95% CI 0.88 to 1.07) and for cumulative clinical pregnancy rate after fresh and frozen-thawed cycles (2 trials, N=1656; Analysis 1.10; OR 1.16, 95% CI 0.93 to 1.44). There was no indication of statistical heterogeneity (I^2 of 0%).

Figure 15. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.11 Clinical pregnancy by fresh/frozen policy.

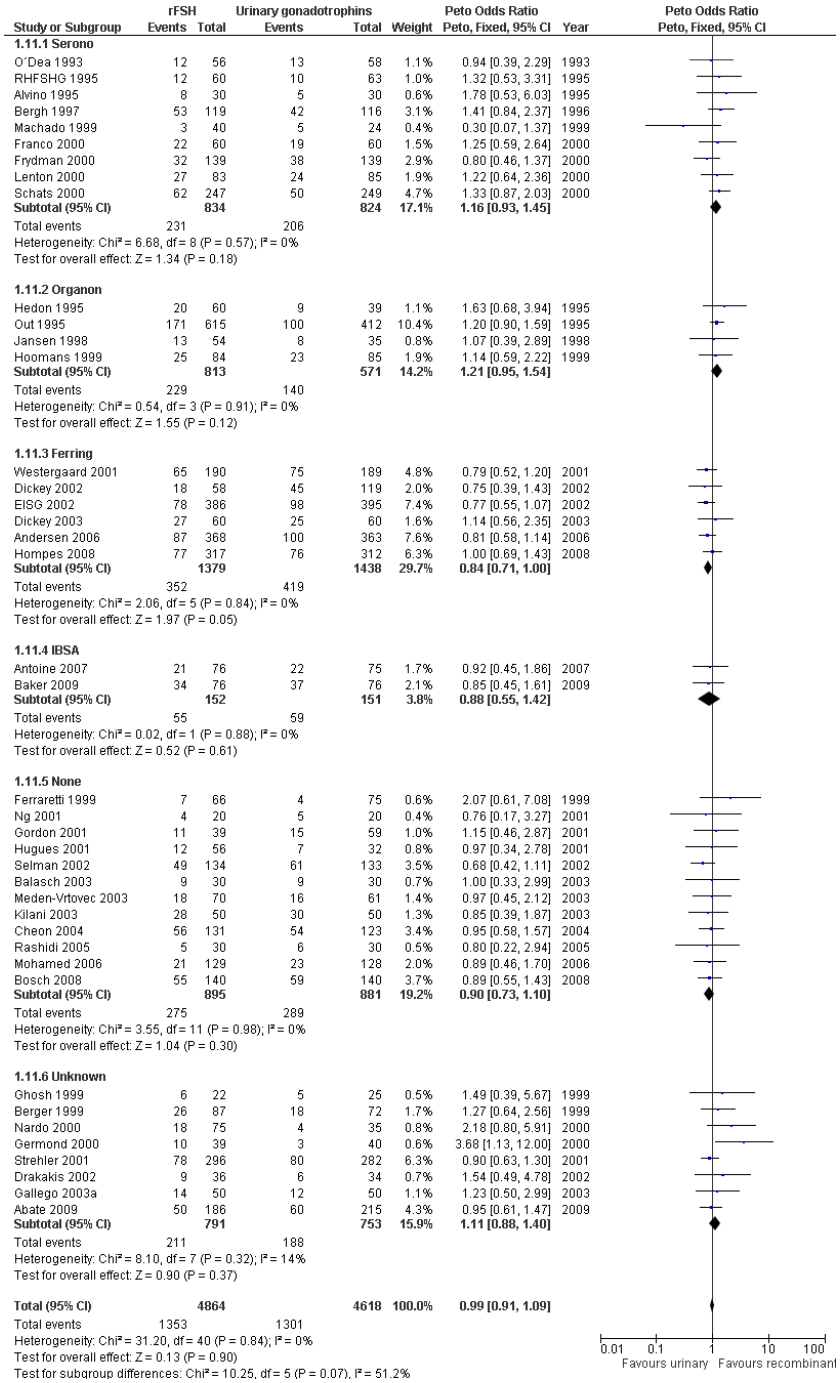


1.12 Clinical pregnancy rate grouped by pharmaceutical sponsor

See Analysis 1.11

Of the 41 trials with data on clinical pregnancies nine trials were sponsored by Serono, four trials were sponsored by Organon - now MSD, six trials were sponsored by Ferring, two trials were sponsored by IBSA, 12 trials were not sponsored by a pharmaceutical company and for eight trials sponsoring was unknown (for the corresponding forest plot see Figure 16).

Figure 16. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.12 Clinical pregnancy by sponsor.



There was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and urinary gonadotrophins for the trials sponsored by Sereno (9 trials, N=1658; Analysis 1.11; OR 1.16, 95% CI 0.93 to 1.45), the trials sponsored by Organon (4 trials, N=1384; OR 1.21, 95% CI 0.95 to 1.54), the trials sponsored by IBSA (2 trials, N=303; Analysis 1.11; OR 0.88, 95% CI 0.55 to 1.42), and the non-sponsored trials (12 trials, N= 1776; Analysis 1.11; OR 0.90, 95% CI 0.73 to 1.10). However, there were borderline significantly fewer live births after rFSH as compared to urinary gonadotrophins for the trials sponsored by Ferring (6 trials, N=2817; Analysis 1.11; OR 0.84, 95% CI 0.71 to 1.00). To evaluate whether this is a pharmaceutical effect or really a result from the interventions done an additional unplanned sub analysis was performed (see last results section **Extra unplanned analysis)** There was no indication of statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

Further secondary outcomes

There were no data available on patient acceptability or satisfaction for trials that compared rFSH and urinary gonadotrophins.

There was no evidence of a statistically significant difference in multiple pregnancy rate per woman (25 trials, N=6329; Analysis 1.12; OR 0.91, 95% CI 0.76 to1.09) for rFSH versus urinary gonadotrophins (for the corresponding forest plot see Figure 17), nor for multiple pregnancy rate as expressed per clinical pregnancy (25 trials, N=6329; Analysis 1.13; OR 0.96, 95% CI 0.78 to 1.18) (for the corresponding forest plot see Figure 18). For both multiple pregnancy outcomes the I^2 was 0%.

Figure 17. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.15 Multiple pregnancy (per woman).

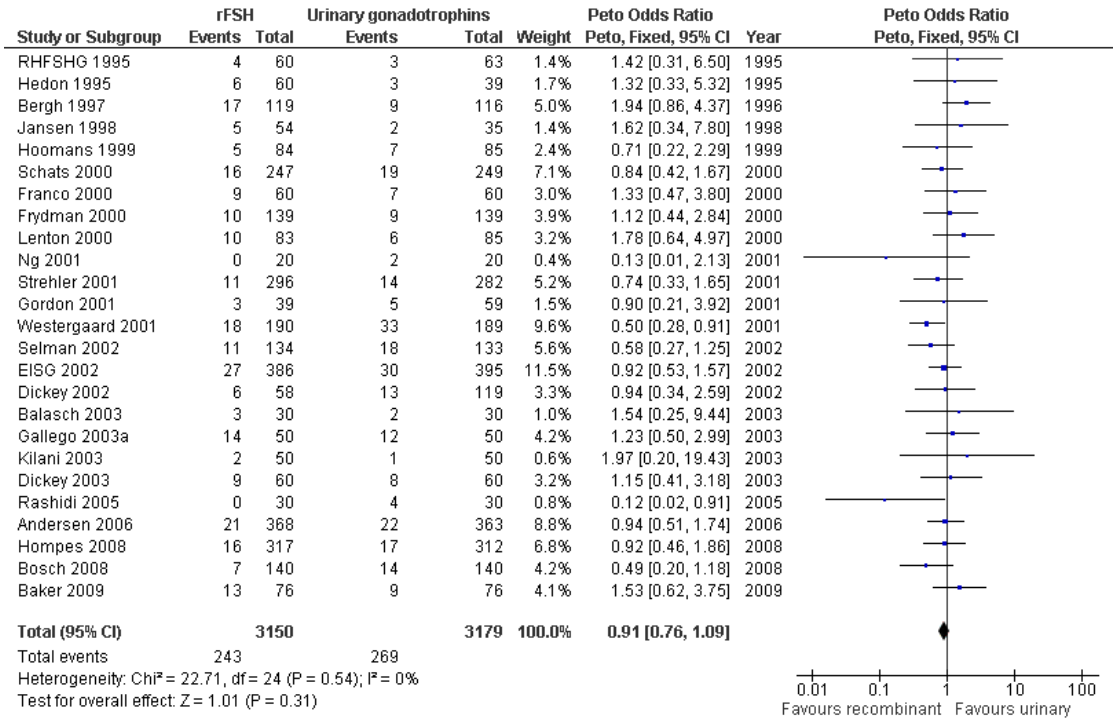
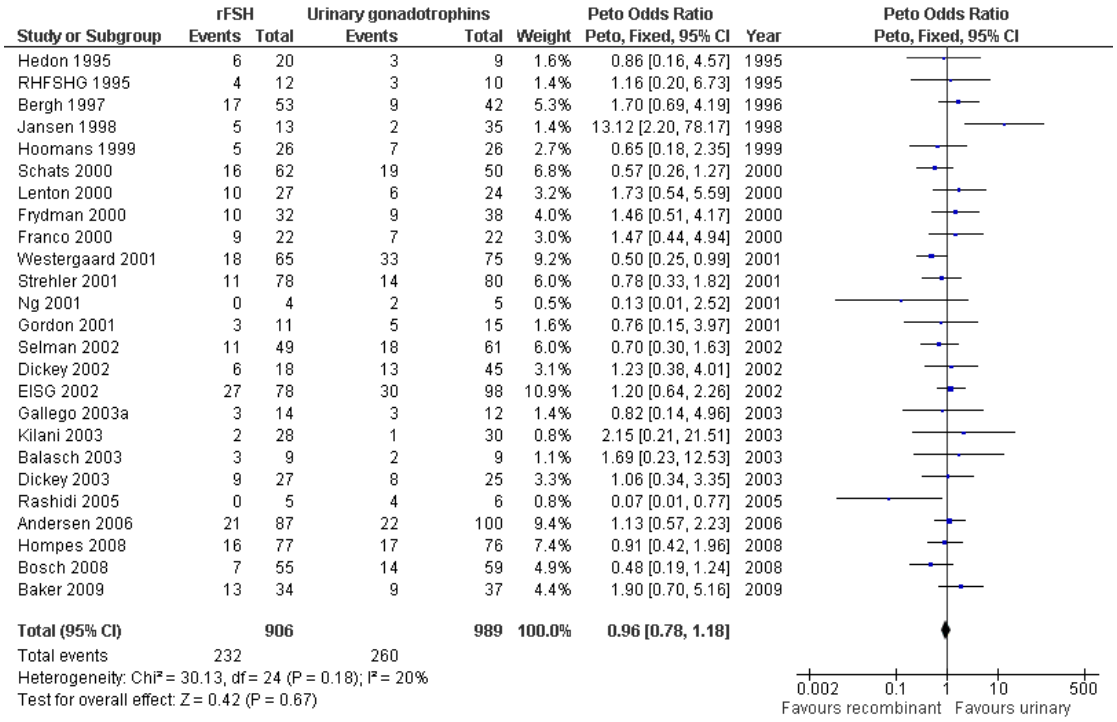
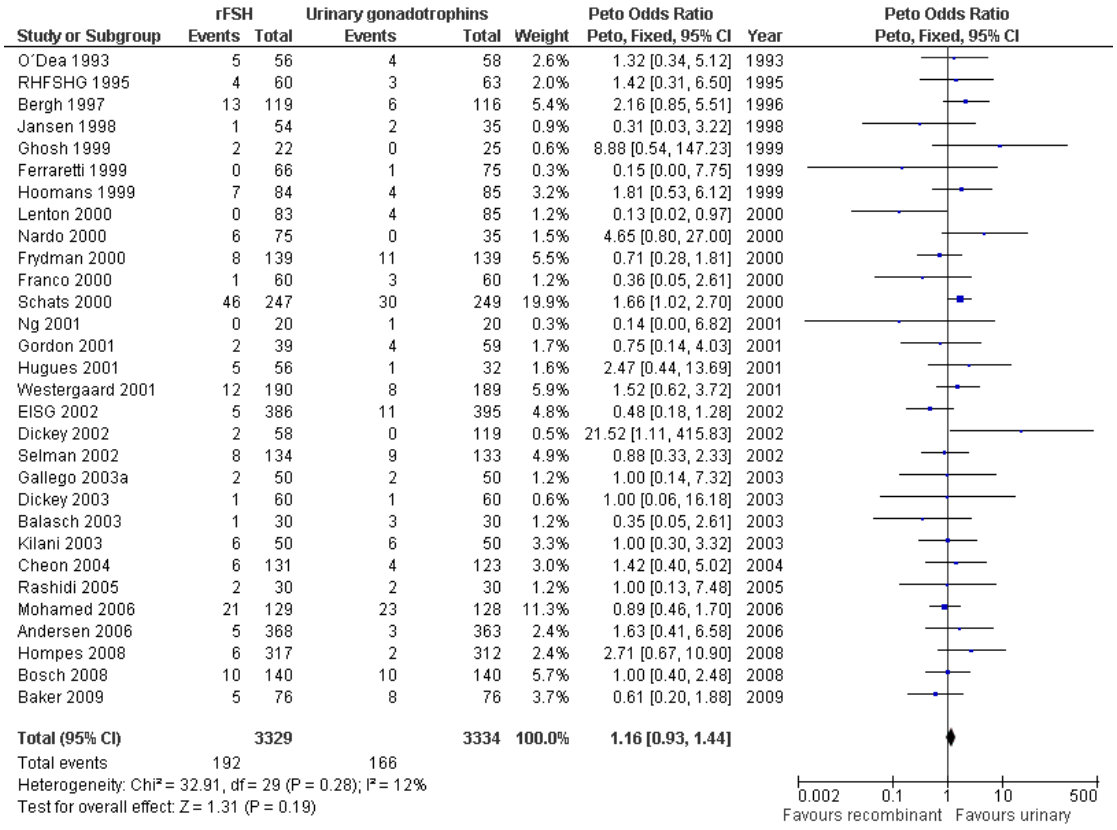


Figure 18. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.16 Multiple pregnancy (per pregnancy).



There was no evidence of a statistically significant difference in miscarriage rate (30 trials, N=6663; Analysis 1.14; OR 1.16, 95% CI 0.95 to 1.47) with an I^2 of 0 (for the corresponding forest plot see Figure 19).

Figure 19. Forest plot of comparison: 1 rFSH versus urinary gonadotrophins: primary analyses, outcome: 1.17 Miscarriage (per woman).



For the oocytes retrieved there was data from 37 trials, entailing 8564 couples. However, as oocytes could not be retrieved per woman randomised and because there was very large statistical heterogeneity between the trials data was not presented in a forest plot and a mean difference (MD) was not calculated. Data are presented under additional tables (Table 2).

Data differed largely between the individual trials for amount of gonadotrophins used (IU) and for duration of ovarian stimulation (days) (I^2 of 96% and 90% respectively). Data was not presented in a forest plot and was not pooled. Data are presented under additional tables (Table 3 and Table 4).

2 Sensitivity analyses for rFSH versus urinary gonadotrophins excluding lower quality trials

Data are presented in "Data and analyses" under "2 Sensitivity analyses excluding lower quality trials". These sensitivity analyses were done for the outcomes live birth, OHSS and clinical pregnancy only and excluded trials that were not ITT and/or that did perform multiple cycles. Live birth, OHSS and clinical pregnancy data are presented grouped for the types of urinary gonadotrophins and grouped for type of down-regulation.

Primary outcomes

Primary efficacy outcome: Live birth

One trial was excluded in the sensitivity analyses as this trial performed multiple cycles and results were presented per cycle and not per woman (Cheon 2004). In the primary analysis there was no evidence of a statistically significant difference between rFSH and urinary gonadotrophins in live births or pregnancy ongoing beyond 20 weeks (28 trials, N=7339; Analysis 1.5; OR 0.97, 95% CI 0.87 to 1.08; I^2 of 0%) and exclusion of this trial did not affect the result (27 trials, N=7085; Analysis 2.1; OR 0.98, 95% CI 0.87 to 1.09; I^2 of 0%) .

2.1 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by the different urinary gonadotrophins

See Analysis 2.1

The one trial with data on live births that was excluded in the sensitivity analysis compared rFSH with FSH-HP. Exclusion of this trial from the subgroup *rFSH versus FSH-HP* did not affect

the outcome of the primary analyses as presented in Analysis 1.1 .
Of the 27 trials with data on live births 11 trials compared rFSH versus HMG/HP-HMG, 5 trials compared rFSH with FSH-P and 13 trials compared rFSH with FSH-HP.
There were significantly fewer live births after rFSH as compared to HMG (OR 0.84, 95% CI 0.72 to 0.99; 11 trials, N=3197; Analysis 2.1). There was no indication of statistical heterogeneity. Visual inspection of the forest plot showed that the OR and 95%CI of the individual trials largely overlapped and the I^2 was 0%. Pooling using a random effects model resulted in the same OR.
There was no evidence of a statistically significant difference in live births between rFSH and FSH-P (5 trials, N=1430; Analysis 2.1; OR 1.26, 95% CI 0.96 to 1.64; I^2 of 0%) and between rFSH and FSH-HP (12 trials, N=2458; Analysis 2.1; OR 1.05, 95% CI 0.87 to 1.26; I^2 of 0%)

2.2 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by down regulation protocol

See Analysis 2.2
The one trial with data on live births that was excluded in the sensitivity analysis used a short GnRHa protocol. Exclusion of this trial from the subgroup *long agonist protocol* did not affect the outcome of the primary analyses presented in Analysis 1.2.
Of the 27 trials with data on live births 1 trial used an antagonist protocol, 22 trials used a long GnRH agonist protocol, three used a short GnRH agonist protocol, and two did not use down-regulation.
There was no evidence of a statistically significant difference in live births between rFSH and urinary gonadotrophins for any of the down regulation protocols (antagonist protocol, 1 trial, N= 280; Analysis 2.2; OR 0.88, 95% CI 0.53 to 1.45), (long GnRHa protocol, 22 trials, N=6437; Analysis 2.2; OR 0.98, 95% CI 0.87 to 1.10), (short GnRHa protocol, 1 trial, N=148; Analysis 2.2; OR 0.65, 95% CI 0.25 to 1.71), (no down regulation, 2 trials, N=220; Analysis 2.2; OR 1.17, 95% CI 0.62 to 2.20). There was no indication of statistical heterogeneity (I^2 of 0%).

2.3 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by fresh/frozen policy

See Analysis 2.3
The one trial with data on live births that was excluded in the sensitivity analysis performed only fresh cycles. Exclusion of this trial from the subgroup *fresh cycles* did not affect the outcome of the primary analyses in Analysis 1.3.
Of the 27 trials with data on live births the outcome of frozen-thawed cycles was known for only three trials. There was no evidence of a statistically significant difference between rFSH and urinary gonadotrophins for live births after fresh cycles (24 trials, N=4698; Analysis 2.3; OR 0.98, 95% CI 0.85 to 1.12) and for cumulative live birth rate after fresh and frozen-thawed cycles (3 trials, N=2387; Analysis 2.3; OR 1.01, 95% CI 0.84 to 1.22). There was no indication of statistical heterogeneity (I^2 of 0%).

2.4 Live birth (or pregnancy ongoing beyond 20 wk's) grouped by pharmaceutical sponsor

See Analysis 2.4
The one trial with data on live births that was excluded in the sensitivity analysis was not a commercially sponsored trial. Exclusion of this trial from the subgroup *none* did not affect the outcome of the primary analyses as presented in Analysis 1.3 .
Of the 27 trials with data on live births six trials were sponsored by Serono, three trials were sponsored by Organon - now MSD, six trials were sponsored by Ferring, one trials was sponsored by IBSA, 10 trials were not sponsored by a pharmaceutical company and for one trials sponsoring was unknown.
There was no evidence of a statistically significant difference in live births between rFSH and urinary gonadotrophins for the trials sponsored by Sereno (6 trials, N=1410; Analysis 2.4; OR 1.25, 95% CI 0.97 to 1.61), the trials sponsored by Organon (3 trials, N=1215; Analysis 2.4; OR 1.28, 95% CI 0.96 to 1.71), the trial sponsored by IBSA (1 trials N=152; Analysis 2.4; OR 1.00, 95% CI 0.52 to 1.92), and the non-sponsored trials (10 trials, N=1381; Analysis 2.4; OR 0.86, 95% CI 0.67 to 1.11). However, there were significantly fewer live births after rFSH as compared to urinary gonadotrophins for the trials sponsored by Ferring (6 trials, N= 2817; Analysis 2.4; OR 0.83, 95% CI 0.69 to 0.98). There was no indication of statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

Primary safety outcome: OHSS

Two trials with data on OHSS were excluded in the sensitivity analyses as it was not certain whether data were according to ITT (Berger 1999, Gallego 2003a). Furthermore, one of the trials use multiple cycles and presented data (Berger 1999). In the primary analysis there was no evidence of a statistically significant difference between rFSH and urinary gonadotrophins in live birth or pregnancy ongoing beyond 20 weeks (32 trials, N=7740; Analysis 1.5; OR 1.18, 95% CI 0.86 to 1.61; I^2 of 0%) for rFSH versus urinary gonadotrophins and exclusion of the two trials did not change that finding (30 trials, N=7475; Analysis 2.5; OR 1.24, 95% CI 0.90 to 1.7).

2.5 OHSS grouped by the different urinary gonadotrophins

See Analysis 2.5
The two trials with data on OHSS that were excluded in the sensitivity analyses compared rFSH with FSH-HP. Exclusion of these trials from the subgroup *rFSH versus FSH-HP* did not affect the outcome of the primary analyses as presented in Analysis 1.5.
Of the 30 trials with data on OHSS, 11 trials compared rFSH versus HMG/HP-HMG, 6 trials compared rFSH with FSH-P and 14 trials compared rFSH with FSH-HP.
There was no evidence of a statistically significant difference in OHSS for rFSH versus HMG (11 trials, N=3197; Analysis 2.5; OR 1.00, 95% CI 0.58 to 1.71), also not for rFSH versus FSH-P (6 trials, N=1490; Analysis 2.5; OR 1.79, 95% CI 0.89 to 3.62), and for rFSH versus FSH-HP (14 trials, N=2788; Analysis 2.5; OR 1.25, 95% CI 0.77 to 2.03; I^2 was 0%).

2.6 OHSS grouped by down regulation protocol

See Analysis 2.6

The two trials with data on OHSS that were excluded in the sensitivity analyses used a long GnRHa protocol. Exclusion of these trials from the subgroup *long agonist protocol* did not affect the outcome of the primary analyses as presented in Analysis 1.6.

Of the 30 trials with data on live birth 1 trial used an antagonist protocol, 27 trials used a long GnRH agonist protocol, two used a short GnRH agonist protocol, and two did not use down-regulation.

There was no evidence of a statistically significant difference in OHSS between rFSH and urinary gonadotrophins for any of the down regulation protocols (antagonist protocol, N=280; Analysis 2.6; OR 1.00, 95% CI 0.14 to 7.17), (long GnRHa protocol, N= 6827; Analysis 2.6; OR 1.25, 95% CI 0.90 to 1.73; OR 1.18, 95% CI 0.86 to 1.62), (short GnRHa protocol, N=148; Analysis 2.6; OR not estimable due to lack of OHSS cases), (no down regulation, N=220; OR not estimable due to lack of OHSS cases). There was no indication of statistical heterogeneity for any of these grouped comparisons (I^2 of 0%).

2.7 OHSS grouped by sponsor

See Analysis 2.7

For the two trials with data on OHSS that were excluded in the sensitivity analyses the sponsoring was unknown. Exclusion of these trials from the subgroup sponsoring *unknown* did not affect the outcome of the primary analyses as presented in Analysis 1.7.

Of the 30 trials with data on OHSS seven trials were sponsored by Serono, four trials were sponsored by Organon - now MSD, six trials were sponsored by Ferring, two trials were sponsored by IBSA, 10 trials were not sponsored by a pharmaceutical company and for one trials sponsoring was unknown.

There was more OHSS in the rFSH group as compared to urinary gonadotrophins in studies sponsored by Serono (7 trials, N=1480; OR 2.08, 95% CI 1.13 to 3.83).

There was no evidence of a statistically significant difference in OHSS between rFSH and urinary gonadotrophins for the trials sponsored by Organon (4 trials, N=1387; Analysis 2.7; OR 1.57, 95% CI 0.78 to 3.18), the trials sponsored by Ferring (6 trials, N=2817; Analysis 2.7; OR 0.93, 95% CI 0.54 to 1.59), the trials sponsored by IBSA (2 trials, N=303; Analysis 2.7; OR 7.29, 95% CI 0.14 to 368), and the non-sponsored trials (10 trials, N=1381; Analysis 2.7; OR 0.66, 95% CI 0.27 to 1.61). There was no indication of statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

Secondary outcomes

Clinical pregnancy rate

Six trials with data on clinical pregnancies were excluded in the sensitivity analyses as it was not certain whether data were presented according to ITT and/or because multiple cycles were done and data were presented per cycle and not per woman (O´ Dea 1993; Berger 1999; Ghosh 1999 ;Machado 1999 Gallego 2003a; Cheon 2004). In the primary analysis there was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and urinary gonadotrophins (41 trials, N=9482; OR 0.99, 95% CI 0.91 to 1.09; I^2 of 0%) and exclusion of the six trials did not change that result (35 trials, N=8744; OR 0.99, 95% CI 0.90 to 1.09; I^2 of 0%).

2.8 Clinical pregnancy rate grouped by the different urinary gonadotrophins

See Analysis 2.8

The six excluded trials all compared rFSH with FSH-HP. Exclusion of these six trials from the subgroup *rFSH versus FSH-HP* did not affect the outcome of the primary analyses as presented Analysis 1.8.

Of the 35 trials with data on clinical pregnancies, 12 trials compared rFSH versus HMG/HP-HMG, seven trials compared rFSH with FSH-P and 17 trials compared rFSH with FSH-HP.

There were significantly fewer clinical pregnancies after rFSH as compared to HMG (OR 0.85, 95% CI 0.74 to 0.99; I^2 of 0%; 12 trials, N=3775; Analysis 2.8). There were significantly more clinical pregnancies after rFSH as compared to FSH-P (OR 1.27, 95% CI 1.01 to 1.60; I^2 of 0%; 7 trials, N=1560; Analysis 2.8). There was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and FSH-HP (17 trials, N= 3409; Analysis 2.8; OR 1.05, 95% CI 0.91 to 1.23; I^2 of 0%).

2.9 Clinical pregnancy rate grouped by down regulation protocol

See Analysis 2.9

Of the six excluded trials with data on clinical pregnancies four used a *long agonist protocol* and one used a *short agonist protocol* and one used *no down regulation*. Exclusion of these six trials from the respective down regulation subgroups did not affect the outcome of the primary analyses as presented Analysis 1.9.

Of the 35 trials with data on clinical pregnancies that were included in the sensitivity analysis, one trial used an antagonist protocol, 27 trials used a long GnRH agonist protocol, three used a short GnRH agonist protocol, and five did not use down-regulation.

There was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and urinary gonadotrophins for any of the down regulation protocols (antagonist protocol, N= 280; Analysis 2.9; OR 0.89, 95% CI 0.55 to 1.43), (long GnRHa protocol, N=7298; Analysis 2.9; OR 0.99, 95% CI 0.89 to 1.10), (short GnRHa protocol, N=726; Analysis 2.9; OR 0.90, 95% CI 0.65 to 1.26), (no down regulation, N=440; Analysis 2.9; OR 1.43, 95% CI 0.87 to 2.35). There was no indication of statistical heterogeneity for these grouped comparisons (I^2 was 0%).

2.11 Clinical pregnancy rate grouped by fresh/frozen policy

See Analysis 2.10

Of the 35 trials with data on clinical pregnancies the outcome of frozen-thawed cycles was known for only two trials. There was no evidence of a statistically significant difference between rFSH and urinary gonadotrophins for clinical pregnancy rate after fresh cycles (33 trials, N=8744; Analysis 2.10; OR 1.00, 95% CI 0.91 to 1.10) and for cumulative clinical pregnancy rate after fresh and frozen-thawed cycles (2 trials, N=1656; Analysis 2.10; OR

1.16, 95% CI 0.93 to 1.44). There was no indication of statistical heterogeneity (I^2 of 0%).

2.12 Clinical pregnancy rate grouped by pharmaceutical sponsor

See Analysis 2.11

Of the six excluded trials with data on clinical pregnancies all used fresh cycles. Exclusion of these six trials from the respective fresh and frozen subgroups did not affect the outcome of the primary analyses as presented under 1.11.

Of the 35 trials with data on clinical pregnancies that were included in the sensitivity analysis, seven trials were sponsored by Serono, four trials were sponsored by Organon - now MSD, six trials were sponsored by Ferring, two trials were sponsored by IBSA, 11 trials were not sponsored by a pharmaceutical company and for five trials sponsoring was unknown.

There was no evidence of a statistically significant difference in clinical pregnancy rate between rFSH and urinary gonadotrophins for the trials sponsored by Sereno (7 trials, N=1480; Analysis 2.11; OR 1.22, 95% CI 0.97 to 1.53), the trials sponsored by Organon (4 trials, N=1384; OR 1.21, 95% CI 0.95 to 1.54), the trials sponsored by IBSA (2 trials N=303; Analysis 2.11; OR 0.88, 95% CI 0.55 to 1.42), and the non-sponsored trials (11 trials, N=1522; Analysis 2.11; OR 0.88, 95% CI 0.70 to 1.11). However, there were borderline significantly fewer live births after rFSH as compared to urinary gonadotrophins for the trials sponsored by Ferring (6 trials, N=2817; Analysis 2.11; OR 0.84, 95% CI 0.71 to 1.00). There was no indication of statistical heterogeneity for any of these grouped comparisons (I^2 was 0%).

Extra unplanned analysis

For live birth rate and clinical pregnancy rate statistically significant differences were found only for the subgroup of trials that compared rFSH versus HMG/HP-HMG (Figure 6) and for the subgroup of trials that were sponsored by Ferring (Figure 9). Of the six trials that were sponsored by the pharmaceutical company Ferring four were trials that compared rFSH and HMG/HP-HMG. To evaluate whether the differences in live birth rate and clinical pregnancy rate are (partly) due to a sponsor effect we also pooled the data of five mostly small non-sponsored trials (N=548) that compared rFSH and HMG/HP-HMG (Gordon 2001; Ng 2001; Kilani 2003; Balasch 2003; Bosch 2008) and we pooled the data of the four large Ferring-sponsored trials (N=2520) that compared rFSH and HMG/HP-HMG (Westergaard 2001;EISG 2002; Andersen 2006; Hompes 2008).

The pooled OR for clinical pregnancy rate of the five non-sponsored trials was 0.84 (95% CI 0.58 to 1.21). The pooled OR for clinical pregnancy rate of the four trials that had been sponsored by Ferring was 0.84 (95% CI 0.70 to 1.00).

The pooled OR for live birth rate of the five non-sponsored trials was 0.90 (95% CI 0.62 to 1.31). The pooled OR for live birth rate of the four trials that had been sponsored by Ferring was 0.81 (95% CI 0.68 to 0.98).

DISCUSSION

Summary of main results

This review compared the effectiveness of recombinant gonadotrophin (rFSH) with the three main types of urinary gonadotrophins (i.e. HMG, FSH-P and FSH-HP) for ovarian stimulation in women undergoing IVF or ICSI treatment cycles. Overall, there was no evidence of a difference in pregnancy outcomes when rFSH was compared to urinary gonadotrophins as a whole. Comparing rFSH with HMG/HP-HMG resulted in a lower live birth rate in the rFSH group though differences were small. There was no proof of a difference in live births when comparing rFSH with FSH-P or with FSH-HP and there was no evidence of a difference observed in OHSS for any of the comparisons.

There was no evidence of differences in live births, OHSS or clinical pregnancy when rFSH was compared to urinary gonadotrophins as a whole in any of the down regulation groups. There was also no evidence of a difference in cumulative live birth and clinical pregnancy rates following frozen-thawed cycles for rFSH versus urinary gonadotropins. Stratification for sponsoring did only result in a difference in the trials that were sponsored by Ferring. The live birth and clinical pregnancy rate were lower for rFSH compared to urinary FSH in the Ferring sponsored trials. This will be discussed further under the sub header Potential biases in the review process.

Overall completeness and applicability of evidence

Of the 42 trials that were included in the primary analyses all 42 trials had data on clinical pregnancy but only 28 trials had data on live birth and 32 trials had data on OHSS. In the sensitivity analysis excluding the trials of lower quality 35 trials had data on clinical pregnancy, 27 trials had data on live birth and 30 trials had data on OHSS. For the trials that compared rFSH and HMG the data was most complete - these trials were all published after 2001. The data of trials that compared rFSH and uFSH-P and uFSH-HP was more incomplete as these included older trials that had been published before 2000 in a time when clinical pregnancy was still an accepted endpoint.

The evidence is broadly applicable for standard IVF and ICSI cycles.

The data on oocyte retrieval, gonadotrophin dose used and duration of stimulation was generally not presented per woman randomised. Therefore, these outcomes are likely to be biased and no conclusions on the basis of these comparisons should be drawn.

The preference of patients for a particular type of gonadotrophin was not evaluated in any trial. As all gonadotrophins are now given subcutaneously and with so few clinical differences a clear preference profile for a trial is not easy to make. Differences in preference are likely to be influenced by the way of presenting the

drug (using a pen, needing only a single administration). This was however not the aim of the present study.

Quality of the evidence

Most included studies used computer generated randomisation with a proper method of allocation concealment. The quality of the trials varied from low to moderate and appeared to be high in some of the larger sponsored trials.

Potential biases in the review process

The majority of the included trials were industry sponsored and this may have introduced a bias in favour of the gonadotrophin produced by the sponsor. The subgroup analyses in which we grouped the primary outcomes for pharmaceutical sponsoring suggest that live birth and clinical pregnancy rate were lower for rFSH compared to urinary FSH in the Ferring sponsored trials. However, further analysis of the Ferring sponsored trials and the non-sponsored trials that compared HMG/HP-HMG with rFSH showed comparable summary OR and confidence intervals that overlapped. Hence, though we cannot rule out that a sponsor effect is involved in this finding the potential effect of this sponsor bias appears to be limited.

We only did grouped analyses for down-regulation method, use of fresh or fresh and frozen cycles and sponsoring. There were more differences between trials that we did not explore further in sub analyses. For instance, the fertilisation method may affect the effectiveness of gonadotrophins (Al-Inany 2009) and a sub optimal dose may also have impact on the results.

Agreements and disagreements with other studies or reviews

Our results are in agreement with all the previous reviews (Daya 1998; Larizgoitia 2000;Daya 2002;Van Wely 2003 NCC-WCH 2004; Al-Inany 2008; Al-Inany 2009; Coomarisamy 2008), although there appears to be a difference with two older reviews that found rFSH to result in more clinical pregnancies than FSH-P and FSH-HP (Daya 1998; Daya 2002). This review also found evidence of a higher clinical pregnancy rate for rFSH in comparison to FSH-P but no evidence of a difference between rFSH and FSH-HP. The difference between the Daya reviews and the present review can however be explained. If we were to have combined only the trials that were performed before 2001 the clinical pregnancy rate would indeed have been in significantly in favour of rFSH. In other words, this difference in clinical pregnancy rate between rFSH and FSH-HP was only found in the older trials performed before 2000 and not in the trials performed after 2000, which explains why this difference was no longer detectable.

AUTHORS' CONCLUSIONS

Implications for practice

It appears that all available gonadotrophins are equally effective and safe. The choice of one or the other product will depend upon the availability of the product, the convenience of its use, and the associated costs.

Implications for research

We included 42 trials, entailing 9606 couples. Any specific differences are likely to be too small to justify further research.

ACKNOWLEDGEMENTS

We would like to thank authors of papers and representatives of pharmaceutical companies for providing extra information.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abate 2009

Methods	Open randomised controlled trial in three centre's in Italy. Based on a computer-generated randomisation list. Randomisation after adequate down-regulation, stratified by centre Allocation concealment unclear Timing March 2007 to October 2008. Power calculation not stated.
Participants	401 women with indication for IVF or ICSI, <3 prior oocyte retrievals, age 26-38 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: FSH-HP (Fostimon) Starting dose 225 IU. Down regulation with GnRHa (triptorelin acetate 0.1 mg/day s.c.) long protocol Transfer of 1to3 embryos IVF or ICSI.
Outcomes	Ongoing pregnancy rate Clinical pregnancy rate Number of pregnancy loss OHSS? Number of oocytes retrieved Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only. Funding is unclear. Additional information requested but not retrieved

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Based on a computer-generated randomisation list
Allocation concealment?	Unclear	No reference, and no acknowledgement of support from independent trials unit or industry
Blinding? All outcomes	No	The study was not formally blinded
Incomplete outcome data addressed? All outcomes	No	Summary outcome data tabled make no mention of exclusions, but clear from per-

Abate 2009 (*Continued*)

		centages given that not all participants included in all analyses
Free of selective reporting?	No	OHSS was an outcome according to the methods section but was not reported on, the pregnancy rates were presented as percentages
Free of other bias?	Yes	

Alvino 1995

Methods	Open randomised controlled trial Method of randomisation: a blocked randomisation code, inadequate concealment Power calculation not reported Not blinded
Participants	60 women undergoing IVF, <4 previous cycles, age 23to36 yrs
Interventions	Intervention: rFSH (Gonal F) Control: FSH-P (Metrodin). Both 225 IU daily for 5 days. Long down regulation with GnRHa (Leuprolide 0.5mg daily) IVF in all cycles Transfer of 2to3 embryos
Outcomes	Clinical pregnancy rate Number of embryo transferred OHSS rate Dose of gonadotrophin used
Notes	One treatment cycle only Funded by Serono

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	a computer generated blocked randomization code
Allocation concealment?	No	No reference to concealment
Blinding? All outcomes	No	Study described as "open"
Incomplete outcome data addressed? All outcomes	No	3 withdrawals noted, but not clear how many analysed in each group

Alvino 1995 (*Continued*)

Free of selective reporting?	Unclear	This cannot be clarified from the abstract
Free of other bias?	Yes	

Andersen 2006

Methods	Randomised, open-label, assessor-blind, parallel-group RCT Based on a computer-generated randomisation list by an independent statistician not involved in the study Sequentially numbered sealed envelopes used to conceal treatment allocation Blinded; all investigators, embryologists, laboratory personnel and sponsor staff, including the statistician responsible for analysis All handling of study medication was done by nurses and precaution taken to ensure treatment assignments were not available to the investigators Patients instructed not to discuss their drug assignment with the investigator All information regarding treatment allocation kept in locked cupboard not accessible by the investigator All randomisation envelopes inspected and accounted for before breaking of the blind Power calculation carried out
Participants	731 women with indication for IVF, <4 previous cycles, age 21 to 37 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: HP-HMG (Menopur) Starting dose 225 IU. Down regulation with GnRHa (triptorelin acetate 0.1 mg/day s.c., long protocol Transfer of 1to2 embryos All cycles IVF, no ICSI.
Outcomes	Live birth rate Ongoing pregnancy Clinical pregnancy rate Number of pregnancy loss Multiple pregnancy rate OHSS rate Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only. Frozen embryos derived from the study are followed-up for 3 yrs. Data not yet available Funded by Ferring.

Risk of bias

Item	**Authors' judgement**	**Description**

Andersen 2006 (*Continued*)

Adequate sequence generation?	Yes	Based on a computer-generated randomisation list by an independent statistician not involved in the study
Allocation concealment?	Yes	Sequentially numbered sealed envelopes used to conceal treatment allocation
Blinding? All outcomes	No	Open label study, but attempted blinding of all investigators, embryologists, laboratory personnel and sponsor staff, including the statistician responsible for analysis
Incomplete outcome data addressed? All outcomes	Yes	All pregnancy data were presented according to ITT principles. However, number of oocytes retrieved was presented per patient with oocytes. Dose of gonadotrophin used and treatment duration were presented per patient that received gonadotrophins. The actual number of women with oocyte retrieval and the number of women that received at least one dosage of gonadotrophins however were reported
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Antoine 2007

Methods	Randomized, controlled, investigator-blind multi-center trial (abstract) Based on a computer-generated randomisation list by an independent statistician not involved in the study Sequentially numbered sealed opaque envelopes used to conceal treatment allocation Blinded; all physicians and embryologists. Power calculation carried out (no of oocytes)
Participants	One hundred fifty IVF patients, <3 previous cycles, age 18to39 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: HP-FSH (Fostimon) Starting dose of 225 IU. Down regulation long protocol GnRHa. Both IVF and ICSI. Transfer of 1to3 embryos

Antoine 2007 (*Continued*)

Outcomes	Clinical pregnancy rate OHSS rate Number of oocytes retrieved Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only Funded by Institut Biochimique SA (IBSA), Switzerland. Additional information requested and retrieved from dr Cometti from IBSA Switserland

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Based on a computer-generated randomisation list by an independent statistician not involved in the study
Allocation concealment?	Yes	Sequentially numbered sealed opaque envelopes used to conceal treatment allocation
Blinding? All outcomes	No	All physicians and embryologists but not double blinded
Incomplete outcome data addressed? All outcomes	Unclear	This can not be determined from the extended abstract
Free of selective reporting?	Unclear	This can not be determined from the extended abstract
Free of other bias?	Unclear	This can not be determined from the extended abstract

Baker 2009

Methods	Randomized, controlled, investigator-blind multi-center trial Based on a computer-generated randomisation list by an independent statistician not involved in the study Sequentially numbered sealed opaque envelopes used to conceal treatment allocation Blinded; all physicians and embryologists. All handling of study medication was done by the study coordinators and precaution taken to ensure treatment assignments were not available to the physician investigators Study coordinators and patients instructed not to discuss their drug assignment with their physician All information regarding treatment allocation kept in locked cupboard not accessible by the treating physicians Power calculation carried out (no of oocytes)
Participants	One hundred fifty-two IVF patients, <3 previous cycles, age 18to39 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: HP-FSH (Fostimon) Starting dose of 300 IU. Down regulation after oral contraceptive pills with daily leuprolide acetate (long protocol) Both IVF and ICSI. Transfer of 1to3 embryos
Outcomes	Live birth rate Clinical pregnancy rate OHSS rate Number of oocytes retrieved Number of pregnancy loss Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only Funded by Institut Biochimique SA (IBSA), Switzerland. Additional information requested and retrieved from dr Valerie Baker

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Based on a computer-generated randomisation list by an independent statistician not involved in the study
Allocation concealment?	Yes	Sequentially numbered sealed envelopes
Blinding? All outcomes	No	Physicians and embryologists blinded, but not participants
Incomplete outcome data addressed? All outcomes	Yes	Main analyses based on numbers randomised

Baker 2009 (*Continued*)

Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Balasch 2003

Methods	Randomised, open-label, single-centre study. Allocation by using computer generated table on-site. Embryologist blinded. Ratio HMG versus rFSH was 1:1. Timing of trial unclear, 60 patients were randomised. Power calculation was not done
Participants	Sixty couples undergoing ICSI and having unexplained or male-related primary infertility. No previous IVF/ICSI cycles and age 26to37 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: HMG (Pergonal) im Starting dose 150 IU. Long luteal GnRHa protocol with a single depot triptorelin injection ICSI only. Transfer of 2to3 embryos
Outcomes	Live birth rate Clinical pregnancy rate OHSS rate Number of oocytes retrieved Number of pregnancy loss Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only No Funding. Additional information requested and retrieved from dr Balasch

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Allocation by using computer generated table on-site. Pairs of individuals matched prior to randomisation. Not clear from description whether pairs were allocated concurrently or sequentially
Allocation concealment?	No	Inadequate due to use of table on-site

Balasch 2003 (*Continued*)

Blinding? All outcomes	No	Embryologist was blinded but as the allocation was inadequate the effect of blinding cannot be considered adequate
Incomplete outcome data addressed? All outcomes	No	30 pairs of women allocated, only 50 individuals analysed and unclear whether these were 25 of the original pairs: "25 pairs of patients ... were finally considered" but also describes cancellation rate as "13.3% (4 patients) and 20% (6 patients)" in the two groups, implying that loss was not 5 pairs
Free of selective reporting?	Unclear	Key results not reported in valid format as unpaired analyses presented
Free of other bias?	No	Inappropriate analysis methods applied

Berger 1999

Methods	Randomised, open-label, multi-centre study (Abstract). Randomisation and allocation not described. Ratio rFSH vs FSH-HP was 1:1. No party was blinded. Timing of trial unclear. Power calculation was not done.
Participants	165 cycles in 148 couples undergoing IVF or ICSI. Number of previous cycles not known, female age <40
Interventions	Intervention: rFSH (Puregon) highly purified FSH (Metrodin-HP) Starting dose 150 IU for rFSH and 225 for FSH-HP. Long luteal GnRHa protocol with a single depot triptorelin injection ICSI only. Transfer of 2 embryos
Outcomes	Clinical pregnancy rate OHSS rate Number of oocytes retrieved Dose of gonadotrophin used
Notes	some couples had more than one cycle Funding unclear.

Risk of bias

Item	**Authors' judgement**	**Description**

Berger 1999 (*Continued*)

Adequate sequence generation?	Unclear	Described as "randomised" but no further detail
Allocation concealment?	Unclear	No reference in this conference abstract
Blinding? All outcomes	No	Described as "open"
Incomplete outcome data addressed? All outcomes	Unclear	No reference in this conference abstract
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	No	148 participants but 165 cycles counted as if statistically independent

Bergh 1997

Methods	RCT Computer-generated randomisation list. Only authorised access to randomisation list. Allocation using sealed numbered opaque envelopes. Blinded: administering physician and assessor Power calculation carried out
Participants	235 women undergoing assisted reproductive techniques, <4 previous ART cycles, female age 18to38
Interventions	Intervention: rFSH (Gonal-F) Control: highly purified FSH (Metrodin-HP) Starting dose Long down regulation with GnRHa (buserelin 300 uG) 3 times/day intranasally IVF and ICSI Transfer of 2to3 embryos
Outcomes	Dose of gonadotrophin used Clinical pregnancy rate Ongoing pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS rate Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Duration of treatment

Bergh 1997 (*Continued*)

Notes	One treatment cycle only Funded by Serono Extra information from dr Bergh on randomisation procedure

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list.
Allocation concealment?	Yes	Only authorised access to randomisation list, allocation using sealed numbered opaque envelopes (determined by correspondence with author)
Blinding? All outcomes	No	Administering physician and assessor but not participants
Incomplete outcome data addressed? All outcomes	Yes	Four post-randomisation exclusions described: one withdrew consent and three logistical errors 12 excluded from urinary arm "primarily because of poor ovarian response", but able to re-create ITT analysis for key outcomes
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Bosch 2008

Methods	Randomized, controlled, single-center trial. Randomisation based on a computer-generated randomisation list. The randomisation list was centralised at the institution's call centre, and the centre was contacted to allocate each randomised patient into a group Timing clear. Power calculation carried out (ongoing pregnancy was primary outcome)
Participants	Two hundred and eighty patients undergoing their first IVF/ICSI treatment. Female age 18to37 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: highly purified HP-HMG (Metrodin-HP) The starting dose for HMG and rFSH was 225 IU/day s.c. for the first two days of stimulation. Then, a serum E_2 determination was performed for individual adjustments. On stimulation Day 6, 0.25 mg of the GnRH antagonist Cetrorelix (Cetrotide®, Serono) was started daily, and continued until the end of stimulation

Bosch 2008 (*Continued*)

	Both IVF and ICSI cycles. Transfer of 1to3 embryos
Outcomes	Live birth rate Ongoing pregnancy Clinical pregnancy rate Number of pregnancy loss Multiple pregnancy rate OHSS rate Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only No pharmaceutical funding Additional information requested and retrieved from dr Bosch

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation based on a computer-generated randomisation list
Allocation concealment?	Yes	The randomisation list was centralised at the institution's call centre, and the centre was contacted to allocate each randomised patient into a group
Blinding? All outcomes	No	Described as "open label".
Incomplete outcome data addressed? All outcomes	Yes	Losses to follow-up described in CONSORT diagram. Possible to recreate ITT analyses
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Cheon 2004

Methods	RCT Methods of randomisation and allocation concealment not reported 'Double-blind' study: both the clinicians and the embryologists were blinded Power calculation not reported
Participants	241 women undergoing 254 cycles of COH for IVF and IVF-ET, < 4 previous cycles, female age 25 to 40 yrs
Interventions	Intervention: rFSH Control: highly purified FSH (Metrodin-HP) Short down regulation with GnRHa (Suprefact) IVF only Transfer of 2to4 embryos
Outcomes	Live birth rate Clinical pregnancy rate Cancellation rate (?? due to OHSS) No.of oocytes retrieved
Notes	No funding Some women underwent more than one cycle. Extra information requested and retrieved from dr Cheon on live birth rates, allocation remained unclear

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as "randomised" but no further detail
Allocation concealment?	Unclear	No reference
Blinding? All outcomes	No	Described as "double-blind" but does not refer to clinicians or participants
Incomplete outcome data addressed? All outcomes	Unclear	Outcmoes analysable for stated numbers of participants, but not clear whether number analysed was same as number randomised
Free of selective reporting?	No	Absence of adverse event reporting. Miscarriages only calculable by subtraction of live births from clinical pregnancies
Free of other bias?	Yes	

Dickey 2002

Methods	RCT, multicentric. Methods of randomisation: blocks-of-three design: SAS ProcPlan. Randomised into three groups Computer-generated central allocation. Power calculation based on oocytes retrieved.
Participants	177 women who met down-regulation criteria and planning to undergo IVF-ET). Female age 18-39 yrs, number of previous cycles not an inclusion criterion (see notes)
Interventions	Intervention: rFSH (Follistim) Control: highly purified FSH (Bravelle) SC Control: highly purified FSH (Bravelle) IM Long down regulation with GnRHa (leuprolide acetate 0.5 mg) daily sc IVF only Transfer of maximally 4 embryos
Outcomes	Dose of gonadotrophin used Clinical pregnancy rate Ongoing pregnancy rate Live birth rate Miscarriage rate OHSS rate Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Duration of treatment
Notes	One treatment cycle only. Funded by Ferring. Additional information was obtained from Ferring USA (via dr Marshall)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated but in blocks of 3 so that every third participant predictable
Allocation concealment?	Unclear	No reference to concealment
Blinding? All outcomes	No	Described as "open-label"
Incomplete outcome data addressed? All outcomes	Yes	10 post randomisation exclusions described. Possible to re-create ITT analyses
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.

Dickey 2002 (*Continued*)

Free of other bias?	Unclear	Suspicion of publication bias. See comments for Dickey 2003.

Dickey 2003

Methods	RCT, multicentric. Methods of randomisation: blocks-of-six design: SAS ProcPlan Computer-generated central allocation. Power calculation based on oocytes retrieved.
Participants	120 women who met down-regulation criteria and planning to undergo IVF-ET (no ICSI). Female age 18to39 yrs, number of previous cycles not an inclusion criterion
Interventions	Intervention: rFSH (Follistim) Control: highly purified FSH (Bravelle) Long down regulation with GnRHa (leuprolide acetate 0.5 mg) daily sc IVF only Transfer of maximally 4 embryos
Outcomes	Dose of gonadotrophin used Clinical pregnancy rate Ongoing pregnancy rate Live birth rate Miscarriage rate OHSS rate Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Duration of treatment
Notes	One treatment cycle only. Funded by Ferring. Additional information was obtained from Ferring USA

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Methods of randomisation: blocks-of-six design: SAS ProcPlan
Allocation concealment?	Unclear	No reference to concealment
Blinding? All outcomes	No	Described as "nearly identical in design to Dickey 2002

Dickey 2003 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Possible to re-create ITT analyses.
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	No	Strong suggestion of publication bias in selection and method of presentation: "This report presents the pooled data from two independent trials...The present data form part of the clinical development program...". Includes data from two arms of Dickey 2002 as if part of single trial.

Drakakis 2002

Methods	RCT Methods of randomisation and allocation concealment not reported Power calculation not reported Not blinded
Participants	70 women undergoing IVF-ET or ICSI-ET
Interventions	Intervention: rFSH Control: urinary FSH
Outcomes	Clinical pregnancy rate No.of oocytes retrieved
Notes	Long down regulation with GnRHa (buserelin acetate intranasally) Funding not stated It was not stated what brand of rFSH or urinary FSH was used, however the urinary FSH contained 75% FSH and 25% LH

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"randomly divided into two groups" without further detail.
Allocation concealment?	Unclear	No reference to concealment
Blinding? All outcomes	No	No reference to blinding and groups treated differently to determine suitable dose

Drakakis 2002 (*Continued*)

Incomplete outcome data addressed? All outcomes	No	Clear from denominator that reported pregnancy rate includes fewer participants than randomised, but not clear for other reported outcomes
Free of selective reporting?	No	Absence of adverse event reporting and no follow-up beyond undefined "pregnancy rate"
Free of other bias?	Yes	

EISG 2002

Methods	RCT Randomisation achieved by computer-generated allocation sequence and copies of randomised list distributed in sealed, opaque numbered envelopes stratified for IVF and ICSI. Size of randomisation blocks was four Power calculation carried out Not blinded.
Participants	781 women undergoing IVF/ICSI. Female age 23/36 yrs and less than 4 previous ART cycles
Interventions	Intervention: rFSH (Gonal F) Control: HMG-HP (Menopur) Starting dose 225 IU. Long luteal GnRHa protocol with triptorelin, buserelin or leuprolid or depot injections with triptorelin or goserelin IVF and ICSI Transfer of 1to3 embryos
Outcomes	Clinical pregnancy rate Ongoing pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS rate Dose of gonadotrophin used Duration of stimulation Both IVF and ICSI.
Notes	Long down regulation with GnRHa Funded by Ferring

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated allocation sequence.

EISG 2002 (*Continued*)

Allocation concealment?	Yes	Sealed, opaque numbered envelopes.
Blinding? All outcomes	No	Described as "open label".
Incomplete outcome data addressed? All outcomes	Yes	54 post-randomisation exclusions before therapy suggests poor timing of randomisation, but specified by group. Further 34 excluded for "protocol violation" but reasons and allocated group given for all. Possible to re-create ITT analyses
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Unclear	Unclear reporting and selection of different subsets of patients for particular endpoints

Ferraretti 1999

Methods	Randomised trial. Allocation by drawing from a random table. 4-arm RCT, 2 arms used (rFSH vs FSH-HP) Not blinded Power calculation not carried out
Participants	141 women undergoing assisted reproductive techniques with no ovarian response in a previous cycle. Female age 29to45 yrs
Interventions	Intervention: rFSH (Gonal-F) Control: highly purified uFSH (Metrodin-HP) Starting dose 300 IU No down regulation Transfer of maximally 3 embryos
Outcomes	Clinical pregnancy rate Miscarriage rate Number of oocytes retrieved
Notes	One treatment cycle only No funding Extra information retrieved from dr Ferraretti on funding and randomisation procedure

Risk of bias

Item	**Authors' judgement**	**Description**

Ferraretti 1999 (*Continued*)

Adequate sequence generation?	Yes	A random table was used
Allocation concealment?	No	No, allocation done by drawing
Blinding? All outcomes	No	Appears unlikely given treatments compared
Incomplete outcome data addressed? All outcomes	Unclear	Hard to say on basis of available abstract
Free of selective reporting?	Unclear	Unclear reporting
Free of other bias?	Unclear	Unclear reporting

Franco 2000

Methods	RCT Randomisation by drawing lots, using a randomisation table No allocation concealment Power calculation not reported Not blinded
Participants	120 women undergoing ICSI
Interventions	Intervention: rFSH (Gonal-F) Control: highly purified FSH (Metrodin-HP) Starting dose 150 IU rFSH and 225 IU FSH-HP Long GnRHa protocol with leuprolide acetate 0.5 mg daily ICSI only Transfer of maximally 4 embryos
Outcomes	Live birth rate Clinical pregnancy rate Multiple pregnancy rate No of oocytes retrieved OHSS rate
Notes	Funded by Serono

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Apparently self-contradictory information: "by drawing lots, using a randomisation table previously elaborated for the study"

Franco 2000 (*Continued*)

Allocation concealment?	Unclear	No reference.
Blinding? All outcomes	No	No reference and appears unlikely given treatments compared
Incomplete outcome data addressed? All outcomes	Yes	Numbers randomised and analysed were equal
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Frydman 2000

Methods	Double-blind RCT Methods of randomisation was sealed numbered envelopes 'Double-blind' study: unclear which party was blind Power calculation carried out
Participants	278 women undergoing IVF. Female age 18 to 38 yrs and less than 4 previous ART cycles
Interventions	Intervention: rFSH (Gonal-F) Control: highly purified FSH (Metrodin-HP) Starting dose 150 IU daily Downregulation long GnRHa protocol either depot, sc or intranasal IVF only Transfer of 2to5 embryos
Outcomes	Live birth rate Clinical pregnancy rate Multiple pregnancy rate OHSS rate Dose of gonadotrophin used Duration of stimulation
Notes	Long down regulation with GnRHa (Leuprorelin or buserelin) One cycle only Funded by serono Righini (reference at Studies awaiting classification) possible double publication

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation list prepared using a computer program.

Frydman 2000 (*Continued*)

Allocation concealment?	Unclear	No reference
Blinding? All outcomes	Unclear	"Double blind" but no description of which parties. Other studies in review describe double-blind as investigator and embryologist rather than participant
Incomplete outcome data addressed? All outcomes	Yes	Possible to trace drop-out at each stage of treatment
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Gallego 2003a

Methods	RCT Randomisation using a table of random numbers Methods of allocation concealment not clear No blinding Power calculation not reported
Participants	100 women undergoing IVF, aged below 40 yrs, no previous IVF cycles
Interventions	Intervention: rFSH (Puregon) Control: FSH (Neofertinorm, FSH-HP) Starting dose 150 IU for rFSH and 225 IU for FSH-HP daily Downregulation long GnRHa protocol (leuprorelin 0,5 mg/day). IVF only Transfer of maximally 3 embryos
Outcomes	Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS rate No. of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Funding not reported Tried but failed to contact dr Gallego for more information

Risk of bias

Item	**Authors' judgement**	**Description**

Gallego 2003a (*Continued*)

Adequate sequence generation?	Yes	Randomisation using a table of random numbers
Allocation concealment?	Unclear	No reference to concealment
Blinding? All outcomes	No	No reference
Incomplete outcome data addressed? All outcomes	Yes	Possible to trace drop-out at each stage of treatment
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Germond 2000

Methods	Randomised parallel trial in two centre's (abstract). Trial recruited between jantoJuly 1999 Not blinded Power calculation not reported
Participants	79 women undergoing assisted reproductive techniques, above 35 years of age
Interventions	Intervention: rFSH (Gonal-F) Control: highly purified FSH (Metrodin-HP) Starting dose 225 IU No down regulation Transfer of 2to3 embryos
Outcomes	Clinical pregnancy rate
Notes	One treatment cycle only Funding unknown

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No detail in abstract
Allocation concealment?	Unclear	No detail in abstract
Blinding? All outcomes	No	No reference, and appears unlikely given treatments compared

Germond 2000 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	No detail in abstract
Free of selective reporting?	Unclear	No detail in abstract
Free of other bias?	Unclear	No detail in abstract

Ghosh 1999

Methods	Randomised trial (abstract). Allocation using opaque sequentially numbered sealed envelopes Not blinded Power calculation not carried out IVF only
Participants	47 women undergoing IVF, female age <37 yrs, < 4 previous IVF cycles
Interventions	Intervention: rFSH (Puregon) Control: highly purified FSH (Metrodin-HP) Starting dose 150 IU (rFSH) and 225 IU (FSH-HP) resp. Long luteal GnRHa protocol with buserelin s.c. 500 µg daily, reduced to 200 µg IVF only Transfer of maximally 3 embryos
Outcomes	Clinical pregnancy rate Number of oocytes retrieved
Notes	One treatment cycle only Funding unknown Extra information requested but no response Chakravarty (reference at Studies awaiting classification) possible double publication

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated list
Allocation concealment?	Yes	Allocation using opaque sequentially numbered sealed envelopes
Blinding? All outcomes	No	No reference
Incomplete outcome data addressed? All outcomes	Unclear	Appears that randomised and analysed numbers the same for cumulative pregnancy rate, but not necessarily for other outcomes

Ghosh 1999 (*Continued*)

Free of selective reporting?	No	Not all outcomes reported in sufficient detail, and some key outcomes missing
Free of other bias?	Yes	

Gordon 2001

Methods	Randomised clinical single centre trial Assessor blind Randomisation by computer allocation by the hospital pharmacist. A total of 128 patients were studied of whom 29 received HMG, 39 received rFSH and 60 received urinary FSH Power calculation not done
Participants	128 women undergoing IVF, age 18to38 yrs, no previous IVF cycles
Interventions	Intervention: rFSH Control: FSH and HMG (humegon) Starting dose 225 IU. Long luteal GnRHa protocol with buserelin acetate 0.15 mg nasal spray IVF, no ICSI. Transfer of 1to3 embryos
Outcomes	Live birth rate Clinical pregnancy rate Miscarriage rate No. of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Long down regulation with GnRHa (Buserelin) No pharmaceutical funding Extra information requested and retrieved from dr Uma Gordon

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Randomized computer-generated code".
Allocation concealment?	Yes	Third-party allocation by the hospital pharmacist.
Blinding? All outcomes	No	"preparations differed in appearance", but administered by "nursing staff independent of clinician's activities"

Incomplete outcome data addressed? All outcomes	Yes	Numbers randomised and analysed the same.
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Hedon 1995

Methods	RCT Assessor-blind Randomised in blocks in a 3:2 ratio. Randomisation using a randomisation list. Central allocation of a subject number in order of entrance, which corresponded to medication boxes with the medication power calculation not reported
Participants	99 women undergoing IVF, female age 18to39, <4 previous ART cycles
Interventions	Intervention: rFSH (Puregon) Control: FSH-P (Metrodin) Starting dose 150 IU (rFSH) and 225 IU (FSH-P) resp. Long luteal GnRHa protocol with triptorelin 0.1 mg s.c. daily IVF only Transfer of maximally 3 embryos
Outcomes	Clinical pregnancy rate Ongoing pregnancy rate Multiple pregnancy rate No of oocytes retrieved OHSS rate Dose of gonadotrophin used Duration of stimulation
Notes	Funded by Organon 1 cycle only, no cryo cycles included

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation using a randomisation list on a 3:2 ratio..
Allocation concealment?	Yes	Central allocation of a subject number in order of entrance, which corresponded to medication boxes with the medication (size

Hedon 1995 (*Continued*)

		of blocks not known though)
Blinding? All outcomes	No	Assessor-blind only
Incomplete outcome data addressed? All outcomes	Yes	9 participants excluded post-randomisation who did not reach stage of receiving FSH treatment. Possible to re-create ITT analyses for review
Free of selective reporting?	Unclear	Further outcome details (including live birth) given in subsequent publication, raising concern of potential publication bias
Free of other bias?	Yes	

Hompes 2008

Methods	Multicentre RCT in the Netherlands. Allocation by central computer randomisation using an interactive voice response system. Randomisation in permuted blocks of random size stratified on centre. Not blinded. Ratio HMG vs rFSH was 1:1. Trial took place between and , 629 patients were randomised. Power calculation based on ongoing pregnancy rate per cycle (1 first cycle only). Supported by Ferring Pharmaceuticals
Participants	Couples with an indication for IVF or ICSI undergoing their first IVF-ICSI treatment due to male factor, tubal factor, unexplained, combination or other factors. Women were healthy, aged 18to39 (mean 32), no PCOS, no hypogonadotropic hypogonadism, and FSH day above 12 IU-L. BMI was not an exclusion criterion (mean BMI 24)
Interventions	Long GnRHa protocol with triptorelin acetate 0.1 mg/day sc. Ovarian hyperstimulation with HP-HMG (Menopur) sc daily vs rFSH (Follitropin Alpha, Gonal-F), 225 IU sc daily for 5 days, then adjusted. 250 uG sc rHCG when >=3 follicles of >=17 mm. IVF performed in all cycles, 1to2 embryos transferred on day 3. Luteal support with vaginal progesterone gel from day of ET until conformation of clinical pregnancy or neg betaHCG test
Outcomes	Primary endpoint: ongoing pregnancy. Secondary endpoints: live birth, clinical pregnancy, early pregnancy loss, multiple pregnancy, oocytes retrieved, fertilisation rate, embryo quality, OHSS, cancellation rate, total dose of gonadotropin, days of stimulation
Notes	Additional information was obtained from the authors and Ferring Pharmaceuticals in The Netherlands. Clinical pregnancy defined as at least 1 IUG with fetal heartbeat 5to6 weeks after ET. Ongoing pregnancy was defined as at least 1 viable IUG at 10 weeks after ET. Supported by Ferring Pharmaceuticals
Risk of bias	

Hompes 2008 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Allocation by computer randomisation.
Allocation concealment?	Yes	Central procedure using an interactive voice response system
Blinding? All outcomes	No	Described as "open-label".
Incomplete outcome data addressed? All outcomes	Yes	Possible to trace participants dropping out at each stage of treatment and re-create ITT analyses
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Hoomans 1999

Methods	RCT Randomisation using a random number table. Authorised access to randomised list Allocation using sealed envelopes, opaque and numbered 'Open' trial, not blinded Power calculation carried out
Participants	169 women undergoing IVF, female age 18to39 yrs, < 3 previous cycles
Interventions	Intervention: rFSH (Puregon) Control: highly purified FSH (Metrodin-HP) Starting dose 150 IU (rFSH) and 225 IU (FSH-HP) resp. Long luteal GnRHa protocol with buserelin s.c. daily IVF only Transfer of maximally 3 embryos
Outcomes	Clinical pregnancy rate Miscariage rate No of oocytes retrieved OHSS rate Dose of gonadotrophin used Duration of stimulation
Notes	One cycle only Funded by Organon Extra information from dr Hoomans on randomisation procedure and outcomes
Risk of bias	

Hoomans 1999 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation using a random number table.
Allocation concealment?	Yes	Allocation using sealed envelopes, opaque and numbered. Only authorised access to randomised list
Blinding? All outcomes	No	Described as "open"
Incomplete outcome data addressed? All outcomes	Yes	4 participants post-randomisation failed to reach FSH treatment. Sufficient detail given by group on drop outs at all stages to recreate ITT analysis
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Hugues 2001

Methods	RCT Randomisation by random number table Allocation in concealed envelopes Not blinded Power calculation not reported
Participants	88 women undergoing IVF, female age 18to38 yrs,
Interventions	Intervention: rFSH (Follitropin a and Follitropin b) Control: highly purified FSH (Metrodin-HP) Startin dose 100 IU rFSH vs 150 IU FSH-HP Short down regulation with 25 *uG* sc daily GnRHa (decapeptyl) IVF only Transfer of maximally 3 embryos
Outcomes	Pregnancy rate Ongoing pregnancy rate Ectopic pregnancy rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Not funded by a pharmaceutical company

Hugues 2001 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation by random number table
Allocation concealment?	Yes	Allocation in concealed numbered envelopes
Blinding? All outcomes	No	Described as "not blinded".
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Jansen 1998

Methods	RCT Randomisation by subject number from a randomisation list corresponding with patient boxes in which medication was kept Allocation at a ratio of 3:2 (rFSH/HMG) Assessor blind Power calculation carried out
Participants	109 women undergoing IVF, female age <40 yrs, <3 previous ART cycles
Interventions	Intervention: rFSH (Puregon) Control: HMG (Humegon) Starting dose: 150 IU rFSH vs 225 IU HMG IVF only No down regulation Transfer of 1to3 embryos
Outcomes	Clinical pregnancy rate Ongoing pregnancy rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	One cycle only Funded by Organon Additional information was obtained from dr Jansen

Jansen 1998 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation.
Allocation concealment?	Yes	Centralised scheme.
Blinding? All outcomes	No	Assessor blind only.
Incomplete outcome data addressed? All outcomes	Yes	20 participants failed to receive gonadotrophin treatment, and further 23 did not reach embryo transfer. sufficient detail given to re-create ITT analyses
Free of selective reporting?	Unclear	Further outcome details (including live birth) given in subsequent publication, raising concern of potential publication bias
Free of other bias?	Unclear	"the study had to be truncated prematurely due to non-medical factors outside our control"

Kilani 2003

Methods	RCT Random number table made by a computer Randomisation sequence and sealed envelops containing treatment assignments prepared at separate location and conducted by separate personnel Power calculation carried out Blind to ultrasound and laboratory (performing hormone assay) personnel
Participants	100 women undergoing IVF. Female age 18to37, none taken more than 3 IVF/ICSI cycles in the past
Interventions	Intervention: rFSH (Gonal-F) Control: HMG (HMG HP Menopur) Starting dose 150 IU. Long down regulation with GnRHa (Triptorelin) Both IVF and ICSI cycles. transfer of 1to2 embryos
Outcomes	Live birth rate Term pregnancy rate Multiple pregnancy rate Miscarriage rate

Kilani 2003 (*Continued*)

	No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	No pharmaceutical funding.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table made by a computer.
Allocation concealment?	Yes	Numbered, sealed envelopes prepared independently
Blinding? All outcomes	No	Partial only: ultrasound and laboratory personnel
Incomplete outcome data addressed? All outcomes	Yes	Numbers randomised and analysed the same.
Free of selective reporting?	Unclear	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Kornilov 1999

Methods	RCT, four groups (rFSH, FSH-HP, FSH-P, HMG) Randomisation procedure not known No power calculation Not blinded
Participants	124 women underwent 137 cycles if IVF-ET
Interventions	Intervention: rFSH (Gonal-F) 28 cycles Control: FSH-HP (Metrodin HP) 35 cycles, FSH-P (Metrodin) 34 cycles, HMG (Humegon) 40 cycles Starting dose 150 IU - 300 IU. Long down regulation with GnRHa (Triptorelin) IVF cycles. transfer of 2to3 embryos
Outcomes	Clinical pregnancy rate per embryo transfer Multiple pregnancy rate per embryo transfer Miscarriage rate per embryo transfer No of oocytes retrieved Dose of gonadotrophin used

Kornilov 1999 (*Continued*)

	Duration of stimulation
Notes	Pregnancy rate was not presented per randomised woman, treated groups did not match in number (40 vs 28 cycles) and there was a significant difference in age distribution between groups. More information was requested at several instances but the authors did not respond

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No reference to method of randomisation
Allocation concealment?	Unclear	No reference to concealment
Blinding? All outcomes	No	No reference to blinding - unlikely given treatments compared
Incomplete outcome data addressed? All outcomes	No	Unclear on numbers of participants randomised. Percentages rather than numbers given for various outcomes and failure to distinguish 'participants' from 'cycles' prevents assured calculation of drop-out
Free of selective reporting?	No	Absence of OHSS data. Incomplete reporting of other outcomes
Free of other bias?	No	Data described as cycles rather than participants - may include multiple cycles for individual women. Marked difference in average age between groups

Lenton 2000

Methods	RCT (open) Computer-generated randomisation (in blocks of 4), stratified by centre, using sealed envelopes containing the name of the drug to be used Not blinded Power calculation carried out
Participants	168 women undergoing IVF with female age 18to38 and no previous ART cycle
Interventions	Intervention: rFSH (Follitropin alpha, Gonal-F) Control: highly purified FSH (Metrodin-HP) Starting dose: 150 IU daily Downregulation with long GnRHa protocol with buserelin (900 uG intra nasal daily) IVF or ICSI Transfer of 1to2 embryos

Lenton 2000 (*Continued*)

Outcomes	Live birth rate Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Long down regulation with GnRHa (Buserelin) Funded by Serono

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation.
Allocation concealment?	Yes	Sequentially numbered, sealed opaque envelopes.
Blinding? All outcomes	No	Described as "open".
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Machado 1999

Methods	Randomised trial (abstract). Allocation by allocation by drawing straws 4 arm study, 2 arms with CC not included here Not blinded Power calculation not carried out
Participants	79 cycles in 71 women undergoing assisted reproductive techniques. Female age 26to43
Interventions	Intervention: rFSH (Puregon) Control: highly purified FSH (Metrodin-HP) Starting dose 300 IU No down regulation Transfer of maximally 4 embryos

Machado 1999 (*Continued*)

Outcomes	Clinical pregnancy rate
Notes	Some women had more than one cycle Requested extra information but no info yet. No response authors Funded by Serono

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Allocation by allocation by drawing straws allowing no verification of process
Allocation concealment?	No	Allocation by allocation by drawing straws
Blinding? All outcomes	No	Not formally blinded and not well concealed
Incomplete outcome data addressed? All outcomes	Unclear	This could not be determined from the abstract
Free of selective reporting?	No	Complete data was only available for clinical pregnancy
Free of other bias?	No	Some women had more than one cycle.and not possible to distinguish repeat cycles from report

Meden-Vrtovec 2003

Methods	RCT Randomisation by tossing coins Allocation status in sequentially number envelopes Authorised access to randomised list Not blinded No power calculation
Participants	131 women undergoing IVF
Interventions	Intervention: rFSH Control: FSH-P
Outcomes	Pregnancy rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation

Meden-Vrtovec 2003 (*Continued*)

Notes	No down regulation Funded by the Ministry of Science Extra information from dr Meden-Vrtovec on randomisation procedure and on live births

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomisation by tossing coins, allowing no verification of process
Allocation concealment?	Unclear	Allocation status reported in correspondence to use sequentially numbered envelopes. Unclear how this is compatible with coin toss method
Blinding? All outcomes	No	Reported in correspondence.
Incomplete outcome data addressed? All outcomes	Yes	Appears that numbers randomised and analysed were equal.
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	No	Reported in correspondence to be part of a larger trial, raising concern of publication bias

Mohamed 2006

Methods	Randomised, open-label, parallel-group RCT Allocation by computer on site with randomisation based on a computer-generated randomisation list Not blinded Power calculation carried out
Participants	257 women with indication for IVF, age above 39 yrs, number of previous cycles not an inclusion criterion but women nulliparous
Interventions	Intervention: rFSH (Gonal-F) Control: HP-HMG (Fostimon) Starting dose 300 IU. Down regulation with GnRHa (buserelin 0.4 mg/day s.c., long protocol Transfer of maximally 3 embryos All cycles IVF, no ICSI.

Mohamed 2006 (*Continued*)

Outcomes	Clinical pregnancy rate Number of pregnancy loss Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Treatment duration
Notes	One treatment cycle only. Not funded Additional information on randomisation, allocation concealment, funding and on on-going pregnancies was obtained from dr Sbracia

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list.
Allocation concealment?	Unclear	No reference to concealment
Blinding? All outcomes	No	No actual blinding
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses
Free of selective reporting?	No	Multiple pregnancies not reported although these must have been known from the fetal heart beat monitoring at 4 weeks after transfer. Outcome definitions not clear
Free of other bias?	Yes	

Nardo 2000

Methods	RCT Methods of randomisation and allocation concealment not reported Assessor-blind Power calculation not reported
Participants	110 women undergoing IVF
Interventions	Intervention: rFSH (Gonal F, Puregon) Control: highly purified FSH (Metrodin-HP) Starting dose: Long down regulation with GnRHa (Leuprorelin)

Nardo 2000 (*Continued*)

Outcomes	Take home baby rate Pregnancy rate OHSS rate Miscarriage rate No of oocytes retrieved Duration of stimulation
Notes	Funding not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No reference to method of randomisation.
Allocation concealment?	Unclear	No reference to concealment.
Blinding? All outcomes	No	Assessor-blind only.
Incomplete outcome data addressed? All outcomes	Yes	Numbers randomised and analysed appear to be equal.
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Ng 2001

Methods	RCT Randomisation using computer generated random numbers, in sealed sequential envelopes opened by nurses not involved in the study Assessor-blind Power calculation carried out
Participants	40 women undergoing ICSI, female age <39, no details on number of previous ART cycles
Interventions	Intervention: rFSH (Gonal F) Control: HMG (Pergonal) Starting dose 300 IU for 2 days, then 150 IU. Long down regulation with GnRHa (Buserelin) 0.15 mg nasal spray 4 times daily ICSI in all cycles. Transfer of 1to3 embryos.

Ng 2001 (*Continued*)

Outcomes	Live birth rate Clinical pregnancy rate Multiple pregnancy rate Ectopic pregnancy rate Miscarriage rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	No pharmaceutical funding. Extra information obtained on randomisation procedure, funding and pregnancy data from dr Ng

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation using computer generated random numbers.
Allocation concealment?	Yes	Allocation using sealed sequential envelopes opened by nurses not involved in the study
Blinding? All outcomes	No	Assessor-blind only
Incomplete outcome data addressed? All outcomes	Yes	Numbers randomised and analysed were equal
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Out 1995

Methods	RCT multicentric (18 centre's) Randomisation using a randomisation list. Central allocation of a subject number in order of entrance, which corresponded to medication boxes with the medication Assessor blind Power calculation carried out Randomised at a ratio of 3:2 (rFSH:FSH-P)
Participants	1027 women undergoing IVF, female age 18to39 and <4 previous IVF cycles

Out 1995 (*Continued*)

Interventions	Intervention: rFSH (Puregon) Control: FSH-P (Metrodin) Starting dose: 150 IU rFSH vs 225 IU FSH-P Long down regulation with GnRHa (Buserelin 150 uG 4 time daily) IVF only Transfer of maximally 3 embryos
Outcomes	Clinical pregnancy rate Ongoing pregnancy rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Funded by Organon (all authors were from Organon NL) Extra information on randomisation procedure

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No reference to randomisation method
Allocation concealment?	Unclear	Description of sequentially numbered medication boxes, but no reference to concealment
Blinding? All outcomes	No	Assessor-blind only
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses
Free of selective reporting?	Unclear	Further outcome details (including live birth) given in subsequent publication, raising concern of potential publication bias
Free of other bias?	Yes	

O′ Dea 1993

Methods	Randomised trial (abstract). Allocation method unknown. Not blinded Power calculation not carried out IVF only
Participants	47 women undergoing IVF
Interventions	Intervention: rFSH (Puregon) Control: highly purified FSH (Metrodin-HP) Starting dose 150 IU (rFSH) and 225 IU (FSH-HP) resp. Long luteal GnRHa protocol with leuprolide acetate 0.5 mg s.c. daily Unclear how many embryos were transferred
Outcomes	Clinical pregnancy rate Miscarriage rate
Notes	One treatment cycle only Funded by Serono More information asked - study too old

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No reference to method.
Allocation concealment?	Unclear	No reference to concealment.
Blinding? All outcomes	No	Described as "open".
Incomplete outcome data addressed? All outcomes	Unclear	This could not be determined from the abstract
Free of selective reporting?	No	Only usable data on clinical pregnancy and miscarriage rate.
Free of other bias?	Unclear	This could not be determined from the abstract

Rashidi 2005

Methods	Randomised controlled single centre trial. Randomisation by a computer-generated list of random numbers, which were placed in sealed envelopes Embryologists were blinded to treatment. Power calculation carried out (based on metaphase II oocyte number)
Participants	Sixty women undergoing ovarian stimulation for ICSI. Female age <=35 yrs
Interventions	Intervention: rFSH Control: HMG Starting dose 150 IU Down regulation in a long protocol with decapeptyl 3.75 mg IM Transfer of maximally 4 embryos
Outcomes	Live birth rate Clinical pregnancy rate Number of pregnancy loss Multiple pregnancy rate OHSS rate Number of oocytes retrieved Number of embryo transferred Dose of gonadotrophin used Treatment duration
Notes	No pharmaceutical funding

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated list of random numbers.
Allocation concealment?	Unclear	No detail beyond "sealed envelopes".
Blinding? All outcomes	No	Embryologist only
Incomplete outcome data addressed? All outcomes	Yes	Numers randomised and analysed were equal.
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

RHFSHG 1995

Methods	RCT Randomisation using computer-generated random number sequence in sealed opaque numbered envelopes No power calculation reported No blinding
Participants	127 women undergoing IVF, female age 18to38 yrs and < 4 previous IVF cycles
Interventions	Intervention: rFSH Control: FSH-P Starting dose 225 IU daily Long down regulation with GnRHa (Buserelin 200 uG s.c. daily) IVF in all cycles. Transfer of maximally 5 embryos.
Outcomes	Live birth rate Ongoing pregnancy rate Clinical pregnancy rate Multiple pregnancy rate Ectopic pregnancy rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Funded by Serono

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number sequence.
Allocation concealment?	Yes	Sealed opaque numbered envelopes.
Blinding? All outcomes	No	Described as "open".
Incomplete outcome data addressed? All outcomes	Unclear	4 post-randomisation exclusions - 3 neither treatment and 1 both treatments received - not reported intended group allocation. Otherwise possible to trace participants reaching each stage
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Schats 2000

Methods	RCT (Data pooled from 2 studies) Randomised using computer-generated list. Allocation list held in Pharmacy. Sequentially numbered sealed envelopes used Assessor blind Power calculation carried out
Participants	496 women undergoing IVF/ICSI with female age 18to38 and <3 previous ART cycles
Interventions	rFSH (Gonal F) Control: FSH (Metrodin HP) Starting dose: 150 IU daily Long down regulation with GnRHa (Buserelin or Leuprolide) IVF or ICSI Transfer of maximally 3 embryos.
Outcomes	Delivery rate Clinical pregnancy rate Miscarriage rate Multiple pregnancy rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	One cycle only Funded by Serono Extra information from dr Schats on the allocation procedure

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated list.
Allocation concealment?	Yes	Held in Pharmacy. Sequentially numbered sealed envelopes.
Blinding? All outcomes	No	Partial: assessor-blind
Incomplete outcome data addressed? All outcomes	Yes	Possible to trace participants reaching each stage
Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Unclear	Not clear how and when the decision was taken to combine the two studies ('Feronia'

Schats 2000 (*Continued*)

		and 'Apis') "to make the study more powerful" (communication from author)

Selman 2002

Methods	RCT Randomisation by using computer-generated list. Allocation using sequentially numbered sealed envelopes No power calculation No blinding
Participants	267 women undergoing a first IVF/ICSI cycle with female age between 18to38 yrs
Interventions	Intervention: rFSH (Gonal F) Control: highly purified FSH (Metrodin-HP, Fostimon) Starting dose: 225 IU daily Long down regulation with GnRHa (Triptorelin) Transfer of maximally 3 embryos
Outcomes	Live birth rate Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	One cycle only No funding dr Selman provided extra information

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation by using computer-generated list.
Allocation concealment?	Yes	Allocation using sequentially numbered sealed envelopes.
Blinding? All outcomes	No	Described as "open".
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses

Selman 2002 (*Continued*)

Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

Strehler 2001

Methods	RCT, open label, single centre Randomisation based on a computer-generated randomisation list. Allocation by computer Timing January 1998 and June 1999 Power calculation not reported
Participants	578 women undergoing IVF of ICSI, female age <40 and <5 previous ART cycles
Interventions	Intervention: rFSH (Gonal F) Control: HMG (Menogon) Starting dose 150to450 IU Short down regulation with GnRHa (Nefarelin acetate) IVF and ICSI Transfer of 1to3 embryos
Outcomes	Clinical pregnancy rate Multiple pregnancy rate No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Funding not stated Extra information from dr Strehler.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation.
Allocation concealment?	Yes	Central allocation by computer.
Blinding? All outcomes	No	No reference to blinding and seems unlikely given treatments
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses
Free of selective reporting?	Unclear	Key outcomes - live birth and OHSS rates - not reported. Live birth may not have been recorded, but OHSS or its absence should

Strehler 2001 (*Continued*)

		have been apparent in the study timeframe
Free of other bias?	Yes	

Westergaard 2001

Methods	RCT, single centre Randomisation based on a computer-generated randomisation list. Computerised allocation on day 14 after adequate down-regulation Trial took place between October 1998 and January 2000 Not blinded No power calculation performed
Participants	379 women undergoing IVF, female age 21to39, first IVF attempt 71%
Interventions	Intervention: rFSH (Gonal F) Control: HMG (Menogon) Starting dose: 225 IU Long luteal GnRHa protocol with buserelin acetate 0.15 mg nasal spray 4 times daily or 0.5 mg SC for 14 days IVF and ICSI Transfer of 1to2 embryos
Outcomes	Live birth rate Clinical pregnancy rate Multiple pregnancy rate OHSS No of oocytes retrieved Dose of gonadotrophin used Duration of stimulation
Notes	Unconditionally supported by Ferring dr Westergaard provided extra information on funding, randomisation procedure and drop-outs (there where no drop-outs)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation list.
Allocation concealment?	Unclear	On-site computer program.
Blinding? All outcomes	No	No reference to blinding and seems unlikely given treatments
Incomplete outcome data addressed? All outcomes	Yes	Drop-outs described in sufficient detail to allow re-creation of ITT analyses

Westergaard 2001 (*Continued*)

Free of selective reporting?	Yes	Key outcomes reported in sufficient detail for inclusion.
Free of other bias?	Yes	

rFSH - recombinant follicle stimulating hormone
uFSH - urinary follicle stimulating hormone
uFSH-HP highly purified follicle stimulating hormone
HMG human menopausal gonadotrophin
HP-HMG - highly purified menotropin
GnRHa - gonadotrophin-releasing hormone agonist
OHSS - ovarian hyperstimulation syndrome
s.c. - subcutaneously
IM - intra muscular
COH - controlled ovarian hyperstimulation
IVF - in vitro fertilisation
ICSI - intracytoplasmic sperm injection
ET - embryo transfer

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

Study	Reason for exclusion
Dickey 2003b	Abstract. Duplicate of Dickey 2003 study.
Duijkers 1997	Quasi randomised. Used alternating day allocation. Included 20 couples. Published in a Thesis.
Manassiev 1997	Not truly randomised, allocation by area of residence.
Martinez 2008	Compared two down regulations methods besides HMG vs rFSH in oocyte donors (leuprorelin + human menopausal gonadotropins (HMG) versus ganirelix + recombinant follicle-stimulating hormone (rFSH))
Pacchiarotti 2007	Compared rFSH with a combination of uFSH and rFSH in a RCT
Raga 1999	The study was randomised as rFSH versus uFSH-HP in poor responders. However, in both study arms HMG (150 IU daily) was added during the first four days of stimulation
Serhal 2000	Not truly randomised, allocation by alternating weeks.

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

Chakravarty 2000

Methods	RCT
Participants	Couples undergoing IVF or ICSI
Interventions	rFSH vs uFSH-HP in agonist cycles
Outcomes	Clinical pregnancy rate
Notes	Double publication of Gosh?

Kahn 1999

Methods	Prospective, randomised study over multiple cycles including cryo cycles
Participants	not known yet
Interventions	rFSH versus urinary FSH
Outcomes	Live birth rate
Notes	Apparant long-term treatment of couples that were initially randomised in the Out et al trial (1995)

Olivennes F 1999

Methods	Randomised small study with 30 couples
Participants	Couples undergoing IVF
Interventions	rFSH vs HMG in antagonist cycles
Outcomes	Not clear, according to Professors Engel and Olivennes there was no difference in clinical outcomes
Notes	ESHRE abstract Tours

Reyftmann 1997

Methods	not known yet
Participants	not known yet
Interventions	not known yet
Outcomes	Not clear

Reyftmann 1997 (*Continued*)

Notes	Not able to get abstract or more data on trial

Righini 1998

Methods	RCT
Participants	Couples undergoing IVF
Interventions	rFSH versus uFSH-HP
Outcomes	Not clear
Notes	IFFS abstract

Strowitzki 2007

Methods	RCT
Participants	Couples undergoing IVF or ICSI
Interventions	Fixed antagonist protocol + HP-HMG or rFSH
Outcomes	Clinical and ongoing pregnancy?
Notes	Not able to get abstract or more data on trial

DATA AND ANALYSES

Comparison 1. rFSH versus urinary gonadotrophins: primary analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth (or ongoing pregnancy) by urinary gonadotrophin	28	7339	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.87, 1.08]
1.1 rFSH versus HMG/ HMG-HP	11	3197	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.72, 0.99]
1.2 rFSH versus FSH-P	5	1430	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.96, 1.64]
1.3 rFSH versus FSH-HP	13	2712	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.86, 1.22]
2 Live birth (or ongoing pregnancy) by down regulation protocol	28	7339	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.87, 1.08]
2.1 With antagonist protocol	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.53, 1.45]
2.2 With long agonist protocol	22	6437	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.87, 1.10]
2.3 With short agonist protocol	3	402	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.54, 1.31]
2.4 With no down-regulation protocol	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.62, 2.20]
3 Live birth (or ongoing pregnancy) by fresh/frozen policy	28	7339	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.88, 1.10]
3.1 Fresh cycles	25	4952	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.85, 1.11]
3.2 Fresh plus frozen-thawed cycles	3	2387	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.84, 1.22]
4 Live birth (or ongoing pregnancy) by sponsor	28	7339	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.87, 1.08]
4.1 Serono	6	1410	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.97, 1.61]
4.2 Organon	3	1215	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.96, 1.71]
4.3 Ferring	6	2817	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.70, 0.98]
4.4 IBSA	1	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.52, 1.92]
4.5 None	11	1635	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.70, 1.09]
4.6 Unknown	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.46, 4.47]
5 OHSS by urinary gonadotrophin	32	7740	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.86, 1.61]
5.1 rFSH versus HMG/ HMG-HP	11	3197	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.58, 1.71]
5.2 rFSH versus FSH-P	6	1490	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [0.89, 3.62]
5.3 rFSH versus FSH-HP	16	3053	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.70, 1.75]
6 OHSS by down regulation protocol	32	7740	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.86, 1.61]
6.1 With antagonist protocol	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.14, 7.17]
6.2 With long agonist protocol	27	7092	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.86, 1.62]
6.3 With short agonist protocol	2	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

6.4 With no down-regulation protocol	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
7 OHSS by sponsor	32	7740	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.86, 1.61]
7.1 Serono	7	1480	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.13, 3.83]
7.2 Organon	4	1384	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.78, 3.18]
7.3 Ferring	6	2817	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.54, 1.59]
7.4 IBSA	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.29 [0.14, 367.55]
7.5 None	10	1381	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.27, 1.61]
7.6 Unknown	3	375	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.17, 1.53]
8 Clinical pregnancy by urinary gonadotrophin	41	9482	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.91, 1.09]
8.1 rFSH versus HMG/ HMG-HP	12	3775	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.74, 0.99]
8.2 rFSH versus FSH-P	7	1560	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [1.01, 1.60]
8.3 rFSH vs FSH-HP	23	4147	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.91, 1.20]
9 Clinical pregnancy by down regulation protocol	41	9482	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.91, 1.09]
9.1 With antagonist protocol	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.55, 1.43]
9.2 With long agonist protocol	31	7718	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.90, 1.11]
9.3 With short down-regulation protocol	4	980	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.70, 1.21]
9.4 With no down-regulation protocol	5	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.77, 1.97]
10 Clinical pregnancy by fresh/ frozen policy	41	9482	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.91, 1.10]
10.1 Fresh cycles	39	7826	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.88, 1.07]
10.2 Fresh plus frozen cycles	2	1656	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.93, 1.44]
11 Clinical pregnancy by sponsor	41	9482	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.91, 1.09]
11.1 Serono	9	1658	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.93, 1.45]
11.2 Organon	4	1384	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.95, 1.54]
11.3 Ferring	6	2817	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.71, 1.00]
11.4 IBSA	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.55, 1.42]
11.5 None	12	1776	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.73, 1.10]
11.6 Unknown	8	1544	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.88, 1.40]
12 Multiple pregnancy (per woman)	25	6329	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.76, 1.09]
13 Multiple pregnancy (per pregnancy)	25	1895	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.78, 1.18]
14 Miscarriage (per woman)	30	6663	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.93, 1.44]

Comparison 2. Sensitivity analyses excluding lower quality trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth (or pregnancy ongoing) by urinary gonadotrophin	27	7085	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.87, 1.09]
1.1 rFSH versus HMG/ HMG-HP	11	3197	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.72, 0.99]
1.2 rFSH versus FSH-P	5	1430	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.96, 1.64]
1.3 rFSH versus FSH-HP	12	2458	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.87, 1.26]
2 Live birth (or pregnancy ongoing) rFSH vs FSH-P by down-regulation	27	7085	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.87, 1.09]
2.1 With antagonist protocol	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.53, 1.45]
2.2 With long agonist protocol	22	6437	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.87, 1.10]
2.3 With short agonist protocol	2	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.25, 1.71]
2.4 With no down-regulation protocol	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.62, 2.20]
3 Live birth (or ongoing pregnancy) by fresh/frozen policy	27	7085	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.89, 1.10]
3.1 Fresh cycles	24	4698	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.85, 1.12]
3.2 Fresh plus frozen-thawed cycles	3	2387	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.84, 1.22]
4 Live birth (or ongoing pregnancy) by sponsor	27	7085	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.87, 1.09]
4.1 Serono	6	1410	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.97, 1.61]
4.2 Organon	3	1215	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.96, 1.71]
4.3 Ferring	6	2817	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.70, 0.98]
4.4 IBSA	1	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.52, 1.92]
4.5 None	10	1381	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.67, 1.11]
4.6 Unknown	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.46, 4.47]
5 OHSS by urinary gonadotrophin	30	7475	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.90, 1.71]
5.1 rFSH versus HMG/ HMG-HP	11	3197	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.58, 1.71]
5.2 rFSH versus FSH-P	6	1490	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [0.89, 3.62]
5.3 rFSH versus FSH-HP	14	2788	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.77, 2.03]
6 OHSS by down regulation protocol	30	7475	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.90, 1.71]
6.1 With antagonist protocol	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.14, 7.17]
6.2 With long agonist protocol	25	6827	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.90, 1.73]
6.3 With short agonist protocol	2	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
6.4 With no down-regulation protocol	2	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
7 OHSS by sponsor	30	7475	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.90, 1.71]

7.1 Serono	7	1480	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.13, 3.83]
7.2 Organon	4	1384	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.78, 3.18]
7.3 Ferring	6	2817	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.54, 1.59]
7.4 IBSA	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.29 [0.14, 367.55]
7.5 None	10	1381	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.27, 1.61]
7.6 Unknown	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.10, 4.60]
8 Clinical pregnancy by urinary gonadotrophin	35	8744	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.90, 1.09]
8.1 rFSH versus HMG/ HMG-HP	12	3775	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.74, 0.99]
8.2 rFSH versus FSH-P	7	1560	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [1.01, 1.60]
8.3 rFSH vs FSH-HP	17	3409	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.91, 1.23]
9 Clinical pregnancy by down regulation protocol	35	8744	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.90, 1.09]
9.1 With antagonist protocol	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.55, 1.43]
9.2 With long agonist protocol	27	7298	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.89, 1.10]
9.3 With short down-regulation protocol	3	726	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.65, 1.26]
9.4 With no down-regulation protocol	4	440	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.87, 2.35]
10 Clinical pregnancy by fresh/ frozen policy	35	8744	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.91, 1.10]
10.1 Fresh cycles	33	7088	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.87, 1.07]
10.2 Fresh plus frozen cycles	2	1656	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.93, 1.44]
11 Clinical pregnancy by sponsor	35	8744	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.90, 1.09]
11.1 Serono	7	1480	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.97, 1.53]
11.2 Organon	4	1384	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.95, 1.54]
11.3 Ferring	6	2817	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.71, 1.00]
11.4 IBSA	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.55, 1.42]
11.5 None	11	1522	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.70, 1.11]
11.6 Unknown	5	1238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.83, 1.38]

ADDITIONAL TABLES

Table 1. Methodological quality of trials

Methodology	Adequate	Unclear	Inadequate
Randomisation	Computer-generated, random number table, lots, coin toss, etc	'random' stated without further explanation	[Study excluded]
Concealment	Third party, sequentially numbered coded drugs containers or envelopes	Missing or inadequate detail e.g. "sealed envelopes"	Open, not able to validate e.g. lots, coin toss, shuffle
Blinding	Double blinded, i.e. both the patient and the doctor	Unclear whether blinding was used	Not double blinded, not blinded

Table 1. Methodological quality of trials (*Continued*)

Incomplete outcome data addressed	No losses to follow-up or evidence that any losses to follow-up were low and comparable between groups (i.e. all data presented as ITT)	Unclear whether all data is presented according to ITT	Not all data is presented according to ITT and losses to follow-up are considerable
Selective reporting	Major outcomes had been reported in sufficient detail to allow analysis, independently of their apparent statistical significance	Unclear whether major outcomes were reported in sufficient details (often in abstracts)	Major outcomes had not been reported in sufficient detail to allow analysis
Other bias	No evidence of miscellaneous errors or circumstances that might influence internal validity of trial results	It is unknown whether there are miscellaneous errors or circumstances that might influence internal validity of trial results	Evidence of miscellaneous errors or circumstances that might influence internal validity of trial results

Table 2. Number of oocytes retrieved

Study	recombinant FSH			Urinary gonadotrophins			SMD [95% CI)
	mean	SD	N	mean	SD	N	
Out 1995	10.84	5.7	585	8.95	5.7	396	1.89 [1.16, 2.62]
RHFSHG 1995	9.3	5.0	55	10.7	5.3	59	-1.40 [-3.29, 0.49]
Hedon 1995	9.7	5.8	57	8.9	5.8	33	0.80 [-1.69, 3.29]
Bergh 1997	12.2	5.5	119	7.6	4.4	102	4.60 [3.29, 5.91]
Jansen 1998	11.2	6.8	54	8.3	6.2	35	2.90 [0.16, 5.64]
Ghosh 1999	12.2	4.7	22	14.4	4.3	25	-2.20 [-4.79, 0.39]
Berger 1999	9.1	5.1	47	11.9	7.3	53	-2.80 [-5.25, -0.35]
Hoomans 1999	8.84	5.0	83	9.79	5.0	82	-0.95 [-2.48, 0.58]
Kornilov 1999	14.4	6.0	28	13.8	5.7	109	0.60 [-1.87, 3.07]
Ferraretti 1999	4.1	2.4	66	3.7	2.3	75	0.40 [-0.38, 1.18]
Lenton 2000	10.2	6.0	68	10.8	6.1	69	-0.60 [-2.63, 1.43]

Table 2. Number of oocytes retrieved (*Continued*)

Nardo 2000	3.8	6.0	75	3.8	6.0	35	0.00 [-2.41, 2.41]
Schats 2000	13.1	7.7	232	11.4	7.6	231	1.70 [0.31, 3.09]
Frydman 2000	11.0	5.9	130	8.8	4.8	116	2.20 [0.86, 3.54]
Franco 2000	10.7	6.8	60	10.5	5.7	60	0.20 [-2.05, 2.45]
Ng 2001	12.6	8.9	17	9.6	8.1	16	3.00 [-2.80, 8.80]
Gordon 2001	12.0	6.0	34	10.0	7.0	49	2.00 [-0.81, 4.81]
Westergaard 2001	12.9	6.8	188	12.9	6.7	186	0.00 [-1.37, 1.37]
Hugues 2001	7.8	4.9	56	8.8	5.7	30	-1.00 [-3.41, 1.41]
Strehler 2001	12.29	7.8	296	9.67	5.92	282	2.62 [1.49, 3.75]
Drakakis 2002	10.8	5.2	36	12.0	7.5	29	-1.20 [-4.42, 2.02]
Selman 2002	8.9	4.7	133	8.7	3.4	131	0.20 [-0.79, 1.19]
Dickey 2002	13.6	6.9	56	13.7	6.3	111	-0.10 [-2.25, 2.05]
EISG 2002	14.0	8.5	339	12.8	8.5	361	1.20 [-0.06, 2.46]
Dickey 2003	11.9	6.9	60	11.8	6.3	60	0.10 [-2.26, 2.46]
Kilani 2003	6.8	3.9	43	7.9	4.6	44	-1.10 [-2.89, 0.69]
Balasch 2003	9.1	4.35	25	11.79	4.55	25	-2.69 [-5.16, -0.22]
Meden-Vrtovec 2003	7.1	5.3	70	6.1	4.2	61	1.00 [-0.63, 2.63]
Gallego 2003a	10.4	5.48	43	10.49	7.79	45	-0.09 [-2.89, 2.71]
Cheon 2004	14.6	9.2	131	15.4	6.9	123	-0.80 [-2.79, 1.19]
Rashidi 2005	8.7	8.5	30	9.0	6.2	30	-0.30 [-4.06, 3.46]
Andersen 2006	11.8	5.7	368	10.0	5.4	363	1.80 [1.00, 2.60]
Mohamed 2006	6.8	3.2	121	6.2	2.8	120	0.60 [-0.16, 1.36]

Table 2. Number of oocytes retrieved (*Continued*)

Hompes 2008	10.77	6.64	247	7.86	4.54	247	2.91 [1.91, 3.91]
Antoine 2007	11.9	5.7	72	10.9	4.9	73	1.00 [-0.73, 2.73]
Baker 2009	17.1	9.4	70	16.3	9.2	70	0.80 [-2.28, 3.88]
Bosch 2008	14.4	8.1	126	11.3	6.0	122	3.10 [1.33, 4.87]
Abate 2009	5.0	2.6	186	6.0	2.8	215	-1.00 [-1.53, -0.47]

Table 3. Amount of gonadotrophin used (IU)

Study	recombinant FSH			urinary gonadotrophins			MD [95% CI]
	mean	SD	N	mean	SD	N	
Hedon 1995	2265.0	743.0	57	2213.0	743.0	33	52.00 [-266.54, 370.54]
Out 1995	2138.0	715.0	585	2385.0	715.0	396	-247.00 [-338.19, -155.81]
RHFSHG 1995	2270.0	714.0	60	2095.0	591.0	63	175.00 [-57.24, 407.24]
Alvino 1995	2400.0	487.0	30	2250.0	731.0	30	150.00 [-164.31, 464.31]
Bergh 1997	1643.0	383.0	119	2393.0	1005.0	102	-750.00 [-956.82, -543.18]
Jansen 1998	1410.0	228.0	54	1365.0	228.0	35	45.00 [-51.97, 141.97]
Berger 1999	2475.0	488.0	89	2445.0	405.0	76	30.00 [-106.27, 166.27]
Kornilov 1999	1590.0	709.0	28	2027.0	704.0	109	-437.00 [-730.99, -143.01]
Hoomans 1999	1479.0	285.0	83	2139.0	285.0	82	-660.00 [-746.97, -573.03]
Schats 2000	1695.0	375.0	232	1823.0	383.0	231	-128.00 [-197.05, -58.95]
Lenton 2000	1673.0	488.0	68	1823.0	488.0	69	-150.00 [-313.44, 13.44]
Franco 2000	1913.0	975.0	60	1898.0	810.0	60	15.00 [-305.73, 335.73]
Nardo 2000	2486.0	800.0	75	2780.0	800.0	35	-294.00 [-614.97, 26.97]
Frydman 2000	2070.0	765.0	130	3053.0	1020.0	116	-983.00 [-1210.48, -755.52]

Table 3. Amount of gonadotrophin used (IU) (*Continued*)

Westergaard 2001	2242.0	375.0	190	2280.0	435.0	189	-38.00 [-119.79, 43.79]
Gordon 2001	2025.0	350.0	39	1981.0	570.0	59	44.00 [-138.26, 226.26]
Strehler 2001	2150.0	797.0	296	1516.0	545.0	282	634.00 [523.14, 744.86]
Hugues 2001	1353.0	679.0	52	1981.0	972.0	32	-628.00 [-1012.03, -243.97]
Ng 2001	1800.0	270.0	20	1650.0	270.0	20	150.00 [-17.34, 317.34]
Selman 2002	4538.0	1575.0	134	3878.0	1125.0	133	660.00 [331.87, 988.13]
Dickey 2002	2169.0	685.0	58	2444.0	836.0	111	-275.00 [-510.08, -39.92]
EISG 2002	2775.0	810.0	354	2768.0	817.0	373	7.00 [-111.30, 125.30]
Drakakis 2002	2664.0	832.0	36	3251.0	937.0	29	-587.00 [-1023.08, -150.92]
Kilani 2003	2025.0	795.0	50	1680.0	530.0	50	345.00 [80.16, 609.84]
Dickey 2003	2354.0	779.0	59	2314.0	847.0	57	40.00 [-256.41, 336.41]
Balasch 2003	2449.0	885.0	25	1922.0	379.0	25	527.00 [149.61, 904.39]
Gallego 2003a	1666.0	685.0	43	2262.0	685.0	45	-596.00 [-882.31, -309.69]
Meden-Vrtovec 2003	1253.0	173.0	70	1283.0	270.0	61	-30.00 [-108.95, 48.95]
Cheon 2004	1322.0	526.0	131	2124.0	882.0	123	-802.00 [-982.02, -621.98]
Rashidi 2005	2138.0	800.0	30	2250.0	800.0	30	-112.00 [-516.85, 292.85]
Mohamed 2006	5533.0	2398.0	121	3213.0	1527.0	120	2320.00 [1812.85, 2827.15]
Andersen 2006	2385.0	622.0	368	2508.0	729.0	363	-123.00 [-221.30, -24.70]
Antoine 2007	2349.0	779.0	72	2526.0	802.0	73	-177.00 [-434.34, 80.34]
Hompes 2008	1781.0	468.0	256	1932.0	628.0	250	-151.00 [-247.68, -54.32]
Baker 2009	2715.0	905.0	76	2641.0	841.0	76	74.00 [-203.76, 351.76]
Bosch 2008	2624.0	801.0	140	2481.0	994.0	140	143.00 [-68.46, 354.46]

Table 3. Amount of gonadotrophin used (IU) (*Continued*)

Abate 2009	3536.0	1099.0	186	2106.0	719.0	215	1430.00 [1245.12, 1614.88]

Table 4. Duration of ovarian stimulation

Study	recombinant FSH			Urinary gonadotrophins			MD [95% CI)
	mean	SD	N	mean	SD	N	
Hedon 1995	10.2	2.1	57	10.3	2.1	33	-0.10 [-1.00, 0.80]
Out 1995	10.7	2.0	595	11.3	2.0	396	-0.60 [-0.85, -0.35]
RHFSHG 1995	9.9	2.3	60	9.4	1.8	63	0.50 [-0.23, 1.23]
Bergh 1997	11.0	1.6	119	13.5	3.7	102	-2.50 [-3.27, -1.73]
Jansen 1998	6.2	0.97	54	6.0	0.97	35	0.20 [-0.21, 0.61]
Hoomans 1999	9.9	1.5	83	9.6	1.5	82	0.30 [-0.16, 0.76]
Kornilov 1999	8.1	1.7	28	8.9	18.0	109	-0.80 [-4.24, 2.64]
Franco 2000	10.1	1.8	60	10.3	1.9	60	-0.20 [-0.86, 0.46]
Lenton 2000	10.2	2.1	68	10.7	1.7	69	-0.50 [-1.14, 0.14]
Nardo 2000	10.4	1.6	75	10.9	2.1	35	-0.50 [-1.28, 0.28]
Schats 2000	11.6	1.9	232	12.4	2.7	231	-0.80 [-1.23, -0.37]
Frydman 2000	11.7	1.9	130	14.5	3.3	116	-2.80 [-3.48, -2.12]
Strehler 2001	9.5	3.2	259	9.1	2.1	248	0.40 [-0.07, 0.87]
Ng 2001	9.0	3.7	20	10.0	3.0	20	-1.00 [-3.09, 1.09]
Westergaard 2001	9.9	1.5	190	10.0	1.5	189	-0.10 [-0.40, 0.20]
Gordon 2001	10.0	1.5	39	9.3	1.5	59	0.70 [0.09, 1.31]
Hugues 2001	12.9	2.0	52	12.6	2.0	32	0.30 [-0.58, 1.18]
Selman 2002	13.7	1.4	134	13.4	1.5	133	0.30 [-0.05, 0.65]

Table 4. Duration of ovarian stimulation (*Continued*)

Drakakis 2002	9.8	1.3	36	9.2	1.2	29	0.60 [-0.01, 1.21]
EISG 2002	11.0	2.7	354	11.2	2.6	373	-0.20 [-0.59, 0.19]
Dickey 2002	9.0	1.4	58	9.5	1.6	111	-0.50 [-0.97, -0.03]
Dickey 2003	9.3	1.7	59	9.0	1.6	57	0.30 [-0.30, 0.90]
Balasch 2003	14.7	3.15	25	12.67	2.2	25	2.03 [0.52, 3.54]
Meden-Vrtovec 2003	7.0	1.2	70	6.9	1.3	61	0.10 [-0.33, 0.53]
Gallego 2003a	10.47	1.3	43	9.89	1.15	45	0.58 [0.07, 1.09]
Kilani 2003	12.9	3.5	50	11.0	2.8	50	1.90 [0.66, 3.14]
Cheon 2004	9.2	1.8	131	9.5	1.8	123	-0.30 [-0.74, 0.14]
Rashidi 2005	8.0	3.7	30	8.0	4.5	30	0.00 [-2.08, 2.08]
Andersen 2006	10.1	1.7	368	10.4	1.9	363	-0.30 [-0.56, -0.04]
Hompes 2008	11.88	2.57	256	12.6	3.13	250	-0.72 [-1.22, -0.22]
Bosch 2008	10.0	1.9	140	9.9	1.8	140	0.10 [-0.33, 0.53]
Abate 2009	13.3	1.2	186	12.3	1.0	215	1.00 [0.78, 1.22]

WHAT'S NEW

Last assessed as up-to-date: 19 October 2010.

Date	Event	Description
15 March 2011	Amended	Minor edit. Added to the Plain language summary the word significantly: Comparing rFSH with HMG/HP-HMG resulted in a "significantly" lower live birth rate in the rFSH group though differences were small. Added the grading HIGH for the primary adverse outcome OHSS to the summary of findings table
15 March 2011	Amended	Minor edit. Added to the abstract how many people selected studies and extracted data. Added dates to the searches in the abstract

(*Continued*)

21 February 2011	Amended	Minor edit made EISG study was reported in the table as having been conducted with Puregon whereas it should be Gonal F- this is now corrected

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 2, 2011

Date	Event	Description
3 February 2011	Amended	Minor edit to with the addition of the correct DOI to the reference Van Wely 2002
19 November 2007	New citation required and conclusions have changed	Substantive amendment of protocol

CONTRIBUTIONS OF AUTHORS

MvW searched the literature, contacted authors of studies, entered the data, did the analyses, wrote the review, and responded to reviewer comments.

IK developed and wrote the draft of the protocol, developed the title and the intended methods of the review, entered the protocol into RevMan; and responded to peer reviewers' comments on the protocol, searched the literature, entered part of the data and contacted authors of studies.

AV developed the intended methods of the review, provided statistical expertise, checked the data and the risk of bias tables.

JT helped to develop the protocol and the intended methods of the review.

AB helped to develop the protocol and the intended methods of the review, searched the literature and entered part of the data.

FV helped to write the review and was consultant on clinical issues.

AI helped to develop the protocol, the title and the intended methods of the review, responded to peer reviewers' comments and was consultant on clinical issues.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- None, Not specified.
- Academic Medical Center, Netherlands.

Review was partly written during working hours, i.e. partly paid by salary

External sources

- None, Not specified.
- No external support, no grants, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol and review was written by different authors. The protocol was written by the following authors: Irene Kwan, Hesham G Al-Inany, Anna L Burt, Jane Thomas, Andy Vail. The review was written by the following authors: Madelon van Wely, Irene Kwan, Anna L Burt, Jane Thomas, Andy Vail, Fulco Van der Veen, Hesham G Al-Inany.

An extra unplanned sub analysis was done to evaluate whether a sponsor effects was due to the sponsoring or due to the treatment given in these sponsored studies. Indeed this last option appeared more likely.

NOTES

Three previously published Cochrane reviews have been superseded by this review . These three reviews are now withdrawn Van Wely 2002; Daya 2003 and Daya 2000.

INDEX TERMS

Medical Subject Headings (MeSH)

Birth Rate; Fertilization in Vitro [*methods]; Follicle Stimulating Hormone [*therapeutic use]; Gonadotropins [*therapeutic use; urine]; Live Birth [epidemiology]; Ovulation Induction [*methods]; Recombinant Proteins [therapeutic use]; Sperm Injections, Intracytoplasmic [methods]

MeSH check words

Female; Humans; Pregnancy