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[Intervention Review]

Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology

Mohamed AFM Youssef[1], Fulco Van der Veen[2], Hesham G Al-Inany[1], Monique H Mochtar[3], Georg Griesinger[4], Mohamed Nagi Mohesen[5], Ismail Aboulfoutouh[6], Madelon van Wely[2]

[1]Department of Obstetrics & Gynaecology, Faculty of Medicine, Cairo University, Cairo, Egypt. [2]Center for Reproductive Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands. [3]Department of Obstetrics and Gynaecology, Center for Reproductive Medicine, Academic Medical Center, Amsterdam, Netherlands. [4]UKSH, Campus Lűbeck, Lűbeck, Germany. [5]Department of Obstetrics & Gynaecology, Beni-Suef University, Beni Suef, Egypt. [6]Department of Obstetrics and Gynaecology, Egyptian International Fertility IVF Center (EIFC-IVF), Cairo University, Cairo, Egypt

Contact: Mohamed AFM Youssef, Department of Obstetrics & Gynaecology, Faculty of Medicine, Cairo University, Cairo, Egypt. mohamedyoussef1973@gmail.com, m.a.youssef@amc.uva.nl.

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ABSTRACT

Background

Human chorionic gonadotropin (HCG) is routinely used for final oocyte maturation triggering in in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) cycles, but the use of HCG for this purpose may have drawbacks. Gonadotropin-releasing hormone (GnRH) agonists present an alternative to HCG in controlled ovarian hyperstimulation (COH) treatment regimens in which the cycle has been down-regulated with a GnRH antagonist. This is an update of a review first published in 2010.

Objectives

To evaluate the effectiveness and safety of GnRH agonists in comparison with HCG for triggering final oocyte maturation in IVF and ICSI for women undergoing COH in a GnRH antagonist protocol.

Search methods

We searched databases including the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and trial registers for published and unpublished articles (in any language) on randomised controlled trials (RCTs) of gonadotropin-releasing hormone agonists versus HCG for oocyte triggering in GnRH antagonist IVF/ICSI treatment cycles. The search is current to 8 September 2014.

Selection criteria

RCTs that compared the clinical outcomes of GnRH agonist triggers versus HCG for final oocyte maturation triggering in women undergoing GnRH antagonist IVF/ICSI treatment cycles were included.

Data collection and analysis

Two or more review authors independently selected studies, extracted data and assessed study risk of bias. Treatment effects were summarised using a fixed-effect model, and subgroup analyses were conducted to explore potential sources of heterogeneity. Treatment effects were expressed as mean differences (MDs) for continuous outcomes and as odds ratios (ORs) for dichotomous outcomes, together

with 95% confidence intervals (CIs). Primary outcomes were live birth and rate of ovarian hyperstimulation syndrome (OHSS) per women randomised. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methods were used to assess the quality of the evidence for each comparison.

Main results

We included 17 RCTs (n = 1847), of which 13 studies assessed fresh autologous cycles and four studies assessed donor-recipient cycles. In fresh autologous cycles, GnRH agonists were associated with a lower live birth rate than was seen with HCG (OR 0.47, 95% CI 0.31 to 0.70; five RCTs, 532 women, I^2 = 56%, moderate-quality evidence). This suggests that for a woman with a 31% chance of achieving live birth with the use of HCG, the chance of a live birth with the use of an GnRH agonist would be between 12% and 24%.

In women undergoing fresh autologous cycles, GnRH agonists were associated with a lower incidence of mild, moderate or severe OHSS than was HCG (OR 0.15, 95% CI 0.05 to 0.47; eight RCTs, 989 women, I^2 = 42%, moderate-quality evidence). This suggests that for a woman with a 5% risk of mild, moderate or severe OHSS with the use of HCG, the risk of OHSS with the use of a GnRH agonist would be between nil and 2%.

In women undergoing fresh autologous cycles, GnRH agonists were associated with a lower ongoing pregnancy rate than was seen with HCG (OR 0.70, 95% CI 0.54 to 0.91; 11 studies, 1198 women, I^2 = 59%, low-quality evidence) and a higher early miscarriage rate (OR 1.74, 95% CI 1.10 to 2.75; 11 RCTs, 1198 women, I^2 = 1%, moderate-quality evidence). However, the effect was dependent on the type of luteal phase support provided (with or without luteinising hormone (LH) activity); the higher rate of pregnancies in the HCG group applied only to the group that received luteal phase support without LH activity (OR 0.36, 95% CI 0.21 to 0.62; I^2 = 73%, five RCTs, 370 women). No evidence was found of a difference between groups in risk of multiple pregnancy (OR 3.00, 95% CI 0.30 to 30.47; two RCTs, 62 women, I^2 = 0%, low-quality evidence).

In women with donor-recipient cycles, no evidence suggested a difference between groups in live birth rate (OR 0.92, 95% CI 0.53 to 1.61; one RCT, 212 women) or ongoing pregnancy rate (OR 0.88, 95% CI 0.58 to 1.32; three RCTs, 372 women, I^2 = 0%). We found evidence of a lower incidence of OHSS in the GnRH agonist group than in the HCG group (OR 0.05, 95% CI 0.01 to 0.28; three RCTs, 374 women, I^2 = 0%).

The main limitation in the quality of the evidence was risk of bias associated with poor reporting of methods in the included studies.

Authors' conclusions

Final oocyte maturation triggering with GnRH agonist instead of HCG in fresh autologous GnRH antagonist IVF/ICSI treatment cycles prevents OHSS to the detriment of the live birth rate. In donor-recipient cycles, use of GnRH agonists instead of HCG resulted in a lower incidence of OHSS, with no evidence of a difference in live birth rate.

Evidence suggests that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate (pregnancy beyond 12 weeks) and a higher rate of early miscarriage (less than 12 weeks). GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers (for whatever reason), women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation.

PLAIN LANGUAGE SUMMARY

Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology cycles

Review question

We reviewed the evidence on the effects of GnRH agonists on final oocyte maturation triggering in GnRH antagonist IVF/ICSI treatment cycles.

Background

Oocyte maturation triggering is the final differentiation process of an immature oocyte before fertilisation in unstimulated or stimulated cycles with assisted reproductive techniques. Two hormones can be used to trigger oocyte maturation: human chorionic gonadotropin (HCG), which is the standard treatment, and gonadotropin-releasing hormone agonist (GnRH agonist). In this review, we assessed the benefits and harms of GnRH agonists as oocyte maturation triggers. Evidence is current to September 2014.

Study characteristics

We included 17 studies of 1817 women. Researchers assessed fresh or donor cycles in women at varying risk of ovarian hyperstimulation syndrome (OHSS). The authors of four studies stated that the studies were commercially funded. Most studies failed to disclose their funding source.

Key results

GnRH agonist triggers significantly reduce the risk of ovarian hyperstimulation but also lower the chance of pregnancy in fresh autologous IVF/ICSI treatment cycles compared with HCG. GnRH agonist use as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers (for whatever reason), women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation.

Quality of the evidence

The overall quality of the evidence was moderate for most comparisons. The main limitation in the quality of the evidence was risk of bias associated with poor reporting of study methods.

Summary of findings for the main comparison. GnRH agonist compared with HCG for oocyte maturation triggering in antagonist-assisted reproductive technology

GnRH agonist compared with HCG for oocyte maturation triggering in antagonist-assisted reproductive technology

Population: subfertile women
Settings: assisted reproductive technology: autologous cycles
Intervention: GnRH agonist
Comparison: HCG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	HCG for oocyte maturation triggering	GnRH agonist				
Live birth	313 per 1000	176 per 1000 (124 to 242)	OR 0.47 (0.31 to 0.70)	532 (5 studies)	⊕⊕⊕⊖ Moderate[a,d]	
OHSS (mild, moderate or severe): overall risk	5 per 1000	1 per 1000 (0 to 2)	OR 0.15 (0.05 to 0.47)	989 (8 studies)	⊕⊕⊕⊖ Moderate[b]	
OHSS (moderate or severe): overall risk	5 per 1000	1 per 1000 (0 to 3)	OR 0.21 (0.07 to 0.66)	989 (8 studies)	⊕⊕⊕⊖ Moderate[c]	Low event rate: 4 of 9 RCTs reported no events in either arm
OHSS (mild, moderate or severe) in women at high risk of OHSS	308 per 1000	26 per 1000 (4 to 131)	OR 0.06 (0.01 to 0.34)	212 women (3 studies)	⊕⊕⊕⊖ Moderate[b]	
Ongoing pregnancy	256 per 1000	194 per 1000 (157 to 238)	OR 0.7 (0.54 to 0.91)	1198 (11 studies)	⊕⊕⊖⊖ Low[d,e]	
Miscarriage	67 per 1000	111 per 1000 (73 to 165)	OR 1.74 (1.10 to 2.75)	1198 (11 studies)	⊕⊕⊕⊖ Moderate[e]	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR**: Odds ratio.

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

[a]One of the studies at high risk of bias because of premature termination.
[b]All studies at high risk of bias in 1 or more domains. None clearly reported blinded outcome assessment.
[c]Most studies at high risk of bias in 1 or more domains. None clearly reported blinded outcome assessment.
[d]Substantial heterogeneity: I^2 = 59% to 66%.
[e]5/11 studies at high risk of bias because of early termination and/or inadequate allocation concealment. None clearly reported blinded outcome assessment.

BACKGROUND

Description of the condition

After oocyte growth is stimulated by gonadotropins, the next step in in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) treatment consists of triggering the oocytes to go through the last stage of maturation, so that they can be retrieved and fertilised. This final oocyte maturation is usually triggered by human chorionic gonadotropin (HCG), but use of HCG for this purpose may have drawbacks. Some studies have suggested a negative impact of HCG on endometrial receptivity (Simon 1995; Forman 1998; Simon 1998) and embryo quality (Valbuena 2001; Tavaniotou 2002). In addition, the sustained luteotrophic effect of HCG is associated with increased chances of ovarian hyperstimulation syndrome (OHSS), which is an iatrogenic complication of assisted reproductive technology (ART).

OHSS may be associated with massive ovarian enlargement, ascites, hydrothorax, liver dysfunction and renal failure. It can lead to cancellation of an IVF cycle and the need for prolonged bed rest or hospitalisation, which may have a significant emotional, social and economic impact or—in its most severe form—may even result in mortality (Delvigne 2003).

Gonadotropin-releasing hormone (GnRH) agonists present an alternative to HCG for triggering endogenous luteinising hormone (LH) release (Gonen 1990; Olivennes 1996; Olivennes 2001; Tay 2002). Use of GnRH agonist triggering is applicable only in IVF with controlled ovarian hyperstimulation (COH) treatment regimens in which the cycle has been down-regulated by a GnRH antagonist. Because of the specific mode of action of the antagonist, the pituitary remains responsive to a GnRH agonist, provided that the GnRH antagonist treatment utilised standard doses (Felberbaum 1995; Orvieto 2006).

Description of the intervention

A midcycle single bolus of GnRH agonist may be injected subcutaneously (0.2 to 0.5 mg of triptorelin, leuprorelin or buserelin) (Itskovitz-Eldor 2000; Humaidan 2005) or administered intranasally (200 µg buserelin) (Pirard 2006).

How the intervention might work

A single injection of a GnRH agonist results in an acute release of LH and follicle-stimulating hormone (FSH)—the so-called flare-up. Serum LH and FSH levels rise after four hours and 12 hours, respectively, and are elevated for 24 to 36 hours. The amplitude of the surges is similar to that seen in the normal menstrual cycle, but, in contrast to the natural cycle, the LH surge consists of two phases: a short ascending limb (> 4 hours) and a long descending limb (> 20 hours). This has no bearing on luteal phase steroid levels, which are qualitatively similar to those observed in the natural cycle (Segal 1992; Itskovitz-Eldor 2000; Fauser 2002; Nevo 2003; Kol 2004).

Consequently, oocyte maturation triggering with GnRH agonists may provide several advantages over that achieved with HCG. First, GnRH agonists reduce the risk of OHSS due to quick and irreversible luteolysis (Kol 2004). *S*econd, a more physiological LH and FSH surge is induced by the agonists, which may result in better oocyte and embryo quality (Humaidan 2005). Third, GnRH agonists may improve endometrial quality as a result of the lower luteal phase steroid levels (Forman 1998; Simon 1998).

Why it is important to do this review

This is an update of a review first published in 2010 (Youssef 2010). HCG is the standard medication for final oocyte maturation triggering. More recently, GnRH agonists have been proposed, especially as they may prevent OHSS to a large extent. Summarising the available evidence shows what is known about the effectiveness and safety of GnRH agonists in comparison with HCG and hence will help fertility experts and women to make informed decisions on final oocyte maturation triggering by GnRH antagonists in IVF/ICSI treatment cycles.

OBJECTIVES

To evaluate the effectiveness and safety of GnRH agonists in comparison with HCG for triggering final oocyte maturation in IVF and ICSI for women undergoing COH in a GnRH antagonist protocol.

METHODS

Criteria for considering studies for this review

Types of studies

- Only published and unpublished randomised controlled trials (RCTs) were included in the review.
- Non-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days and participant numbers), as they are associated with high risk of bias, were excluded from the review.
- Cross-over trials were excluded, as the design is not valid in this context.

Types of participants

Inclusion criteria

- Subfertile couples undergoing IVF or ICSI for therapeutic reasons or for oocyte donation and randomly assigned to receive a GnRH agonist or HCG for final oocyte maturation triggering.

Exclusion criteria

- Women who were not undergoing IVF or ICSI (i.e. those undergoing intrauterine insemination (IUI)).

Types of interventions

- GnRH agonists in comparison with HCG for final oocyte maturation triggering in GnRH antagonist–controlled hyperstimulation cycles, IVF or ICSI followed by embryo transfer (ET) with or without luteal phase support, in autologous or donor cycles.

Types of outcome measures

Primary outcomes

- Live birth rate (LBR) per woman randomised: live birth defined as delivery of a live fetus after 20 completed weeks of gestation.
- Incidence of OHSS per woman randomised (mild, moderate or severe): detected by clinical, laboratory or imaging grading of OHSS.

Secondary outcomes

- Ongoing pregnancy rate (OPR) per woman randomised: ongoing pregnancy defined as pregnancy beyond 12 weeks.
- Clinical pregnancy rate (CPR) per woman randomised: clinical pregnancy defined as presence of a fetal heart rate with transvaginal ultrasound.
- Early miscarriage rate per woman randomised.
- Multiple pregnancy rate per woman randomised.

Search methods for identification of studies

All published and unpublished RCTs of GnRH agonists versus HCG for final oocyte maturation triggering were sought, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator, using the following search strategy.

Electronic searches

2014 update

We searched the following electronic databases, trial registers and websites to 8 September 2014: the MDSG Specialised Register of Controlled Trials (Appendix 1), the Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 2), MEDLINE (Appendix 3), EMBASE (Appendix 4), PsycINFO (Appendix 5) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL)(Appendix 6). Other electronic sources of trials included the following.

- Trial registers for ongoing and registered trials: http://www.controlled-trials.com, http://clinicaltrials.gov/ct2/home, http://www.who.int/trialsearch/Default.aspx.
- Citation indexes: http://scientific.thomson.com/products/sci/ Conference abstracts.
- Conference abstracts in the Web of Knowledge: http://www.wokinfo.com
- Latin American and Caribbean Health Science Information Database (LILACS) database, for trials from the Portuguese and Spanish-speaking world: http://bases.bireme.br/cgi -bin/ wxislind.exe/iah/online/?IsisScript=iah/i ah.xis&base=LILACS&lang=i&form=F.
- PubMed: www.ncbi.nlm.nih.gov/pubmed/.
- Open System for Information on Grey Literature in Europe (OpenSIGLE) database (http://opensigle.inist.fr/) and Google for grey literature.

MEDLINE and EMBASE search strategies use different filters for identifying randomised trials. The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.0.1, Chapter 6, 6.4.11). EMBASE and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

Searching other resources

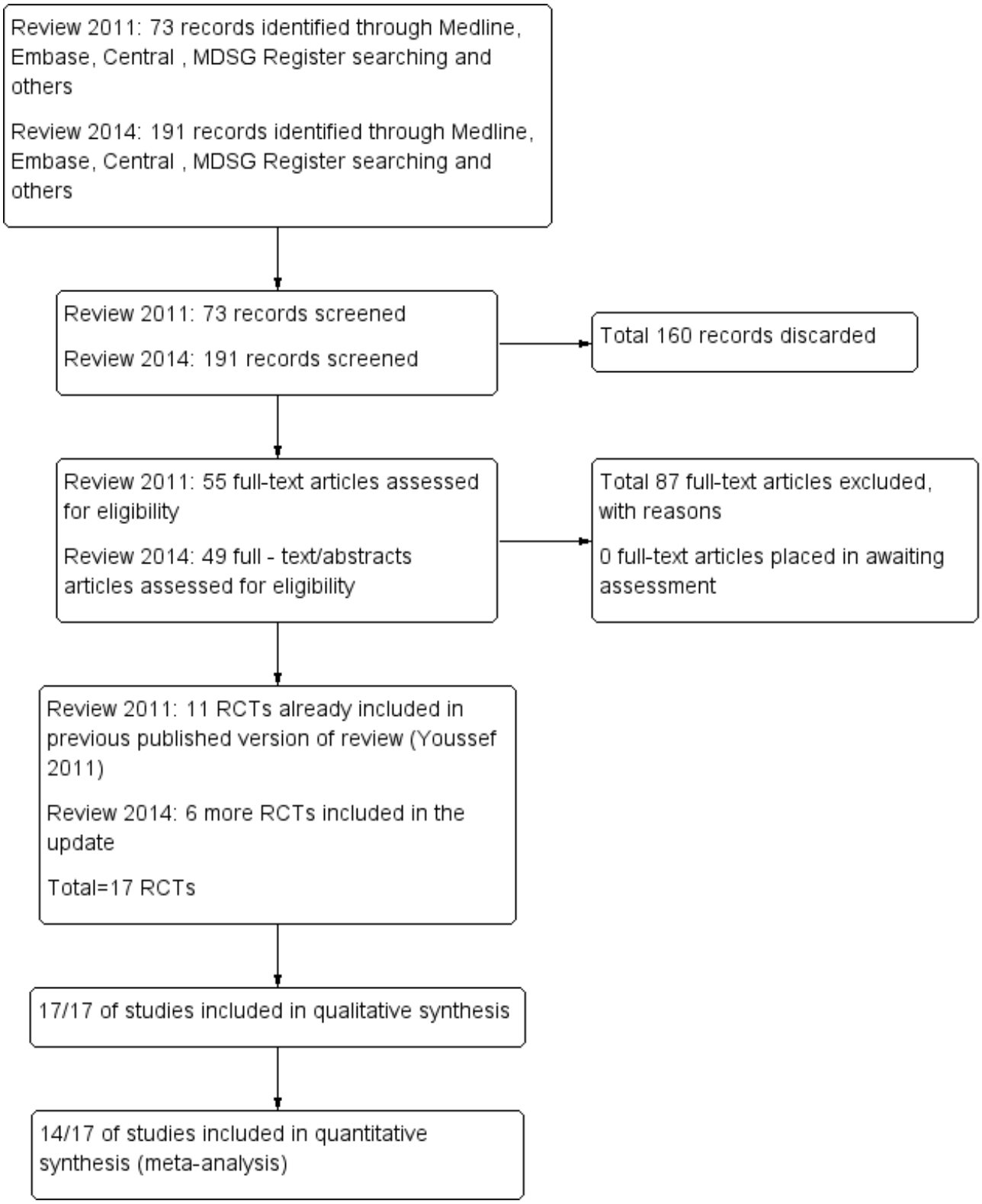
- Reference lists of relevant clinical practice guidelines, review articles and studies.
- Letters seeking information about unpublished or incomplete RCTs sent to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

- After an initial screen of titles and abstracts retrieved by the search, conducted by MAFMY and MVW, the full texts of all potentially eligible studies were retrieved. These full-text articles were examined for compliance with the inclusion criteria, and review authors selected studies eligible for inclusion in the review. We corresponded with study investigators as required to clarify study eligibility. The selection process was documented on a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

- Two review authors independently extracted data from eligible studies using a standard data extraction form that they designed and pilot-tested. Disagreements were resolved by discussion or by consultation with a third review author. Extracted data included study characteristics and outcome data (see data extraction table for details, Characteristics of included studies).
- Data entry was carried out by the same two review authors.

Studies were analysed for the following quality criteria and methodological details.

Trial characteristics

Study design

- Method of randomisation.
- Multi-centre or single-centre design.
- Presence or absence of blinding to treatment allocation.
- Number of participants randomised, excluded or lost to follow-up.
- Presence of intention-to-treat (ITT) analysis.
- Presence of a power calculation.

Characteristics of study participants

- Subfertile women undergoing IVF/ICSI treatment cycles.
- At high or low risk to develop OHSS.

Interventions used

- Types of ovarian hyperstimulation protocols used.
- Types of final oocyte maturation triggering used: route of administration, duration and dose.
- Types of luteal phase support provided: dose, duration and route of administration.

Outcomes

- LBR.
- Incidence of OHSS.
- Ongoing pregnancy rate.
- Clinical pregnancy rate.
- Miscarriage rate.
- Multiple pregnancy rate.

Assessment of risk of bias in included studies

Two review authors independently assessed the included studies for risk of bias using the risk of bias assessment tool of The Cochrane Collaboration (Higgins 2011) to assess allocation (random sequence generation and allocation concealment); blinding of participants, personnel and outcome assessors; incomplete outcome data; selective reporting; and other bias. Disagreements were resolved by discussion or by consultation with a third review author.

Randomisation

Randomisation was considered adequate if any random method of allocation was described and was verifiable, that is,

- using a computerised random number generator; or
- referring to a number table.

Concealment of allocation (selection bias)

- This was considered adequate if a third-party system; serially numbered sealed, opaque envelopes; or a similar system was described. Concealment was stated as 'unclear ' if no information was available pertaining to allocation concealment.

Blinding of participants and personnel (performance bias)

- This was examined with regard to likelihood of bias influencing primary outcomes. We considered it unlikely that blinding would influence findings for live birth, but likely that blinding could influence findings for OHSS, so unblinded studies were rated as having high risk of bias for this outcome.

Blinding of outcome assessors (detection bias)

- This was examined with regard to likelihood of bias influencing primary outcomes. We considered it unlikely that blinding would influence findings for live birth, but likely that blinding could influence findings for OHSS, so unblinded studies were rated as having high risk of bias for this outcome.

Incomplete outcome data

- Low risk of bias was allocated if no outcome data were missing, or if missing outcome data were balanced in numbers across intervention groups with similar reasons provided for missing data across groups.

Selective outcome reporting

- Low risk of bias was allocated if all of a study's primary, secondary and additional outcomes of interest in the review were reported in a prespecified way; when fewer outcome measures were reported than planned, this was considered to be a source of bias.

Other potential sources of bias

We considered other potential forms of bias (e.g. baseline imbalance of groups, premature discontinuation of study).

Measures of treatment effect

For dichotomous data (e.g. live birth rates), the numbers of events in control and intervention groups of each study were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for each individual trial.

Unit of analysis issues

The primary analysis was per woman randomised (e.g. live birth rate or miscarriage rate per woman randomised, defined as the number of women achieving a live birth divided by the number of women treated). Data per cycle were not included in the analysis.

Dealing with missing data

When possible, data were extracted to allow for an ITT analysis, defined as including all randomised participants in the denominator. When appropriate, study authors were contacted to provide further information or missing data. Data obtained in this manner were included in our analyses. Women lost to follow-up were assumed to be not pregnant.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the measure of the I^2 statistic. An I^2 measurement greater than 50% was taken to indicate substantial heterogeneity

(Higgins 2011). We tested the effect of using a random-effects model when heterogeneity was substantial.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If 10 or more studies were included in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

Data from primary studies were combined using the fixed-effect model in the following comparisons.

- GnRH agonist versus HCG in fresh autologous cycles.
- GnRH agonist versus HCG in donor-recipient cycles.
  - An increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. OHSS, miscarriage), was displayed graphically in the meta-analyses to the right of the centre-line (i.e. in favour of GnRH agonist), and a decrease in the odds of an outcome to the left of the centre-line (i.e. in favour of HCG).
  - For the meta-analysis, the number of women experiencing the event in each group of the trial was recorded. Meta-analysis of binary data was performed using the Mantel-Haenszel method with a fixed-effect model, and the OR and the 95% CI were calculated using RevMan 5 software.
  - We performed a separate analysis for oocyte donor-recipient cycles.

Subgroup analysis and investigation of heterogeneity

We considered clinical and methodological differences between studies that might account for any heterogeneity.

When data were available, we conducted subgroup analyses to determine separate evidence within the following subgroups in studies of autologous cycles.

Type of luteal phase support (for the outcomes of live birth, OHSS and ongoing pregnancy)

- Luteal phase support with LH activity (single or two doses of HCG, recLH and repeated GnRH doses)
- Luteal phase support without LH activity (progesterone only or progesterone plus oestradiol).

Risk of OHSS (for the outcome of OHSS)

- Studies of women with low OHSS risk: Low risk was defined as studies excluding women with polycystic ovary syndrome (PCOS) or women with high numbers of ovarian follicles (≥ 14 follicles) ≥ 11 mm in diameter.
- Studies of women with high OHSS risk: High risk was defined as studies including women with PCOS or women with high numbers of ovarian follicles (≥ 14 follicles) ≥ 11 mm in diameter.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding study eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

- we had used a random-effects model for the primary outcomes;
- we had reported risk ratios rather than odds ratios; or
- we had included only moderate or severe OHSS as an outcome (not including mild OHSS).

RESULTS

Description of studies

For details about the studies, please see: Characteristics of included studies, Characteristics of excluded studies and Characteristics of studies awaiting classification.

Results of the search

In searches to date (2011 and 2014), a total of 264 references were identified. Most references identified by the search were excluded at the first screening step, as they were clearly irrelevant (n = 160). The most frequent reasons for exclusion were the following: The article was a review or a commentary/editorial, or the study was clearly of a non-randomised design or reported comparisons of no interest (n = 87); 17 RCTs fulfilled the inclusion criteria (Figure 1).

Included studies

Design

- Seventeen RCTs, 13 in fresh autologous cycles and four in donor-recipient cycles, including 1847 randomly assigned women, met the inclusion criteria and were fully reviewed. Randomisation was done as soon as oocyte maturation triggering was planned in all except one trial. In this trial, randomisation was timed to occur at the beginning of stimulation (Kolibianakis 2005). Three abstracts (Segal 1992; Ossina 2004; Peña 2007) were published in conference proceedings. As it was not possible to obtain further information from the authors of these abstracts, they were excluded from the quantitative analysis. See Characteristics of included studies.
- Ten studies were randomised controlled single-centre studies (Segal 1992; Acevedo 2006; Babayof 2006; Humaidan 2006; Pirard 2006; Peña 2007; Engmann 2008; Galindo 2009; Melo 2009; Papanikolaou 2010). Three studies were two-centre studies (Beckers 2003; Humaidan 2005; Kolibianakis 2005), one was a three-centre study (Humaidan 2010), one was a four-centre study (Humaidan 2013) and two studies were six-centre studies (Fauser 2002; Ossina 2004).
- Nine studies reported sample size calculations for the primary outcome (Beckers 2003; Humaidan 2005; Kolibianakis 2005; Babayof 2006; Engmann 2008; Galindo 2009; Melo 2009; Humaidan 2010; Humaidan 2013). No sample size calculation was performed in three studies (Fauser 2002; Acevedo 2006; Pirard 2006); in five studies, this information was not provided (Segal 1992; Ossina 2004; Humaidan 2006; Peña 2007; Papanikolaou 2010).
- Three studies failed to achieve the intended sample size (Humaidan 2005; Kolibianakis 2005; Humaidan 2013). Nine

studies recruited only a small number of women (Fauser 2002, n = 57; Beckers 2003, n = 40; Humaidan 2005, n = 45; Acevedo 2006, n = 60; Babayof 2006, n = 28; Pirard 2006, n = 30; Engmann 2008, n= 66; Melo 2009, n = 100; Papanikolaou 2010; n = 39).

- Fourteen RCTs were published as full-text articles (Fauser 2002; Beckers 2003; Humaidan 2005; Kolibianakis 2005; Acevedo 2006; Babayof 2006; Humaidan 2006; Pirard 2006; Engmann 2008; Galindo 2009; Melo 2009; Humaidan 2010; Papanikolaou 2010; Humaidan 2013) and three as abstracts (Segal 1992; Ossina 2004; Peña 2007) in conference proceedings.
- For details of study risk of bias, see the Characteristics of included studies table.
- Source of funding (Lundh 2012): Four studies (28%) reported that they received industry funding (Beckers 2003; Engmann 2008; Papanikolaou 2010; Humaidan 2013).

Participants

- Analysed studies (14/17) included 791 women in the intervention groups and 779 in the control groups. All were women with subfertility from 18 to 40 years of age. All participants were undergoing IVF/ICSI treatment cycles followed by fresh ET in autologous or donor cycles.
- The number of randomly assigned participants ranged from 23 (Pirard 2006) to 302 (Humaidan 2010), including both GnRH agonist and HCG groups.
- Baseline characteristics were comparable between groups (Characteristics of included studies).
- Ten studies included women at low risk of developing OHSS (Fauser 2002; Beckers 2003; Humaidan 2005; Kolibianakis 2005; Acevedo 2006; Humaidan 2006; Galindo 2009; Melo 2009; Humaidan 2010; Papanikolaou 2010), and only three studies randomised women with PCOS or with retrieved oocytes with more than 14 follicles (Babayof 2006; Engmann 2008; Humaidan 2013). Risk of OHSS was reported unclearly in four studies (Segal 1992; Ossina 2004; Pirard 2006; Peña 2007).

Intervention

- All included studies compared GnRH agonist versus HCG for final oocyte maturation triggering in GnRH antagonist down-regulated IVF and ICSI cycles.
- Five studies used 250 µg of recombinant HCG (rHCG) for final oocyte maturation triggering in the control group (Acevedo 2006; Babayof 2006; Galindo 2009; Melo 2009; Papanikolaou 2010). A three-arm study compared LH versus rHCG versus GnRH (Beckers 2003). Other included studies used 10,000 IU of urinary HCG for final oocyte maturation triggering, except one (Engmann 2008), which used a dose ranging from 3300 to 10,000 IU, depending on follicular response.
- Luteal phase support: Five studies used progesterone (P) plus oestradiol (E_2) in fresh autologous cycles (Kolibianakis 2005; Humaidan 2005; Babayof 2006; Humaidan 2006; Engmann 2008) and one study in donor-recipient cycles (Acevedo 2006). Two studies used the combination of P + E_2 + single dose of 1500 IU hCG (Humaidan 2010) or two doses of 1500 IU HCG (Humaidan 2013); one study used P only in fresh autologous cycles (Fauser 2002) and two studies in donor-recipient cycles (Galindo 2009; Melo 2009); one study used the combination of P + six doses of recLH (Papanikolaou 2010); one study used repeated administration of GnRH agonist (Pirard 2006); and one study provided no luteal phase support (Beckers 2003).

Outcomes

- Five studies reported live birth rate in fresh autologous cycles (Humaidan 2005; Babayof 2006; Humaidan 2006; Humaidan 2010; Papanikolaou 2010) and one study in donor-recipient cycles (Galindo 2009).
- Eight studies reported OHSS incidence in fresh autologous cycles (Kolibianakis 2005; Babayof 2006; Humaidan 2006; Pirard 2006; Engmann 2008; Humaidan 2010; Papanikolaou 2010; Humaidan 2013) and three studies in donor-recipient cycles (Acevedo 2006; Galindo 2009; Melo 2009).
- All included studies reported ongoing pregnancy rate, clinical pregnancy rate and early miscarriage rate in both groups.
- Multiple pregnancy rate was reported in all donor-recipient cycles and in two studies in fresh autologous cycles (Babayof 2006; Papanikolaou 2010).
- Three studies were published as abstracts with no details on outcome measures (Segal 1992; Ossina 2004; Peña 2007); therefore they were included only in the qualitative research—not in the meta-analysis.

Excluded studies

In searches to date (2011 and 2014), a total of 87 studies were excluded. Reasons for exclusion are explained in the Characteristics of excluded studies table.

Risk of bias in included studies

Risk of bias in the included studies is summarised in Figure 2 and Figure 3.

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

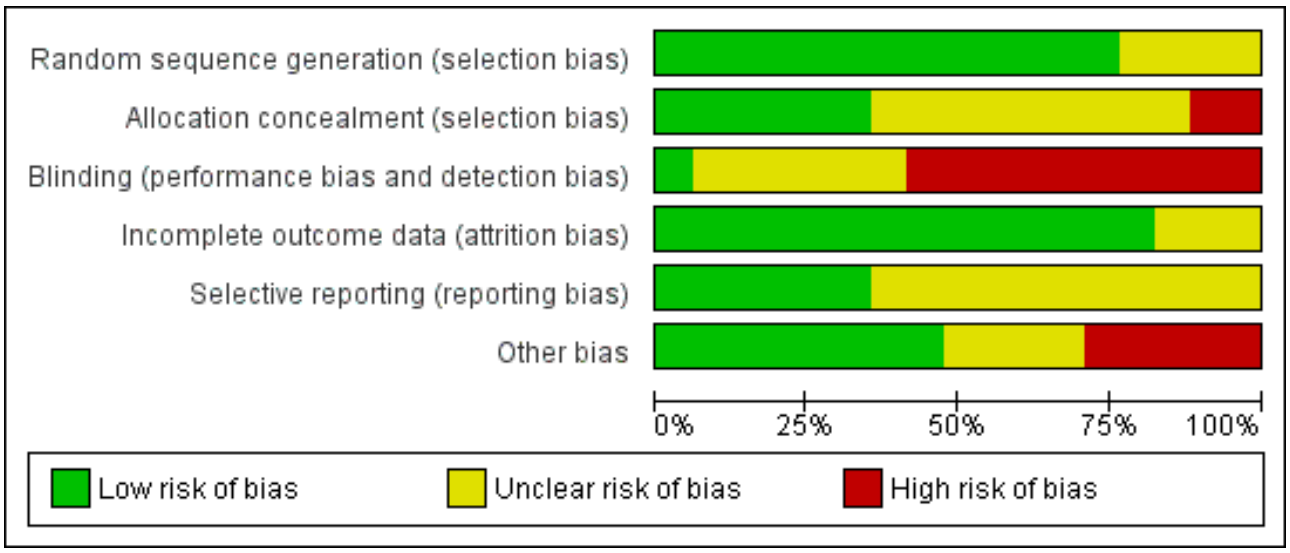
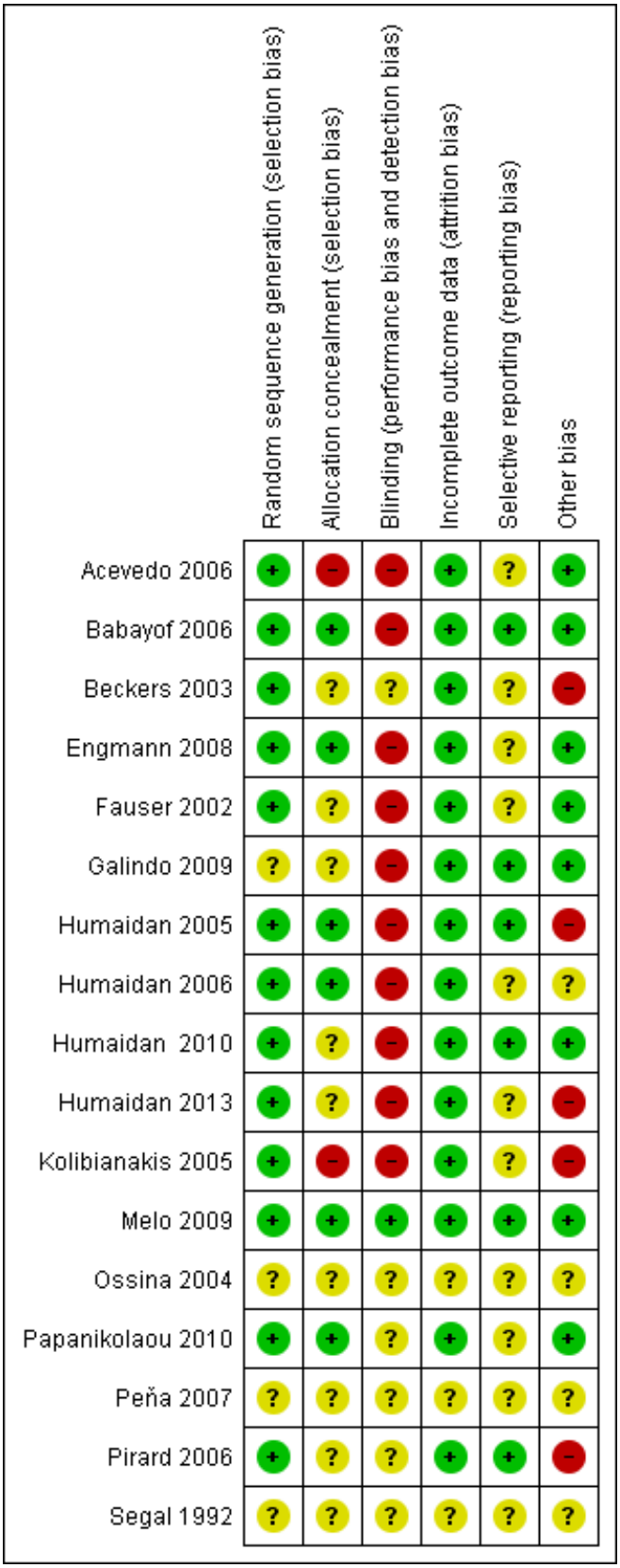


Figure 3. Methodological risk of bias summary: review authors' judgements about each methodological quality item for each included study.



Allocation

- Thirteen studies were rated as having low risk of bias related to sequence generation, and four were rated as having unclear risk of bias in this domain.
- Six studies were rated as having low risk of bias related to allocation concealment, and nine were rated as having unclear risk of this bias. In two trials, the allocation was not adequately concealed; these studies were rated as having high risk of bias (Kolibianakis 2005; Acevedo 2006).

Blinding

- One study clearly reported blinding of assessors (Melo 2009) and was deemed to be at low risk of bias related to blinding. Six studies did not clearly report on blinding and were rated as having unclear risk of bias related to assessment of OHSS. Ten reported lack of blinding and were rated as having high risk of bias related to assessment of OHSS.

Incomplete outcome data

Fourteen studies were rated as having low risk of attrition bias. Three were rated as having unclear risk of bias in this domain.

Intention-to-treat analysis

- We contacted the following investigators of individual studies via email to ask for additional information, so we could perform analyses on an ITT basis (Fauser 2002; Humaidan 2005; Acevedo 2006; Humaidan 2006; Humaidan 2010). We could not identify contact details for the authors of two abstracts (Ossina 2004; Peňa 2007); therefore we excluded these studies from analysis on the basis of missing relevant data.
- Only five studies performed an ITT analysis (Humaidan 2006; Galindo 2009; Humaidan 2010; Papanikolaou 2010; Humaidan 2013).
- In seven studies, no ITT analysis was performed (Fauser 2002; Beckers 2003; Humaidan 2005; Kolibianakis 2005; Acevedo 2006; Pirard 2006; Engmann 2008), and it was unclear whether ITT was used in two studies (Babayof 2006; Melo 2009). However, for all of these studies, the number of women randomised was known; therefore the ITT data could be imputed.

Selective reporting

Six studies were rated as having low risk of selective reporting bias; 11 were rated as having unclear risk of bias in this domain, in most cases because live birth and/or OHSS was not reported.

Other potential sources of bias

For eight studies, no additional potential sources of bias were noted. Four studies were rated as having unclear risk of other bias because they were reported only as abstracts and provided insufficient details on methods.

Five studies were deemed at high risk of other potential bias. All of these studies were prematurely discontinued. In one case (Kolibianakis 2005), study discontinuation was triggered by preplanned stopping rules. In other cases (Beckers 2003; Humaidan 2005; Pirard 2006), the interim analysis was unplanned and/or stopping rules were unclear. Three of these studies were stopped prematurely as the result of a significantly lower pregnancy rate in the GnRH agonist triggering group, and in one trial with six arms, two arms were stopped prematurely for the same reason (Pirard 2006). One study was stopped prematurely before the estimated sample size had been obtained as a result of the death of one of the local principal investigators and job rotations among other investigators (Humaidan 2013).

Effects of interventions

See: **Summary of findings for the main comparison** GnRH agonist compared with HCG for oocyte maturation triggering in antagonist-assisted reproductive technology

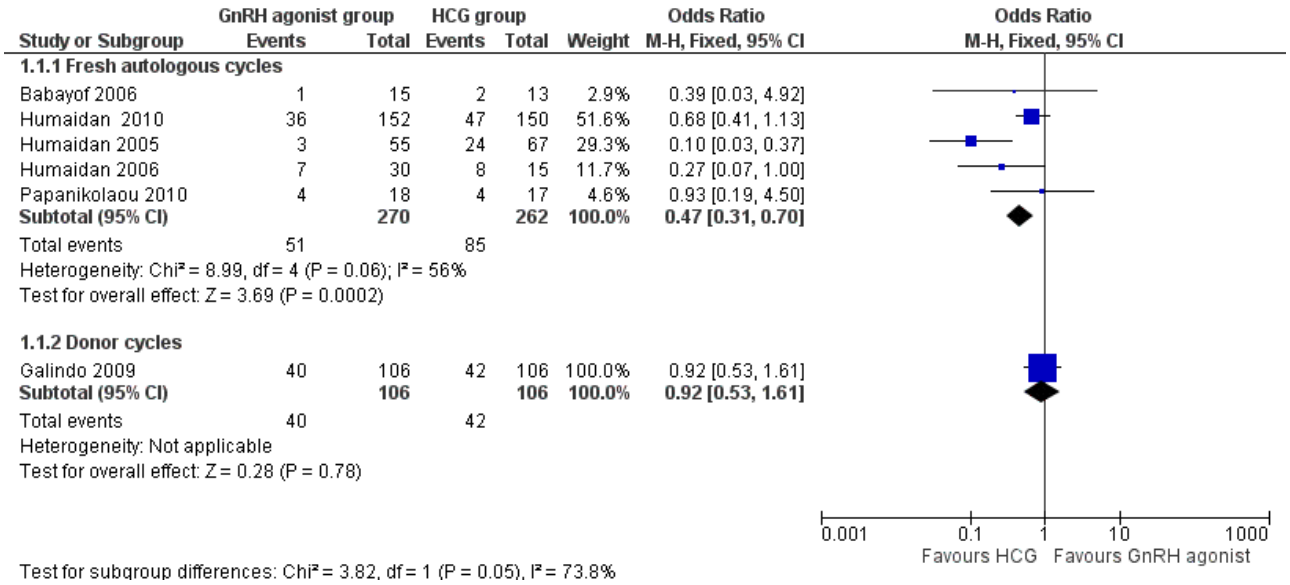
Primary outcomes

1.1 Live birth rate per woman randomised

1.1.1 Fresh autologous cycles

GnRH agonist trigger was associated with a lower live birth rate than was seen with HCG (OR 0.47, 95% CI 0.31 to 0.70; five RCTs, 532 women, I^2 = 56%, moderate-quality evidence). This means that for a woman with a 31% chance of achieving live birth with the use of HCG, the chance of a live birth with the use of a GnRh agonist will be between 12% and 24%. Use of a random-effects model did not substantially affect the results (OR 0.38, 95% CI 0.17 to 0.89), nor did use of risk ratios have a substantial effect. Statistical heterogeneity for this outcome was moderate. The live birth rate varied from 15% to 53% in the HCG group and from 5% to 24% in the agonist group (Analysis 1.1; Figure 4).

Figure 4. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.1 Live birth rate per women randomly assigned.



1.1.2 Donor-recipient cycles

No evidence of a difference in live birth rate was noted between GnRH agonist and HCG groups in donor-recipient cycles (OR 0.92, 95% CI 0.53 to 1.61; one RCT, 212 women) (Analysis 1.1; Figure 4).

1.2 Live birth rate in autologous cycles: subgroup analysis on luteal support approach

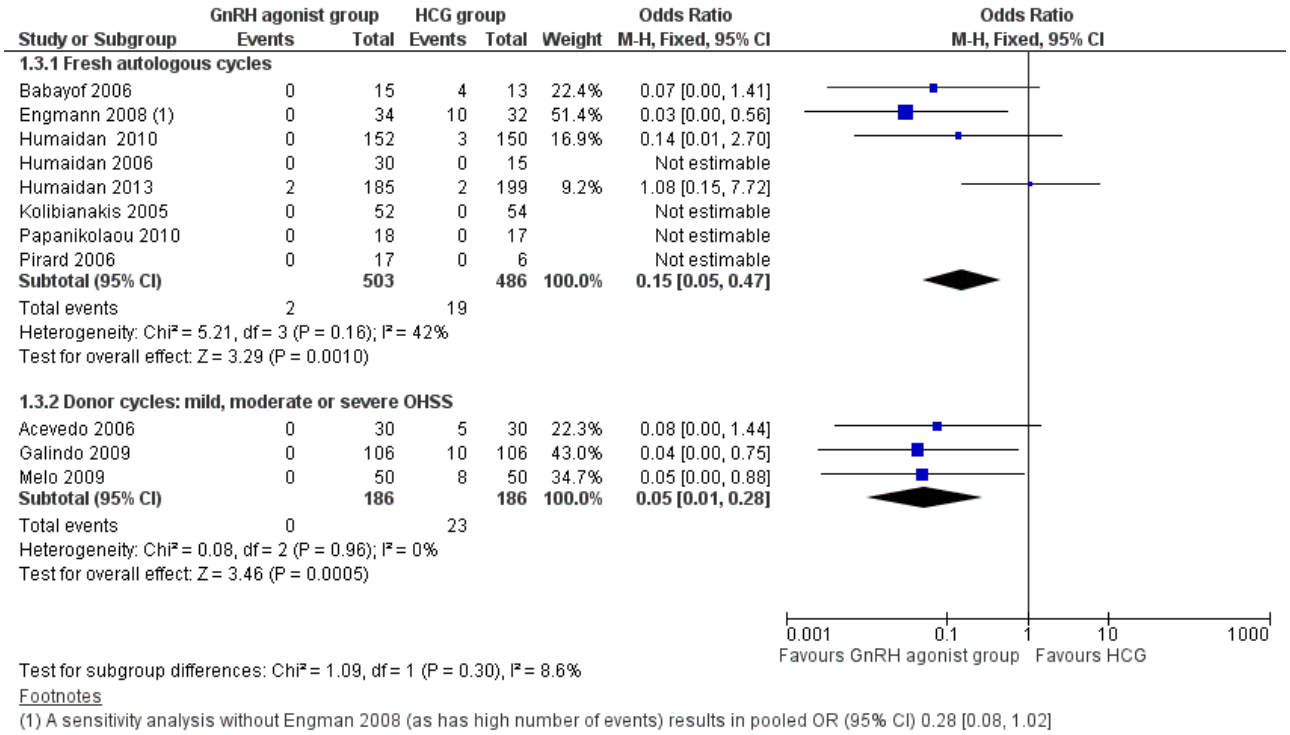
The subgroup analysis based on luteal phase support methods used in the included studies revealed differences in live birth rates between trials that used luteal phase support with LH activity and trials that used luteal phase support without LH activity. Both groups showed evidence of differences in live birth rate in favour of HCG, but this difference was significantly greater in studies that used luteal support without LH activity (studies with luteal phase support with LH activity: OR 0.63, 95% CI 0.40 to 0.98; three RCTs, 382 women, I^2 = 0%; studies with luteal phase support without LH activity: OR 0.13, 95% CI 0.04 to 0.39; two RCTS, 150 women, I^2 = 73%; test for subgroup differences: Chi^2 = 6.65, df = 1 (P value 0.010), I^2 = 85.0%) (Analysis 1.2).

1.3 Ovarian hyperstimulation syndrome (OHSS)

1.3.1 Fresh autologous cycles

GnRH agonist was associated with lower risk of OHSS (mild, moderate or severe) than was seen with HCG (OR 0.15, 95% CI 0.05 to 0.47; eight RCTs, 989 women, I^2 = 42%, moderate-quality evidence; Analysis 1.3). This suggests that for a woman with a 5% risk of OHSS using HCG, the rate would be between nil and 2% with use of a GnRH agonist. Use of a random-effects model did not substantially affect the results (OR 0.17, 95% CI 0.03 to 0.98; I^2 = 42%) (Analysis 1.3; Figure 5).

Figure 5. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.2 OHSS incidence per women randomly assigned.



1.3.2 Donor-recipient cycles

We found evidence of a lower incidence of OHSS in the GnRH agonist group than in the HCG group (OR 0.05, 95% CI 0.01 to 0.28; three RCTs, 374 women, I^2 = 0%) (Analysis 1.3; Figure 5).

1.4 Incidence of OHSS in autologous cycles: subgroup analysis on luteal support approach

The subgroup analysis based on luteal phase support methods used in the included studies found no evidence of a difference in OHSS rates between trials that used luteal phase support with LH activity and trials that used luteal phase support without LH activity (test for subgroup differences: Chi^2 = 3.39, df = 1 (P value 0.07), I^2 = 71%). No evidence was found of a difference between GnRH agonist and HCG groups among women who had luteal phase support with LH activity (OR 0.47, 95% CI 0.11 to 2.09; I^2 = 25%, five RCTs), but the OHSS rate was lower in the GnRH agonist group among women who had luteal phase support without LH activity (OR 0.04, 95% CI 0.01 to 0.34; I^2 = 0%) (Analysis 1.4).

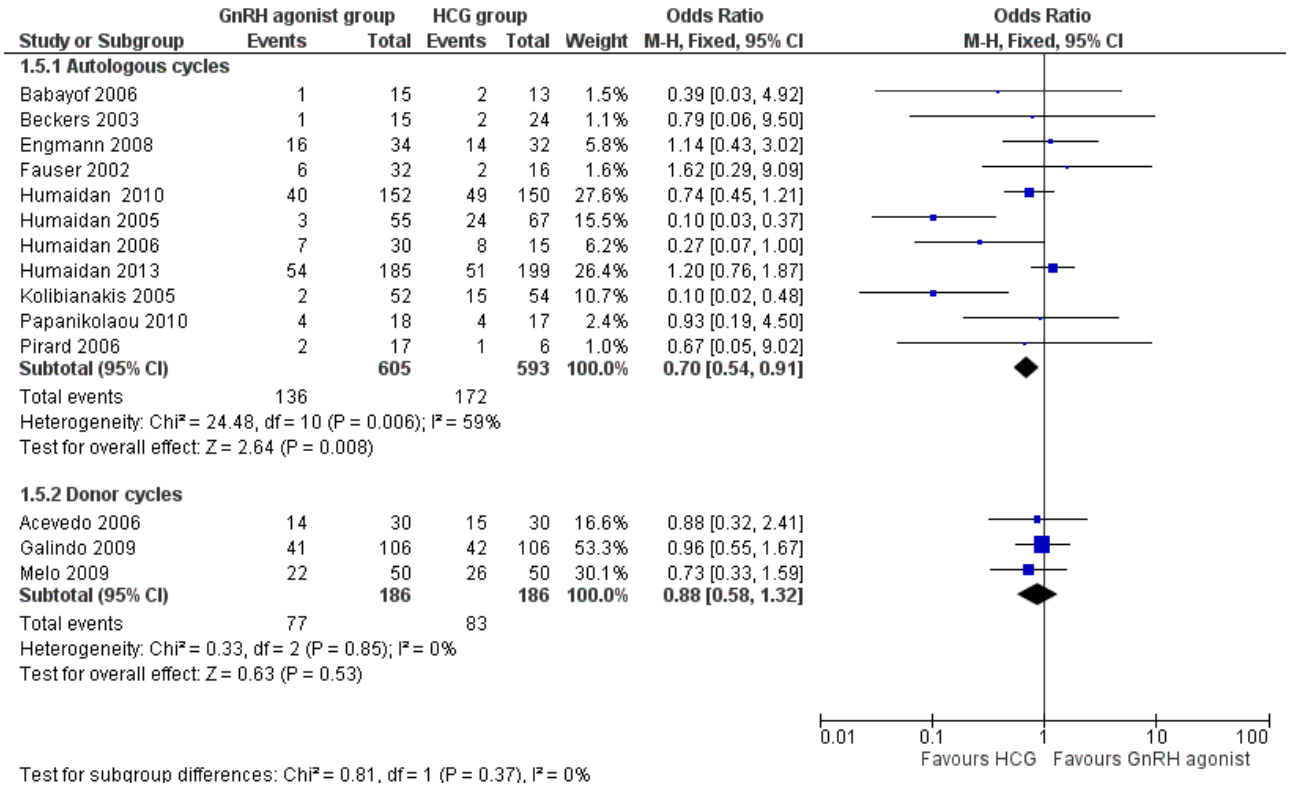
Secondary outcomes

1.5 Ongoing pregnancy rate per woman randomised

1.5.1 Fresh autologous cycles

GnRH agonist trigger was associated with a lower ongoing pregnancy rate when compared with HCG (OR 0.70, 95% CI 0.54 to 0.91; 11 RCTs, 1198 women, I^2 = 54%, moderate-quality evidence) (Analysis 1.5; Figure 6).

Figure 6. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.3 Ongoing pregnancy rate per women randomly assigned.



1.5.2 Donor-recipient cycles

We observed no evidence of differences between groups in ongoing pregnancy rate (OR 0.88, 95% CI 0.58 to 1.32; three RCTs, 374 women, I^2 = 0%) (Figure 5).

1.6 Ongoing pregnancy rate in autologous cycles: subgroup analysis on luteal support approach

The subgroup analysis based on luteal phase support methods used in the included studies indicated differences in ongoing pregnancy rate between trials that used luteal phase support with LH activity and those that used luteal phase support without LH activity (test for subgroup differences: Chi^2 = 8.1, df = 1 (P value 0.004), I^2 = 88%). No evidence was found of differences between groups among women who had luteal phase support with LH activity (OR 0.89, 95% CI 0.65 to 1.21; I^2 = 27%, five RCTs), but the ongoing pregnancy rate in the HCG group was higher among women who had luteal phase support without LH activity (OR 0.36, 95% CI 0.21 to 0.62; I^2 = 73%, five RCTs, 370 women) (Analysis 1.6).

1.7 Clinical pregnancy rate per woman randomised

1.7.1 Fresh autologous cycles

We found no evidence of a difference between groups in clinical pregnancy rate (OR 0.81, 95% CI 0.61 to 1.04; 11 RCTs, 1198 women, I^2 = 49%) (Analysis 1.7).

1.7.2 Donor-recipient cycles

We found no evidence of a difference between groups in clinical pregnancy rate (OR 0.87, 95% CI 0.57 to 1.33; three RCTs, 372 women, I^2 = 0%) (Analysis 1.7).

1.8 Miscarriage rate per woman randomised

1.8.1 Fresh autologous cycles

GnRH agonist trigger was associated with a higher early miscarriage rate when compared with HCG (OR 1.74, 95% CI 1.10 to 2.75; 11 RCTs, 1198 women, I^2 = 1%) (Analysis 1.8).

1.8.2 Donor-recipient cycles

We found no evidence of differences between groups in miscarriage rate (OR 1.14, 95% CI 0.56 to 2.32; three RCTs, 372 women, I^2 = 0%) (Analysis 1.8).

1.9 Multiple pregnancy per woman randomised

1.9.1 Fresh autologous cycles

We found no evidence of differences between groups in multiple pregnancy rate (OR 3.00, 95% CI 0.30 to 30.47; two RCTs, 62 women, I^2 = 0%) (Analysis 1.9).

1.9.2 Donor-recipient cycles

We found no evidence of differences between groups in multiple pregnancy rate (OR 1.73, 95% CI 0.86 to 3.48; three RCTs, 374 women, I^2 = 0%) (Analysis 1.9).

Additional analyses

Subgroup and sensitivity analyses

10.1 OHSS incidence: effect of risk

OHSS in women at low risk of OHSS

No evidence of a difference between GnRh agonist and HCG was noted in the rate of OHSS among women at low risk of OHSS (OR 0.79, 95% CI 0.18 to 3.47; six RCTs, 777 women, I^2 = 66%; Analysis 1.10). Heterogeneity for this analysis was substantial, probably as a result of the low event rate, with four of the six RCTs reporting no events in either arm.

OHSS in women at high risk of OHSS

GnRH agonist was associated with a significantly lower risk of OHSS when compared with HCG among women at high risk of OHSS (OR 0.06, 95% CI 0.01 to 0.34; three RCTs, 212 women, I^2 = 0%; Analysis 1.10).

10.2 Effect of including only moderate or severe OHSS as an outcome

After cases with mild OHSS were excluded, GnRH agonist was associated with lower risk of moderate or severe OHSS when compared with HCG (OR 0.21, 95% CI 0.07 to 0.66; four RCTs, 112 women, I^2 = 20%; Analysis 1.2). The analysis included only 16 events reported by four RCTs. A further five RCTs reported no events in either arm.

Results were similar among women at high risk of OHSS: GnRH agonist was associated with significantly lower risk of moderate or severe OHSS when compared with HCG (OR 0.09, 95% CI 0.02 to 0.52; four RCTs, 112 women, I^2 = 0%; Analysis 1.10).

10.3 Use of risk ratios rather than odds ratios

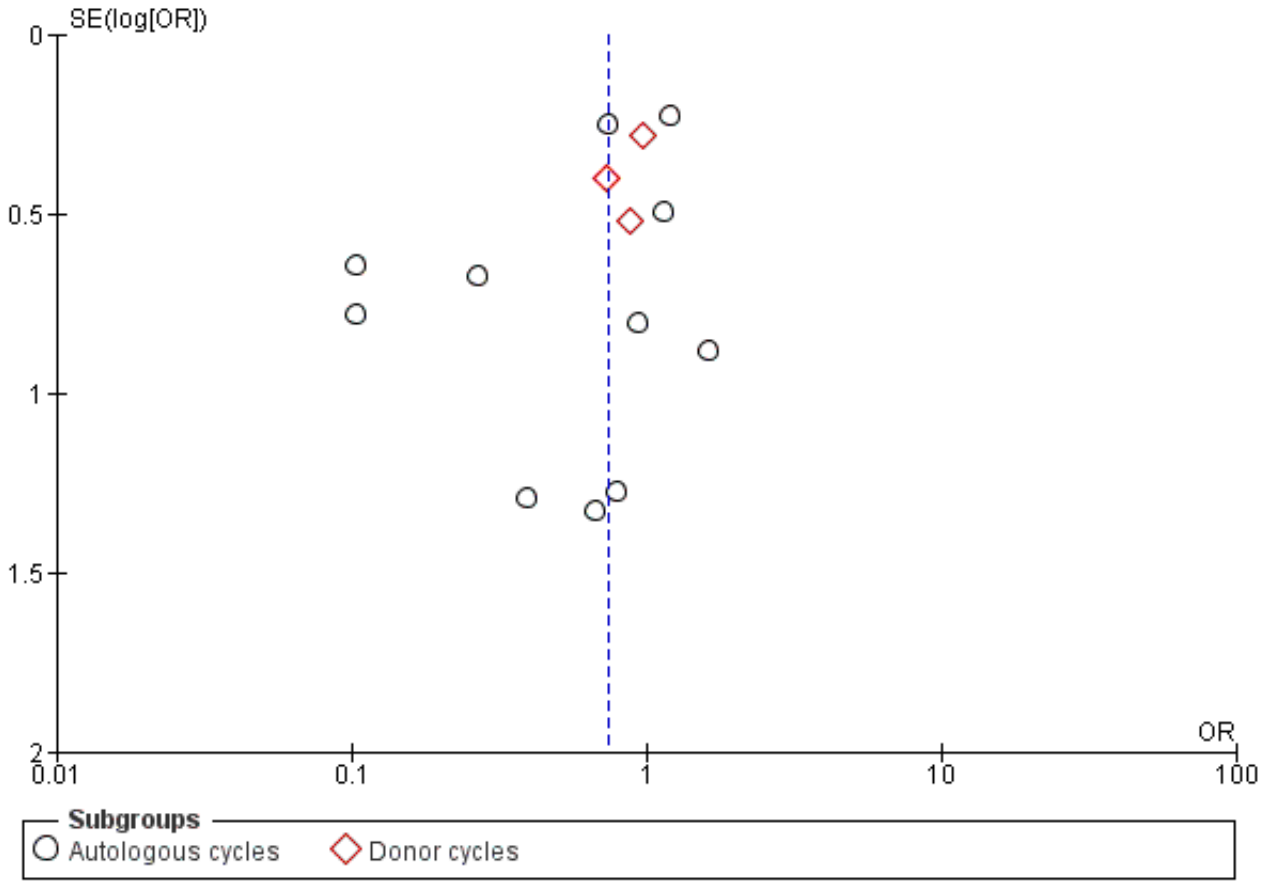
Use of risk ratios rather than odds ratios did not materially affect our findings.

Findings of other subgroup and sensitivity analyses are described above, under the section on relevant comparisons.

Assessment of publication bias

A funnel plot was constructed for the outcome of ongoing pregnancy (Figure 7). This plot was not symmetrical, as a greater number of effect estimates were placed on the left side of the graph. This could imply publication bias, but in this case it seems more likely that the effect was due to the fact that the more extreme effect estimates were derived from studies that did not use luteal support with LH.

Figure 7. Funnel plot of comparison: 1 GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.5 Ongoing pregnancy rate per woman randomised.



DISCUSSION

Summary of main results

This review update on the benefits and harms of GnRH agonist trigger in subfertile women treated with GnRH antagonist in IVF/ICSI treatment cycles found that use of GnRH agonist trigger compared with HCG triggering was associated with a markedly reduced live birth rate and an increased early miscarriage rate but was beneficial in preventing OHSS in fresh autologous cycles among women at high risk of OHSS. No differences between interventions in OHSS incidence were noted among women at low risk of OHSS. Overall (regardless of underlying risk) for a woman with a 5% risk of mild, moderate or severe OHSS with use of HCG, the risk of OHSS with use of a GnRh agonist was between nil and 2%, and for women with a 5% risk of developing moderate or severe OHSS with use of HCG, the risk with use of a GnRH antagonist was between nil and 3% (Summary of findings for the main comparison).

In donor-recipient cycles, use of GnRH agonist instead of HCG also resulted in a lower incidence of OHSS. No evidence was found of a difference in live birth or ongoing pregnancy rate, although the results were consistent with those for fresh autologous cycles.

Overall completeness and applicability of evidence

Kol 2013;

Quality of the evidence

GRADE assessment found that evidence for most review outcomes was of moderate quality. Exceptions included ongoing pregnancy and multiple pregnancy, which were rated as having low-quality evidence. Reasons for downgrading evidence quality included poor reporting of study methods, premature study termination, failure to blind outcome assessment and statistical heterogeneity. For some outcomes, confidence intervals were wide as the result of low event rates (Summary of findings for the main comparison).

The authors of four studies stated that the studies were commercially funded. The authors of most studies failed to disclose their funding source.

Potential biases in the review process

Strengths of this review include comprehensive systematic searching for eligible studies, rigid inclusion criteria for RCTs and data extraction and analysis by two independent review authors. Furthermore, the possibility of publication bias was minimised by inclusion of both published and unpublished studies (such as abstracts from meetings). However, as with any review, we cannot guarantee that we found all eligible studies.

Agreements and disagreements with other studies or reviews

Our results are in agreement with those of a previous review (Griesinger 2006). However, that review included only three small randomised controlled studies (Fauser 2002; Humaidan 2005; Kolibianakis 2005) involving 275 randomised women.

How can poor reproductive outcomes following oocyte triggering with GnRH agonist be explained? In previous studies, oocyte maturity, fertilisation rate and embryo development were comparable between GnRH agonist and HCG-induced final oocyte maturation. This was found both in fresh autologous cycles (Griesinger 2006) and in donor cycles (Bodri 2009; Erb 2009). Furthermore, frozen-thawed cycles with embryos obtained after oocyte triggering with GnRH agonist resulted in high pregnancy rates (Griesinger 2007a; Griesinger 2007b). Hence, oocyte triggering with GnRH agonist appears to have no major impact on oocyte and embryo quality.

It seems more likely that GnRH agonist induces a luteal phase defect. This luteal phase defect may result from the short half-life of the induced LH surge, leading to premature luteolysis of corpus luteum and significantly lower steroidal and non-steroidal hormones, thus affecting endometrial receptivity (Lanzone 1994; Peñarrubia 1998; Nevo 2003; Emperaire 2004; Humaidan 2005). Consequently, further studies have been conducted to evaluate different modified luteal phase strategies with LH activity supplementation in terms of administration of small dosages of HCG around the time of oocyte maturation trigger (Humaidan 2010; Humaidan 2013) or with repeated administration of recLH (Papanikolaou 2010), or without LH supplementation but with the help of progesterone and oestradiol administration (Engmann 2008). Our subgroup analysis shows that, although modified luteal phase support with LH was associated with pregnancy rates almost comparable with those of HCG, the difference in OHSS risk was no longer present. Apparently, available regimens could not compensate for the induced luteal phase defect in GnRH agonist–triggered cycles.

Our meta-analysis of fresh autologous cycles and donor-recipient cycles found that use of a GnRH agonist trigger is associated with a significantly reduced incidence of OHSS when compared with HCG, as none of the women in the pooled studies developed any form of OHSS when in the GnRH agonist group. The shorter half-life of the endogenous LH surge and subsequent pituitary suppression and withdrawal of LH support for the corpora luteum may lead to early luteolysis (Kol 2004; Kol 2008). Moreover, significantly lower luteal levels of inhibins and steroid hormones suggest that the corpora luteum may secrete lower levels of other non-steroidal substances, and the vasoactive properties of vascular endothelial growth factor (VEGF) may be involved in OHSS. This may explain the mechanism of OHSS prevention with the use of GnRH agonists (Nevo 2003; Cerrillo 2011).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence suggests that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate (pregnancy beyond 12 weeks) and a higher rate of early miscarriage (less than 12 weeks). GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers (for whatever reason), women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation.

Implications for research

In women with high risk of OHSS, the utility of GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles should be evaluated in the context of effectiveness versus safety. For these studies, it is important that trial authors clearly report their funding source.

ACKNOWLEDGEMENTS

Marian Showell, Trial Search Co-ordinator for the Cochrane Menstrual Disorders and Subfertility Group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Acevedo 2006

Methods	Randomised, controlled, single-centre, donor-recipient study
Participants	60 oocyte donors 18 to 35 years of age with normal menstrual cycle: no PCOS, endometriosis, hydrosalpinges or severe male factor. 98 recipients 34–47 years of age received oocyte, but only 60 participants were analysed. Baseline characteristics: Most donors had similar basal ovarian conditions: basal FSH 5.2 vs 2.3 mIU/mL; E_2 44.1 vs 32.5 pg/mL
Interventions	**Ovarian stimulation:** fixed dose of 150 IU rFSH on cd 3/4 f + 0.25 mg/d sc orgalutran + 75 IU/d of LH **Intervention:** 0.2 mg, SC triptorelin vs 250 µg/mL SC rHCG **Luteal phase support (recipients):** E_2 plus 600 mg/d natural progesterone
Outcomes	**Donors** **Primary outcome:** OHSS **Secondary outcomes:** FSH and LH units (IU), GnRH antagonist ampoules, E_2 levels, follicle numbers on day 5 of COH and on HCG day **Recipients** Pregnancy rates, implantation rates
Notes	98 recipients were included in the study, but for statistical techniques, only one participant of those who received oocytes from the same donor was included in the analysis Participants received embryos originating from donors; some donors gave oocytes to 2 recipients. Only 1 recipient was randomly included in the statistical analysis

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

Acevedo 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	High risk	Reported that allocation was not concealed (after contact was made with study author)
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Participants, those administering the interventions and those assessing the outcomes were not blinded to group assignment. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available. Live birth rates were not reported
Other bias	Low risk	No other potential bias was identified

Babayof 2006

Methods	Randomised, controlled, single-centre study
Participants	28 women with PCOS for IVF. Basic clinical characteristics: Both groups were similar in age: 30.1 vs 29.3, BMI 24.1 vs 27.1 and cause of infertility; 5.8 vs 5.3 and basal FSH (IU/L) 7.8 vs 4.3
Interventions	**Ovarian stimulation:** adjustable dose of 225 IU SC rFSH + 0.25 mg SC cetrotide **Intervention:** 0.2 mg decapeptyl vs 250 µg rHCG **Number of embryos transferred:** GnRH agonist group vs HCG group (mean: 2.3 ± 0.2 vs 2.2 ± 0.4) **Luteal phase support:** 50 mg/d of progesterone IM ± 4 mg/d E_2 PO (if serum E_2 concentration was below 200 pmol/L ± doubled dose of progesterone if serum progesterone concentration was below 40 nmol/L)
Outcomes	**Primary outcome:** serum levels of inhibin A, VEGF, TNFa, E_2 and progesterone and incidence of OHSS **Secondary outcomes:** ovarian size and pelvic fluid accumulation, live birth, ongoing, chemical, miscarriage, number of oocytes retrieved, number of MII oocytes, fertilisation rate and number of embryos transferred
Notes	**OHSS classification:** Golan 1989 **HCG group:** 2 cases of ET were cancelled, and all embryos were frozen as the result of severe OHSS with accumulation of large amount of free fluid in the pelvis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation list
Allocation concealment (selection bias)	Low risk	An independent nurse dispensed HCG or GnRH agonist according to a randomisation list

Babayof 2006 *(Continued)*

Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Participants, those administering interventions and those assessing outcomes were not blinded to group assignment. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include most expected outcomes
Other bias	Low risk	No other potential bias was identified

Beckers 2003

Methods	Randomised, controlled, 3-arm, 2-centre study
Participants	40 participants for IVF/ICSI. 38 years of age or younger, regular menstrual cycle, both ovaries present, absence of uterine abnormalities, BMI 18 to 29 kg/m^2, no history of poor ovarian response or moderate or severe OHSS Baseline characteristics: comparable between the 2 groups (data not shown)
Interventions	**Ovarian stimulation:** fixed dose of 150 IU r-hFSH on cd 2 or 3 using + 1 mg daily SC antide **Intervention:** 0.2 mg SC triptorelin vs 250 µg/mL SC rHCG vs 1 mg SC r-LH **Number of embryos transferred:** GnRH agonist group vs HCG group: maximum of 2 embryos were transferred after 2 to 5 days of culture **Luteal phase support:** none
Outcomes	**Primary outcomes:** LH (day of oocyte retrieval), day of progesterone maximal level, day of decrease in progesterone **Secondary outcomes:** duration of follicular phase (days), number of days of GnRH antagonist, number of follicles ≥ 11 mm, number of oocytes retrieved, number of participants achieving embryo transfer pregnancy, ongoing pregnancy
Notes	Study was cancelled prematurely because of observed premature luteal phase bleeding and extremely low pregnancy rates Commercial funding: This investigator-driven study was supported by a research grant from Serono International SA, and by 'Stichting Voortplantingsgeneeskunde' Rotterdam

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated with sealed envelopes for both centres; a separate stratified randomisation list was generated by computer
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes. No further details were reported
Blinding (performance bias and detection bias)	Unclear risk	Blindedness was not reported clearly. Risk applies to assessment of OHSS

Beckers 2003 *(Continued)*
FOR OHSS OUTCOME

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available. No data were provided on live birth rate, incidence of OHSS
Other bias	High risk	Study was terminated prematurely because of observed premature luteal phase bleeding and extremely low pregnancy rates

Engmann 2008

Methods	Open-label, parallel, university-based tertiary fertility centre, RCT
Participants	66 women were included. Inclusion criteria: age 20 to 39 years, basal FSH concentration ≤ 10.0 IU/L and undergoing first cycle of IVF with PCOS or PCOM, or undergoing subsequent cycle with a history of high response in previous IVF cycles. Exclusion criteria: women with hypogonadotropic hypogonadism **Baseline characteristics:** 32.0 ± 3.7 vs 33.1 ± 3.6 years
Interventions	**Ovarian stimulation:** Control group: OCP + 112 to 225 IU recFSH on CD2 + midluteal 1 mg leuprolide acetate (SC). Study group: OCP + 112 to 225 IU recFSH on CD2 + flexible GnRH antagonist protocol (SC) I**ntervention:** SC leuprolide in a dose of 1 mg approximately 12 hours after last dose of ganirelix vs SC hCG (Profasi; Serono, Randolph, MA) in a dose ranging from 3300 to 10,000 IU, depending on follicular response **Number of embryos transferred:** GnRH agonist group vs HCG group (mean ± SD: 2.0 ± 0.2 vs 2.2 ± 0.6) **LPS: study group:** 50 mg IM P in oil + 0.1 mg transdermal E_2 patches every other day, starting the day after oocyte retrieval. Both doses were adjusted according to E_2 and P levels on the day of embryo transfer and 1 week after oocyte retrieval. **Control group:** 0 mg IM P in oil
Outcomes	**Primary outcome measures:** OHSS occurrence assessed 1 week after oocyte retrieval and implantation rate assessed at 7 weeks' gestation **Secondary outcome measures:** clinical pregnancy rate assessed at time of ultrasound, mature oocytes assessed at time of retrieval and ovarian volume assessed 1 week after oocyte retrieval
Notes	Supported in part by an unrestricted educational grant from Organon USA, Roseland, New Jersey

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	1:1 by means of computer-generated random numbers with separate randomisation for women undergoing first cycle and for women with a previous high response by the use of stratified randomised blocks
Allocation concealment (selection bias)	Low risk	Research nurse by using a series of consecutively numbered sealed opaque envelopes (1 for each category of previous cycle)
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Not blinded. Risk applies to assessment of OHSS

Engmann 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Most randomly assigned women were analysed using per-protocol (PP) and intention-to-treat analysis (ITT)
Selective reporting (reporting bias)	Unclear risk	Protocol was available and outcomes were prespecified; OHSS, implantation rate (IR), MII, CPR, ovarian volume 1 week after oocyte retrieval. Study reported extra outcomes not stated in the protocol, such as serum luteal phase E_2, P levels, fertilisation rate (FR). Live birth rate not reported
Other bias	Low risk	No other source of potential bias was identified

Fauser 2002

Methods	Randomised, controlled, open-label, 3-arm, 6-international centre study
Participants	57 women for IVF/ICSI. 18 to 39 years of age, regular menstrual cycle (24 to 35 days) and BMI 18 to 29 kg/m^2. Baseline characteristics were comparable between the 3 treatment groups: mean age 30.4 years, height 1.67, BMI 23.3; 98% were Caucasian
Interventions	**Ovarian stimulation:** adjustable dose of 150 to 225 IU rFSH, SC on cd 2 to 3 for the first 5 days + 0.25 mg ganirelix on day 6 of FSH stimulation **Intervention:** 0.2 mg triptorelin vs 0.5 mg leuprorelin vs 10,000 IU HCG **Number of embryos transferred:** GnRH agonist group vs HCG group: No more than 3 embryos were transferred **Luteal phase support:** progestin 50 mg daily, from the day of embryo transfer (ET) for at least 2 weeks or until menses
Outcomes	**Primary outcomes:** FSH, LH, E_2, HCG and P in the luteal phase **Secondary outcomes:** FSH consumption (IU); duration of FSH treatment (days); duration of ganirelix treatment (days); number of oocytes/participant on day of HCG or GnRH agonist proportion of metaphase II oocytes; fertilisation rate; number of embryos obtained/participant; embryo quality; implantation rate; ongoing pregnancy rate
Notes	Sample calculation not performed 57 of 200 participants; only 47 were randomly assigned. Eight participants were not randomly assigned because ovarian response to stimulation was not sufficient. Two participants were not randomly assigned because of high response. One participant in the hCG group did not undergo ET because of fertilisation failure. Duration of fertility was not stated, no data on live birth rate and on OHSS incidence and multiple pregnancy rates were provided Commercial funding: supported by NV Organon

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive telephone randomisation system that stratified for age, primary or secondary infertility and number of follicles. Participants were randomly assigned in a ratio of 1:1:1
Allocation concealment (selection bias)	Unclear risk	Adequate

Fauser 2002 *(Continued)*

Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Outcome assessors and participants were not blind to the intervention. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available. Live birth rate was not reported
Other bias	Low risk	No other potential bias was identified

Galindo 2009

Methods	Randomised, controlled, open-label, single-centre study
Participants	257 oocyte donors 18 to 35 years of age, BMI < 30 kg/m^2, regular (26 to 35 days) menstrual cycles. Patients with previous history of low response to ovarian stimulation, PCO or using OCP were excluded. Baseline characteristics: age 25.8 vs 26.6 years, BMI 22.9 vs 22.8, fertilisation rate 70.1 vs 67.8 274 recipient cycles: ≤ 50 years with POF, reduced ovarian reserve or a history of previous failed IVF cycles. Baseline characteristics: 40.6 vs 40.6 years of age, menopause16% vs 21%, previous failed IVF 23% vs 28%
Interventions	**Ovarian stimulation:** 225 IU of rFSH on cd 2 + 0.25 mg/d cetrotide **Intervention:** 0.2 mg triptorelin SC vs 250 µg rHCG **Luteal phase support:** 800 mg of micronised vaginal progesterone daily
Outcomes	**Donors:** stimulation duration, total FSH dose, final E_2 level and follicular count, fertilisation rate, OHSS incidence **Recipients:** clinical, ongoing and live birth rates, implantation rate and twinning rate
Notes	**Excluded patients:** donors with a final E_2 4.500 pg/mL and/or 20 follicles 14 mm at last control were excluded from randomisation and donors who needed coasting **OHSS classification:** Navot 1992 No conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not reported clearly
Allocation concealment (selection bias)	Unclear risk	Sealed, opaque envelopes. No further details were reported
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Participants, those administering interventions and those assessing outcomes were not blinded to group assignment. Risk applies to assessment of OHSS

Galindo 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Live birth rate was not reported
Other bias	Low risk	No other potential bias was identified

Humaidan 2010

Methods	Randomised, controlled, 3-centre study
Participants	302 normo-gonadotrophic IVF/ICSI participants, 25 to 40 years of age, BMI 18 to 30 kg/m^2, basal FSH < 12 IU/L, menstrual cycle 25 to 34 days, both ovaries present, absence of uterine abnormalities. Each participant contributed with only 1 cycle Baseline characteristics: 31.5 vs 30.9 years of age, BMI 23.8 vs 23.5, basal FSH 6.7 vs 6.7
Interventions	**Ovarian stimulation:** adjustable dose of 150 to 200 IU rFSH + 0.25 mg ganirelix **Intervention:** 0.5 mg buserelin SC plus 1500 IU HCG IM 35 hours after triggering of ovulation vs 10,000 IU HCG **Luteal phase support:** 90 mg/d progesterone vaginal plus 4 mg/d oestradiol, beginning on the day after OPU and continuing until the day of the pregnancy test
Outcomes	**Primary outcomes:** reduction in high early pregnancy loss rate **Secondary outcomes:** MII oocytes retrieved, OHSS incidence, ongoing pregnancy rate
Notes	A total of 305 participants were included in the study, but 3 were not randomly assigned because of inadequate ovarian response Not stated whether investigators received commercial funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes. No further details were reported
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Participants, those administering interventions and those assessing outcomes were not blinded to group assignment. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include most expected outcomes

Humaidan 2010 *(Continued)*

Other bias	Low risk	No other potential bias was identified

Humaidan 2005

Methods	Randomised, controlled, open-label, 2-centre study
Participants	122 normo-gonadotrophic women for IVF or ICSI. 25 to 40 years of age, baseline FSH and LH 12 IU/L, menstrual cycles between 25 and 34 days, BMI 18 to 30 kg/m^2, both ovaries present, absence of uterine abnormalities. Each participant contributed with 1 cycle only Baseline characteristics: 33.4 vs 32.3 years of age, BMI 23.6 vs 23.5, FSH 6.8 vs 6.7
Interventions	**Ovarian stimulation:** adjusted dose of 150 or 200 IU rFSH on cd 2 + 0.25 mg ganirelix **Intervention:** 0.5 mg buserelin SC vs 10,000 IU HCG SC **Number of embryos transferred:** Maximum of 2 embryos were transferred. Mean number of embryos transferred: mean and range: 1.71 (1 to 2) vs 1.64 (1 to 2) **Luteal phase support:** 90 mg/d progesterone vaginally plus oestradiol 4 mg/d per os, commencing from the day following oocyte retrieval and continuing until the day of the pregnancy test
Outcomes	**Primary outcomes:** positive HCG per ET. Clinical pregnancy. Early pregnancy loss **Secondary outcomes:** rate of embryo transfer (ET), numbers of embryos transferred, implantation rate, oocytes retrieved, MII oocytes, pronuclear oocytes, embryos (%); E_2, FSH and LH levels on sd1, day 6 and ovulation induction day; progesterone on ovulation induction day
Notes	Terminated because of differences in clinical outcomes between groups Embryo transfer was cancelled in 7 patients in the GnRH agonist group and in 10 patients in the HCG group as the result of total fertilisation failure or poor embryo development Commercial funding: unclear whether investigators received commercial funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	By a study nurse; using computer-generated random numbers in sealed, unlabelled envelopes, each containing a unique study number
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Participants, those administering interventions and those assessing outcomes were not blinded to group assignment. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include most expected outcomes
Other bias	High risk	Terminated early because of differences in clinical outcomes between groups

Humaidan 2006

Methods	Randomised, controlled, open-label, single-centre study
Participants	45 normo-gonadotrophic women for IVF/ICSI, 25 to 40 years of age, baseline FSH and LH < 12 IU/L, menstrual cycles between 25 and 34 days, BMI 18 to 30 kg/m^2, both ovaries present, absence of uterine abnormalities. Each participant contributed with only 1 cycle Baseline characteristics: The 3 groups were comparable and 100% Caucasian
Interventions	**Ovarian stimulation:** adjusted dose of 150 to 200 IU r-hFSH on cd 2 + 0.25 mg ganirelix **Intervention:** 0.5 mg buserelin SC plus HCG 1500 IU IM 12 hours vs 0.5 mg buserelin SC 1500 IU IM 35 hours after buserelin injection vs 10,000 IU HCG SC **Number of embryos transferred (mean ± SD):** 1.9 ± 0.3 vs 1.9 ± 0.3 vs 1.8 ± 1.5 **Luteal phase support:** 90 mg/d progesterone vaginally plus 4 mg/d oestradiol orally
Outcomes	**Primary outcomes:** serum P and inhibin A concentration **Secondary outcomes:** total dose of FSH (IU), duration of FSH stimulation (days), total dose of antagonist (mg), serum oestradiol (n mol/L) on SI, S6, day of ovulation induction, serum FSH, day of ovulation induction (IU/L), number of oocytes, number of embryos, rate of transfer, number of embryos transferred, positive HCG per embryo transfer, clinical pregnancy per embryo transfer, clinical pregnancy per cycle, implantation rate, early pregnancy loss
Notes	Unclear whether investigators received commercial funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes, each containing a unique study number. Allocation by a study nurse
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Participants, those administering interventions and those assessing outcomes were not blinded to group assignment. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available, but published reports include most expected outcomes
Other bias	Unclear risk	Serum P and inhibin A as primary outcomes, small group of women, funding unclear

Humaidan 2013

Methods	2 randomised, controlled studies; multi-centre study (4 centres)

Humaidan 2013 *(Continued)*

Participants	384 infertile women 25 to 40 years of age; normal menstrual cycles of 25 to 34 days or oligomenorrhoea/amenorrhoea or polycystic ovary syndrome, defined according to Rotterdam criteria (2004), BMI 18 to 35 kg/m^2 and absence of uterine abnormalities. Exclusion criteria included women with hypothalamic dysfunction, diabetes, epilepsy, liver, renal or heart disease or metabolic disorders
Interventions	**Ovarian stimulation:** fixed dose of 150 to 200 IU/d recFSH (Puregon; Organon, Skovlunde, Denmark) from cd 2 or 3 and for the first 4 days, then dose adjusted according to ovarian response. Fixed GnRH antagonist protocol, bolus of 0.25 mg/d ganirelix (Orgalutran; Organon, Skovlunde, Denmark), was initiated on stimulation day 5 **Intervention:** As soon as 2 follicles had reached a diameter of 17 mm, 2 different randomisation lists were available, depending on the number of follicles seen on transvaginal ultrasound examination on the final day of ovarian stimulation: 1 for participants with 14 follicles ≥ 11 mm in diameter (at risk of OHSS) and 1 for participants with ≤ 14 follicles ≥ 11 mm (OHSS low-risk group) • Group at risk of OHSS was randomly assigned to 2 groups: Group A, triggering of final oocyte maturation with a bolus of 0.5 mg buserelin (GnRHa) SC (Suprefact; Hoechst, Hoersholm, Denmark), followed by a single bolus of 1.500 IU HCG IU SC (Pregnyl; Organon, Skovlunde, Denmark) after oocyte retrieval—or Group B, 5.000 IU HCG(Pregnyl; Organon, Skovlunde, Denmark) • OHSS low-risk group was randomly assigned to triggering of final oocyte maturation with the following: Group C, a bolus of 0.5 mg buserelin SC (Suprefact; Hoechst, Hoersholm, Denmark), followed by a bolus of 1.500 IU HCG SC (Pregnyl; Organon, Skovlunde, Denmark) after oocyte retrieval and an additional bolus of 1.500 IU HCG on the day of oocyte retrieval +5; or Group D, 5.000 IU HCG (Pregnyl; Organon, Skovlunde, Denmark) **Number of embryos transferred:** GnRH agonist group vs HCG group (median 1 to 5 vs 1 to 6) embryos transferred **Luteal phase support:** micronised progesterone vaginally, 90 mg twice daily (Crinone; Serono Nordic, Copenhagen, Denmark) and oestradiol (E_2) 4 mg a day per os (Estrofem; Novo Nordisk, Copenhagen, Denmark), commencing on the day following oocyte retrieval and continuing until 7 weeks of gestation
Outcomes	• Primary outcome measures: OHSS rate • Secondary outcome measures: Biochemical pregnancy was defined by plasma b-HCG 10 IU/L on day 12 after embryo transfer • Clinical pregnancy was defined as an intrauterine gestational sac with a heartbeat 3 weeks after a positive HCG test • Ongoing pregnancy was defined as a viable pregnancy at week 11 of pregnancy
Notes	Study was discontinued before the estimated sample size had been obtained as a result of the death of 1 of the local principal investigators and job rotations among other investigators Commercially funded by MSD, Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a study nurse, using computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Sealed, unlabelled envelopes, each containing a unique study number. No further details were reported
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Not blinded. Risk applies to assessment of OHSS

Humaidan 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomly assigned were included in analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol is available, but published reports did not include most expected outcomes (LBR)
Other bias	High risk	Study was discontinued early

Kolibianakis 2005

Methods	RCT, 2-armed, 1:1 randomisation ratio, open-label, parallel design; 2-centre study
Participants	106 women for IVF/ICSI. 39 years of age or younger, normal day 3 serum FSH levels, ≤ 3 previous assisted reproduction technology (ART) attempts, BMI 18 to 29 kg/m^2, regular menstrual cycles, no PCOS or previous poor response to ovarian stimulation, both ovaries present, fresh ejaculated sperm and no embryo biopsy. Participants could enter the study only once Baseline characteristics: 32.4 vs 32.3 years of age, BMI 22.9 vs 23.7, basal FSH 8.2 vs 8.l
Interventions	**Ovarian stimulation:** fixed dose of 200 IU rFSH started on cd 2 + 0.25 mg orgalutran **Intervention:** 0.2 mg triptorelin vs 10,000 IU of HCG **Luteal phase support:** 600 mg/d natural micronised progesterone in 3 separate doses vaginally plus daily 2 × 2 mg oral oestradiol starting 1 day after oocyte retrieval and continued until 7 weeks of gestation in the presence of a positive HCG test. At centre 2, vaginal and intramuscular progesterone was administered, if conception occurred, until 7 weeks of pregnancy
Outcomes	**Primary outcome:** fertilisation rate **Secondary outcomes:** ongoing pregnancy, implantation rates, days of stimulation, total units of rFSH, number of COCs, follicles ≥ 11 mm on the day of triggering, number of follicles ≥ 17 mm on the day of triggering, proportion of MII oocytes, number of 2 PN oocytes, number of embryos transferred, E_2 (pg/mL), progesterone (ng/L)
Notes	Stopped because of differences in pregnancy rate in favour of HCG No data on live birth rate and miscarriage rate Commercial funding: unclear whether investigators received commercial funding Stopping rule after interim analysis: If a difference in pregnancy rates was detected at a probability level of 0.03 at the second interim analysis, the study should be stopped for ethical reasons Funding source unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	High risk	Sequence of randomisation was not concealed

Kolibianakis 2005 *(Continued)*

Blinding (performance bias and detection bias) FOR OHSS OUTCOME	High risk	Outcome assessors and participants were not blinded to the intervention. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available. Live birth rate was not reported
Other bias	High risk	Stopped early because of differences in pregnancy rate in favour of HCG

Melo 2009

Methods	Randomised, controlled, assessor-blinded, parallel-group, single-centre study
Participants	100 oocyte donors, 18 to 34 years of age, regular menstrual cycles, no family history of hereditary or chromosomal disease, normal karyotype, BMI 18 to 29 kg/m^2 and negative screening for sexually transmitted disease. PCOS was excluded. Basic clinical donor characteristics show no differences in age, BMI and antral follicle 96 recipients were women with menopause, 32 (33%); low response, 28 (29%); premature ovarian failure, 27 (28%); and female advanced age, 9 (10%). 18 to 49 years of age, BMI 18 to 29 kg/m^2, male partner without severe male factor (< 5 million fresh spermatozoa/mm^3, < 5% normal forms and/or non-obstructive azoospermia). Exclusion criteria: cases with uterine pathology (submucous or intramural fibroids > 2 cm, polyps, adhesions, adenomyosis or müllerian defects), implantation failure and recurrent miscarriage
Interventions	**Oocyte donors** **Ovarian stimulation:** OCP + adjustable dose of 225 IU rFSH + 0.25 mg cetrotide **Intervention:** 0.2 mg triptorelin SC vs 250 µg rHCG SC **Luteal phase support (recipients):** 800 mg/d micronised intravaginal progesterone
Outcomes	**Donors:** oocytes retrieved, proportion of MII oocytes, fertilisation rate, cleavage rate, top-quality embryos, number of embryos transferred, OHSS rate **Recipients:** implantation rate, clinical pregnancy rate, multiple pregnancy rate, miscarriage rate
Notes	Funding source is unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Third party random assignment by a nurse
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	Low risk	All investigators, embryologists, laboratory personnel and sponsor staff, including the statistician responsible for statistical analysis, were blinded to treatment allocation throughout the study

Melo 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Live birth rate was not reported
Other bias	Low risk	No other potential bias was identified

Ossina 2004

Methods	RCT, multi-centre study (6 centres)
Participants	101 participants (101 IVF/ICSI cycles) analysed
Interventions	COH included recombinant FSH (recFSH; Puregon) in flexible multi-dose GnRH antagonist protocol (orgalutran). Triggering was randomly performed by 10,000 IU HCG (Pregnyl) or 0.1 mg GnRH agonist (triptorelin)
Outcomes	Serum concentrations of LH, FSH, E_2 and P4 were measured at 0, 12, 36 and 108 hours after triggering
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information: Full text was unavailable
Allocation concealment (selection bias)	Unclear risk	Insufficient information: Full text was unavailable
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	Unclear risk	Insufficient information: Full text was unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information: Full text was unavailable
Selective reporting (reporting bias)	Unclear risk	Insufficient information: Full text was unavailable
Other bias	Unclear risk	Insufficient information: Full text was unavailable

Papanikolaou 2010

Methods	Proof-of-concept, single-centre RCT
Participants	35 participants seeking IVF treatment. 4 participants refrained from further treatment (2 for personal problems, 1 became pregnant and 1 as the result of poor response). Inclusion criteria were as follows:

Papanikolaou 2010 *(Continued)*

	younger than 36 years of age, elective single embryo transfer on day 5 and basal FSH less than 12 mIU/mL Exclusion criteria were as follows: polycystic ovary syndrome (PCOS); use of testicular sperm; and endometriosis stages III and IV. Age was 30.6 ±.0.8 vs 30.1 ± 0.7 years
Interventions	**Ovarian stimulation:** fixed dose 187.5 IU of recFSH (Gonal-F; Merck-Serono NV SA, Overijse, Belgium) starting on cd 2 of the cycle with GnRH antagonist, 0.25 mg cetrorelix (Cetrotide; Merck-Serono) on cycle day 7 and continued daily until the day of trigger **Intervention:** 17 participants were randomly assigned to standard treatment group. They received 250 mg recombinant HCG (Ovitrelle, Merck-Serono, Geneva, Switzerland) for ovulation triggering and standard luteal P (600 mg micronised P vaginally administered from day after oocyte retrieval and maintained until 7 weeks of gestation). 18 participants were randomly assigned to the novel protocol. They received 0.2 mg of triptorelin (Ipsen, Boulogne Billancourt, France) for ovulation triggering **Luteal phase support:** standard P luteal support plus 6 doses every other day of 300 IU recombinant LH (Luveris, Merck-Serono), starting on the day of oocyte retrieval up to day 10 after oocyte retrieval
Outcomes	**Primary outcomes:** implantation rates. Clinical pregnancy (defined as cardiac activity at 7 weeks) is similar to implantation rate, as a single blastocyst was transferred **Secondary outcomes:** OHSS incidence
Notes	Medications used in the study were offered by Merck-Serono, Overijse, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Research nurse randomly assigned women to 1 of the 2 arms
Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured by the research nurse
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	Unclear risk	Treating physician was blinded to the allocation group until the day of trigger. Unclear whether outcome assessment was blinded. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	TPP and ITT were provided
Selective reporting (reporting bias)	Unclear risk	Protocol was available, outcomes were as described. Live birth rate was not reported
Other bias	Low risk	No other potential bias was identified

Peña 2007

Methods	RCT, single-centre study
Participants	41 egg donors
Interventions	**GnRH agonist group:** GnRH antagonist/triggering oocyte maturation with HCG; and GnRH antagonist/triggering ovulation with leuprolide acetate (0.6 mg 35.5 hours before egg retrieval (ER), followed 10 hours later by a second dose of 0.6 mg)

Peña 2007 *(Continued)*

	HCG group: down-regulation with leuprolide acetate/triggering oocyte maturation with HCG (5000 to 10,000 IU) 35.5 hours before egg retrieval **Ovulation induction:** carried out in all groups with a combination of recombinant FSH and recombinant LH or urinary HMG; response to treatment was monitored by transvaginal ultrasound and blood oestradiol levels as needed. Initial dose was selected on the basis of ovarian volume and basal antral follicle count and varied between 150 and 225 IU. Dose was then adjusted according to individual response from day 3 of stimulation **Oocyte maturation:** triggered when at least 2 follicles reached a mean diameter of 18 mm. In most cases, eggs from a given donor were shared by 2 recipients, occasionally by 3
Outcomes	Mean number of mature eggs per recipient, mean number of embryos transferred, clinical pregnancy rate, ongoing pregnancy rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information: Full text was unavailable
Allocation concealment (selection bias)	Unclear risk	Insufficient information: Full text was unavailable
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	Unclear risk	Insufficient information: Full text was unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information: Full text was unavailable
Selective reporting (reporting bias)	Unclear risk	Insufficient information: Full text was unavailable
Other bias	Unclear risk	Insufficient information: Full text was unavailable

Pirard 2006

Methods	Randomised, controlled, open, parallel-group, pilot, single-centre trial
Participants	30 infertile participants for IVF/ICSI Baseline characteristics: age and number retrieved were comparable between all groups
Interventions	**Ovarian stimulation:** OCP + 150 to 300 IU HMG/FSH on cd 3 + 0.25 mg orgalutran **Intervention and luteal phase support:** Group A (n = 6) 10,000 IU HCG, followed by vaginal administration of 200 mg micronised progesterone 3 times daily (Group B) (n = 2) (discontinued) 200 µg intranasal (IN) buserelin (Suprefact; Aventis, Brussels, Belgium), followed by 100 µg IN buserelin/2 d; Group C (n = 3) (discontinued) 200 µg IN buserelin, followed by 100 µg IN buserelin/d; Group D (n = 6) 200 µg IN buserelin, followed by 100 µg IN buserelin twice a day (group E) (n = 6) 200 µg IN buserelin, followed by 100 µg IN buserelin 3 times a day Progesterone supplementation for luteal phase support in HCG group

Pirard 2006 *(Continued)*

Outcomes	Luteal phase duration in non-pregnant participants (days), number of participants with luteal phase > 10 days, positive pregnancy test, clinical pregnancy rate, OHSS incidence, retrieved oocytes, retrieved oocytes/follicles > 10 mm, cleaved embryos, cleaved embryos/retrieved oocytes, transferred embryos
Notes	During the course of the study, it became apparent that administration of buserelin every 2 days and every day was associated with severe luteal deficiency; these 2 treatment arms were stopped before completion. Participants who normally would have been included in Group B or C received a further sealed envelope, with new allocation instructions, after discontinuation of these study arms Source of funding was not clearly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated by an independent statistician
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes. No further details were reported
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	Unclear risk	Blinding was not reported clearly. Risk applies to assessment of OHSS
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Live birth rate was not reported
Other bias	High risk	During the course of the study, it became apparent that administration of buserelin every 2 days and every day was associated with severe luteal deficiency; these 2 treatment arms were stopped before completion

Segal 1992

Methods	RCT, single-centre study
Participants	179 women in the IVF programme
Interventions	Subcutaneous injection of leuprolide acetate (500 micrograms) or intramuscular injection of HCG (5000 IU) 34 to 36 hours before oocyte retrieval. Vaginal progesterone (P) suppositories (50 mg) were used 2 times a day for luteal phase support. Subgroup of 41 women had serum oestradiol (E_2) and P levels determined 2 and 7 days after embryo transfer (ET)
Outcomes	Pregnancy rates and luteal phase E_2 and P were compared
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Segal 1992 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information: Full text was unavailable
Allocation concealment (selection bias)	Unclear risk	Insufficient information: Full text was unavailable
Blinding (performance bias and detection bias) FOR OHSS OUTCOME	Unclear risk	Insufficient information: Full text was unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information: Full text was unavailable
Selective reporting (reporting bias)	Unclear risk	Insufficient information: Full text was unavailable
Other bias	Unclear risk	Insufficient information: Full text was unavailable

Abbreviations:
ART: assisted reproductive technology.
BMI: body mass index.
COH: controlled ovarian hyperstimulation.
CPR: clinical pregnancy rate.
ER: egg retrieval.
ET: embryo transfer.
FR: fertilisation rate.
FSH: follicle-stimulating hormone.
GnRH: gonadotropin-releasing hormone.
HCG: human chorionic gonadotropin.
ICSI: intracytoplasmic sperm injection.
IR: implantation rate.
ITT: intention-to-treat.
IVF: in vitro fertilisation.
LH: luteinising hormone.
LPS: luteal phase support
OCP: oral contraceptive pills
OHSS: ovarian hyperstimulation syndrome.
P: progesterone.
PCOM: polycystic ovary morphology
PCOS: polycystic ovary syndrome.
PP: per-protocol.
RCT: randomised controlled trial.
rHCG: recombinant human chorionic gonadotropin.
TNFa: tumor necrosis factor-alpha.
TPP: treatment per protocol
VEGF: vascular endothelial growth factor.

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

Study	Reason for exclusion
Andersen 2006	Overlap with Humaidan 2006
Andreyko 2011	Non-RCT comparison

Study	Reason for exclusion
Awaad 2012	IUI cycles
Bankowaski 2004	Comparative, non-randomised study
Beckers 2002	Overlap with Beckers 2003
Bennett 1997	Retrospective study
Bodri 2009	Retrospective cohort study
Bodri 2010	Prospective, follow-up study
Bodri 2013	Not an RCT
Bracero 2001	Retrospective cohort study
Bukulmez 2005	Retrospective analysis of oocyte donation cycles
Carone 2005	Observational uncontrolled trial
Castillo 2007	Observational trial
Cerrillo 2011	Prospective cohort study evaluating effects of GnRH agonist and HCG treatment on VEGF, angiopoietin-2 and VE-cadherin
Check 1993	Non-RCT
Chen 1998	Incomplete data
Chen 2012	Prospective cohort study
Cunha 2002	RCT, incomplete data
Daneshmand 2006	Retrospective study
De Jong 2001	Case report
Diaz 2003	Randomised, cross-over, non-IVF study
DiLuigi 2010	Non-RCT compared GnRH agonist vs coasting plus HCG
Egbase 2002	IUI treatment
Eldar-Geva 2007	Retrospective study
Emperaire 1992	Study design unclear and data incomplete
Engmann 2005	Retrospective study
Engmann 2006	Overlap with Engmann 2005
Engmann 2006a	Retrospective analysis
Engmann 2011	Subset analysis of participants included in RCT (Engmann 2008)

Study	Reason for exclusion
Engmann 2012	Commentary
Erb 2009	Retrospective study in donor cycles
Fatemi 2013	RCT, randomly assigned 4 donors for 16 cycles and evaluated early luteal phase endocrine profile and double publication of Humaidan 2012
Galera 2005	Non-randomised, uncontrolled study
Garcia-Velasco 2012	Commentary
Garcia-Velasco 2010	RCT in egg donors, all women triggered with GnRH agonist and randomly assigned to receive traditional LPS with or without small dose of HCG
Goto 2003	Non-randomised comparative cohort study
Griesinger 2005	Review
Griesinger 2007a	Randomised observational study, double publication
Griesinger 2007b	Prospective, observational proof-of-concept study
Griesinger 2010	Prospective, clinical cohort study
Griesinger 2011	Prospective, clinical cohort study
Griffin 2012	Retrospective cohort study
Herrero 2010	Observational study
Humaidan 2011	Levels of epidermal growth factor–like peptide amphiregulin in follicular fluid RCT overlap with Humaidan 2013
Humaidan 2012	RCT in 4 donors with different final oocyte maturation and oocyte triggering and luteal phase regimens
Imbar 2012	Cohort study
Itskovitz-Eldor 2000	Preliminary report
Johnston-MacAnanny 2007	Retrospective comparative study
Joo 2012	Non-RCT study
Kaur 2012	Prospective, non-RCT study
Kol 2012	Commentary
Krause 2006	RCT, all women triggered with GnRH agonist, then randomly assigned to different LPS protocols Group A received 5 × 1000 IU HCG, Group B received 5 × 500 IU HCG and Group C received 5 × 250 mg progesterone intramuscularly
Kummer 2013	Retrospective chart review

Study	Reason for exclusion
LaMonica2007	Retrospective comparative study
Lanzone 1994	Case control study
Lanzone 1994a	Study design unclear
Lewit 1996	IUI treatment
Lin 2013	Retrospective observational study
Lin MH 2013	Retrospective cohort study
lliodromiti 2013	Retrospective analysis
Loumaye 2004	Control group: GnRH agonist/HCG
Loumaye 2007	Observational uncontrolled study
Melo 2007	Initial results of Melo 2009
Meltzer 2002	Overlap with Fauser 2002
Nelson 2013	Commentary
Nevo 2003	Part of large RCT evaluating levels of inhibin A and pro-αC during luteal phase
Olivennes 2001	Overlap with Fauser 2002
Orvieto 2006	Prospective observational study
Orvieto 2013	Retrospective study
Parneix 2001	Study design unclearly reported in the abstract
Peñarrubia 1998	Prospective non-randomised study
Ricciarelli 2006	Overlap with Acevedo 2006
Schachter 2007	Used GnRH analogue only for luteal phase support
Schmidt 1995	RCT compared GnRH agonist with HCG in clomiphene citrate–stimulated cycles
Schmidt-Sarosi 1995	Randomised, controlled, IUI treatment
Seyhan 2013	Retrospective analysis
Shalev 1995	RCT, non-IVF cycles
Shanis 1995	No available data
Shapiro 2007	Retrospective study of oocyte donor IVF cycles
Shapiro 2008	Retrospective preliminary study in fresh autologous cycles of IVF
Shapiro 2011	Retrospective study

Study	Reason for exclusion
Shapiro 2011a	Retrospective study
Sismangoul 2009	Prospective randomised cross-sectional study in egg donors
Toner 2006	Retrospective cohort study
Westergaard 2004	Duplicate publication (preliminary result of Humaidan 2005)
Wilkinson 2007	Retrospective analysis of anonymous donor oocyte cycles
Yding 1993	RCT, evaluated endocrine composition of follicular fluid, comparing human chorionic gonadotropin versus a gonadotropin-releasing hormone agonist for ovulation induction

Abbreviations:
GnRH: gonadotropin-releasing hormone.
HCG: human chorionic gonadotropin.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
LPS: luteal phase support
RCT: randomised controlled trial.
VE: vascular endothelial
VEGF: vascular endothelial growth factor.

DATA AND ANALYSES

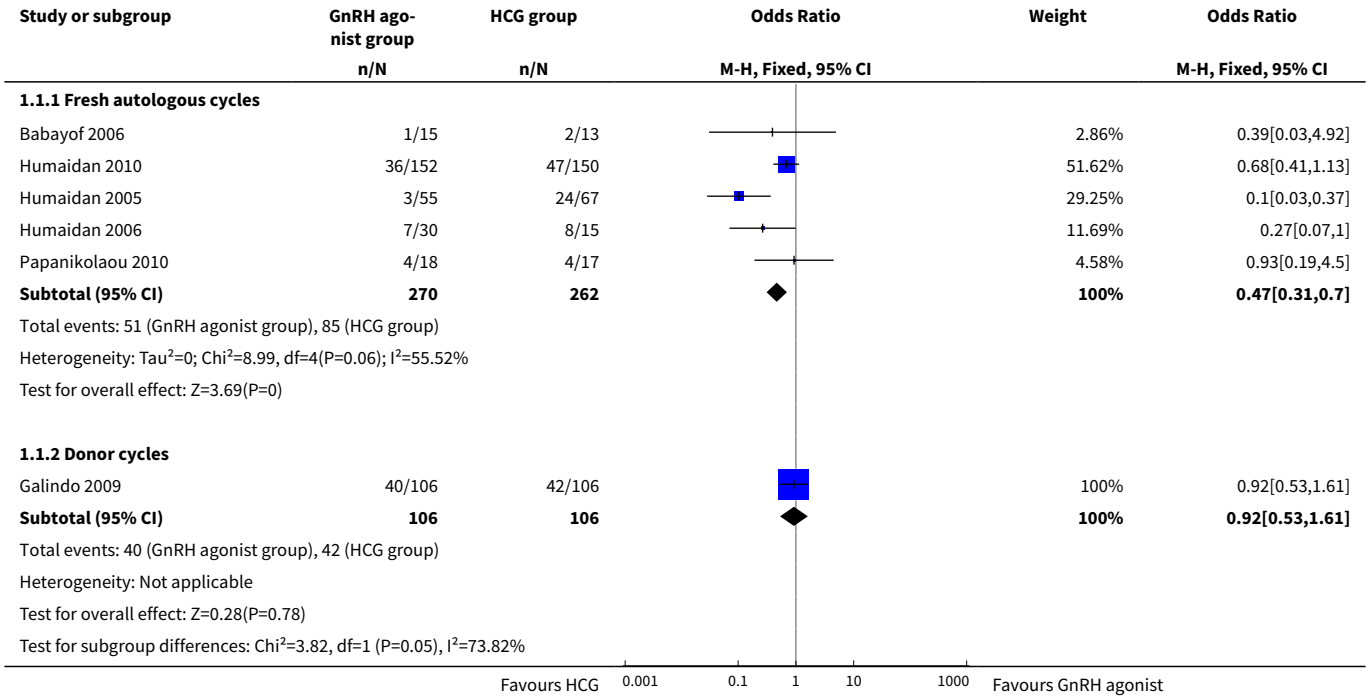
Comparison 1. GnRH agonist versus HCG for oocyte maturation triggering

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman randomised	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Fresh autologous cycles	5	532	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.31, 0.70]
1.2 Donor cycles	1	212	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.53, 1.61]
2 Live birth rate in autologous cycles: luteal phase support approach	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Live birth in studies using modified luteal phase support with LH activity	3	382	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 0.98]
2.2 Live birth in studies using modified luteal phase support without LH activity (P ± E_2)	2	150	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.04, 0.39]
3 OHSS incidence per woman randomised	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Fresh autologous cycles	8	989	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.05, 0.47]
3.2 Donor cycles: mild, moderate or severe OHSS	3	372	Odds Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.28]
4 OHSS rate in autologous cycles: luteal support approach	8	989	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.05, 0.47]
4.1 OHSS in studies using modified luteal phase support with LH activity	5	789	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.11, 2.09]
4.2 OHSS in studies using modified luteal phase support without LH activity	3	200	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.34]
5 Ongoing pregnancy rate per woman randomised	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Autologous cycles	11	1198	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.54, 0.91]
5.2 Donor cycles	3	372	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.58, 1.32]
6 Ongoing pregnancy rate in autologous cycles: luteal phase support approach	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Ongoing pregnancy in studies using modified luteal phase support with LH activity	5	789	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.21]
6.2 Ongoing pregnancy in studies using modified luteal phase support without LH activity ($P \pm E_2$)	5	370	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.21, 0.62]
7 Clinical pregnancy per woman randomised	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Autologous cycles	11	1198	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.04]
7.2 Donor cycles	3	372	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.33]
8 Miscarriage rate per woman randomised	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Autologous cycles	11	1198	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [1.10, 2.75]
8.2 Donor cycles	3	372	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.32]
9 Multiple pregnancy rate per woman randomised	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

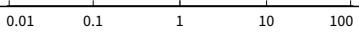
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Autologous cycles	2	62	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.30, 30.47]
9.2 Donor cycles	3	372	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.86, 3.48]
10 Subgroup and sensitivity analyses—OHSS incidence in autologous cycles: risk and severity	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Autologous cycles: studies of women at low OHSS risk reporting mild, moderate or severe OHSS	6	777	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.47]
10.2 Autologous cycles: studies of women at high OHSS risk reporting mild, moderate or severe OHSS	3	212	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.34]
10.3 Autologous cycles: all studies (women at high or low OHSS risk) reporting moderate or severe OHSS	8	989	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.07, 0.66]
10.4 Autologous cycles: studies of women at high OHSS risk reporting moderate or severe OHSS	3	212	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.02, 0.52]

Analysis 1.1. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 1 Live birth rate per woman randomised.



Analysis 1.2. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 2 Live birth rate in autologous cycles: luteal phase support approach.

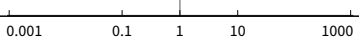
Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Live birth in studies using modified luteal phase support with LH activity					
Humaidan 2010	36/152	47/150		76.04%	0.68[0.41,1.13]
Humaidan 2006	7/30	8/15		17.22%	0.27[0.07,1]
Papanikolaou 2010	4/18	4/17		6.74%	0.93[0.19,4.5]
Subtotal (95% CI)	**200**	**182**		**100%**	**0.63[0.4,0.98]**
Total events: 47 (GnRH agonist group), 59 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=1.95, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=2.03(P=0.04)					
1.2.2 Live birth in studies using modified luteal phase support without LH activity (P ± E2)					
Babayof 2006	1/15	2/13		8.91%	0.39[0.03,4.92]
Humaidan 2005	3/55	24/67		91.09%	0.1[0.03,0.37]
Subtotal (95% CI)	**70**	**80**		**100%**	**0.13[0.04,0.39]**
Total events: 4 (GnRH agonist group), 26 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=3.61(P=0)					
Test for subgroup differences: Chi^2=6.65, df=1 (P=0.01), I^2=84.96%					



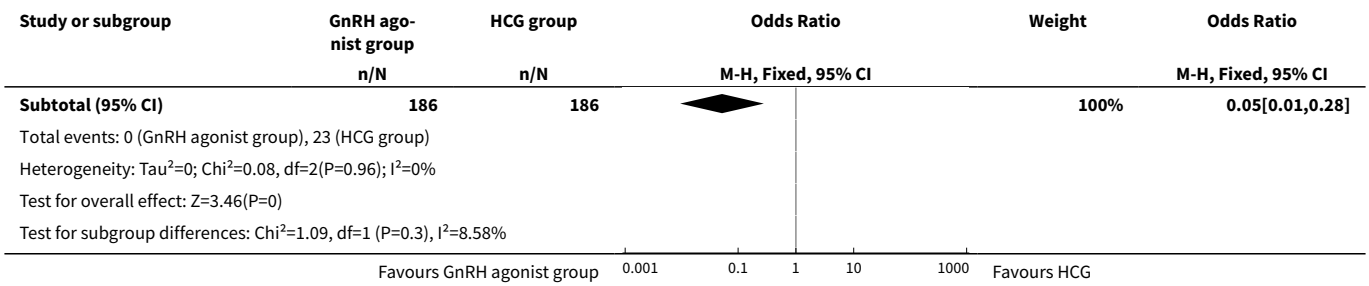
Favours GnRH agonist — Favours HCG

Analysis 1.3. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 3 OHSS incidence per woman randomised.

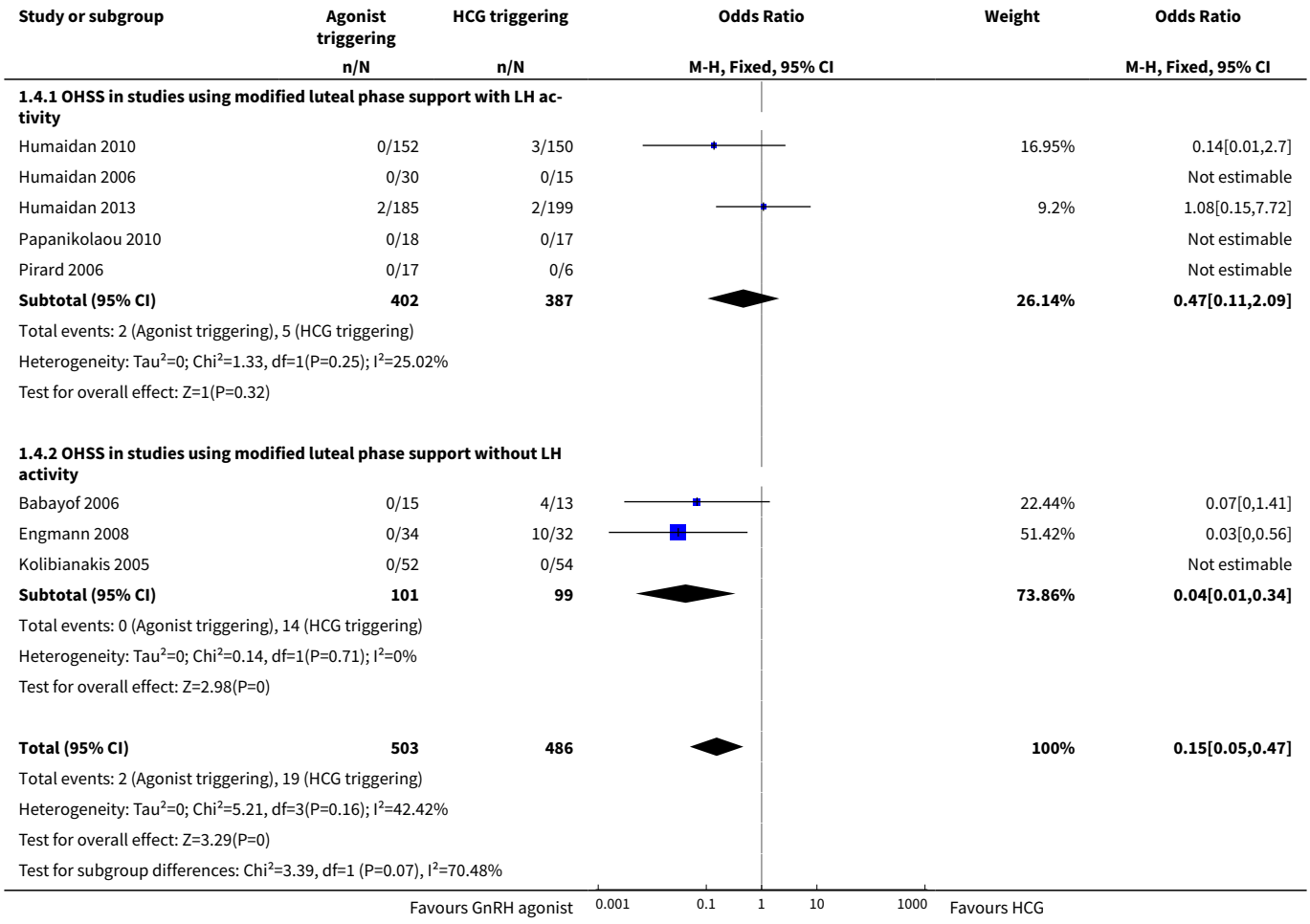
Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Fresh autologous cycles					
Babayof 2006	0/15	4/13		22.44%	0.07[0,1.41]
Engmann 2008	0/34	10/32		51.42%	0.03[0,0.56]
Humaidan 2010	0/152	3/150		16.95%	0.14[0.01,2.7]
Humaidan 2006	0/30	0/15			Not estimable
Humaidan 2013	2/185	2/199		9.2%	1.08[0.15,7.72]
Kolibianakis 2005	0/52	0/54			Not estimable
Papanikolaou 2010	0/18	0/17			Not estimable
Pirard 2006	0/17	0/6			Not estimable
Subtotal (95% CI)	**503**	**486**		**100%**	**0.15[0.05,0.47]**
Total events: 2 (GnRH agonist group), 19 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=5.21, df=3(P=0.16); I^2=42.42%					
Test for overall effect: Z=3.29(P=0)					
1.3.2 Donor cycles: mild, moderate or severe OHSS					
Acevedo 2006	0/30	5/30		22.29%	0.08[0,1.44]
Galindo 2009	0/106	10/106		43.05%	0.04[0,0.75]
Melo 2009	0/50	8/50		34.67%	0.05[0,0.88]



Favours GnRH agonist group — Favours HCG

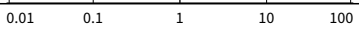


Analysis 1.4. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 4 OHSS rate in autologous cycles: luteal support approach.



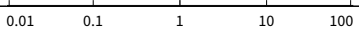
Analysis 1.5. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 5 Ongoing pregnancy rate per woman randomised.

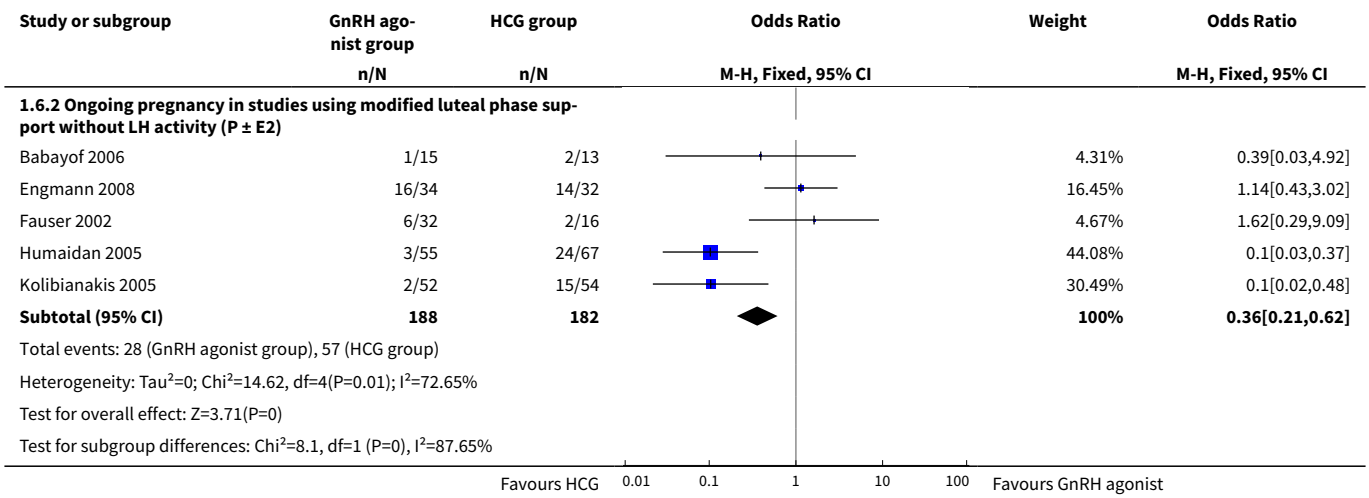
Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Autologous cycles					
Babayof 2006	1/15	2/13		1.52%	0.39[0.03,4.92]
Beckers 2003	1/15	2/24		1.09%	0.79[0.06,9.5]
Engmann 2008	16/34	14/32		5.8%	1.14[0.43,3.02]
Fauser 2002	6/32	2/16		1.65%	1.62[0.29,9.09]
Humaidan 2010	40/152	49/150		27.6%	0.74[0.45,1.21]
Humaidan 2005	3/55	24/67		15.54%	0.1[0.03,0.37]
Humaidan 2006	7/30	8/15		6.21%	0.27[0.07,1]
Humaidan 2013	54/185	51/199		26.43%	1.2[0.76,1.87]
Kolibianakis 2005	2/52	15/54		10.75%	0.1[0.02,0.48]
Papanikolaou 2010	4/18	4/17		2.43%	0.93[0.19,4.5]
Pirard 2006	2/17	1/6		0.99%	0.67[0.05,9.02]
Subtotal (95% CI)	**605**	**593**		**100%**	**0.7[0.54,0.91]**
Total events: 136 (GnRH agonist group), 172 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=24.48, df=10(P=0.01); I^2=59.16%					
Test for overall effect: Z=2.64(P=0.01)					
1.5.2 Donor cycles					
Acevedo 2006	14/30	15/30		16.56%	0.88[0.32,2.41]
Galindo 2009	41/106	42/106		53.31%	0.96[0.55,1.67]
Melo 2009	22/50	26/50		30.14%	0.73[0.33,1.59]
Subtotal (95% CI)	**186**	**186**		**100%**	**0.88[0.58,1.32]**
Total events: 77 (GnRH agonist group), 83 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Chi^2=0.81, df=1 (P=0.37), I^2=0%					



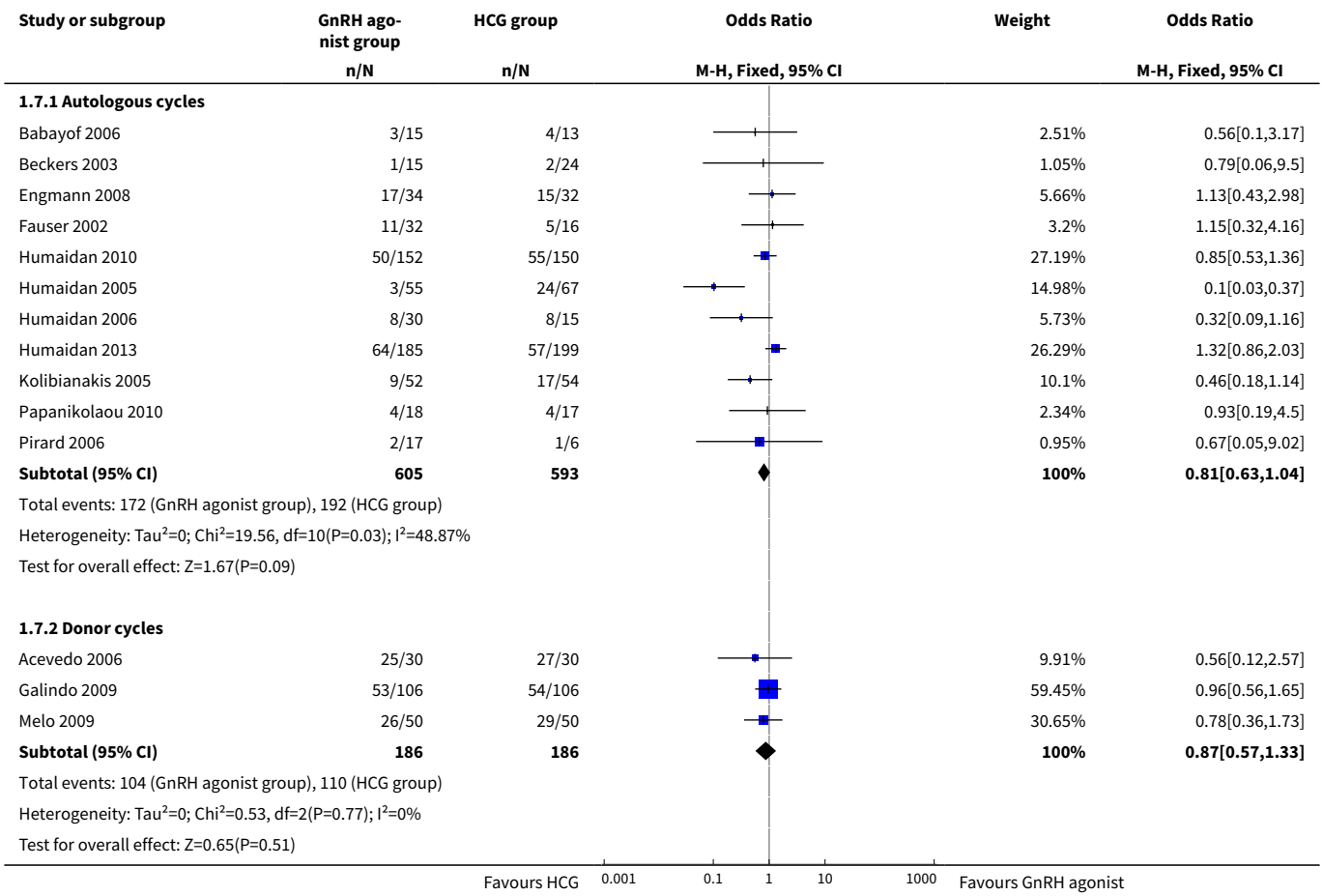
Analysis 1.6. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 6 Ongoing pregnancy rate in autologous cycles: luteal phase support approach.

Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Ongoing pregnancy in studies using modified luteal phase support with LH activity					
Humaidan 2010	40/152	49/150		43.36%	0.74[0.45,1.21]
Humaidan 2006	7/30	8/15		9.76%	0.27[0.07,1]
Humaidan 2013	54/185	51/199		41.51%	1.2[0.76,1.87]
Papanikolaou 2010	4/18	4/17		3.82%	0.93[0.19,4.5]
Pirard 2006	2/17	1/6		1.56%	0.67[0.05,9.02]
Subtotal (95% CI)	**402**	**387**		**100%**	**0.89[0.65,1.21]**
Total events: 107 (GnRH agonist group), 113 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=5.48, df=4(P=0.24); I^2=27.02%					
Test for overall effect: Z=0.75(P=0.45)					



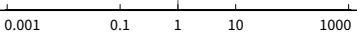


Analysis 1.7. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 7 Clinical pregnancy per woman randomised.



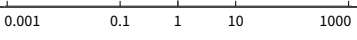
Analysis 1.8. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 8 Miscarriage rate per woman randomised.

Study or subgroup	GnRH group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.8.1 Autologous cycles					
Babayof 2006	4/15	2/13		5.53%	2[0.3,13.26]
Beckers 2003	1/15	1/24		2.53%	1.64[0.09,28.41]
Engmann 2008	1/34	1/32		3.52%	0.94[0.06,15.68]
Fauser 2002	5/32	3/16		11.88%	0.8[0.17,3.88]
Humaidan 2010	13/152	11/150		35.66%	1.18[0.51,2.73]
Humaidan 2005	11/55	1/67		2.54%	16.5[2.06,132.38]
Humaidan 2006	2/30	1/15		4.38%	1[0.08,12]
Humaidan 2013	8/185	5/199		16.23%	1.75[0.56,5.46]
Kolibianakis 2005	7/52	2/54		5.98%	4.04[0.8,20.46]
Papanikolaou 2010	1/18	2/17		6.84%	0.44[0.04,5.37]
Pirard 2006	1/17	1/6		4.9%	0.31[0.02,5.96]
Subtotal (95% CI)	**605**	**593**		**100%**	**1.74[1.1,2.75]**
Total events: 54 (GnRH group), 30 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=10.12, df=10(P=0.43); I^2=1.19%					
Test for overall effect: Z=2.35(P=0.02)					
1.8.2 Donor cycles					
Acevedo 2006	2/30	1/30		6.51%	2.07[0.18,24.15]
Galindo 2009	12/106	12/106		74.24%	1[0.43,2.34]
Melo 2009	4/50	3/50		19.25%	1.36[0.29,6.43]
Subtotal (95% CI)	**186**	**186**		**100%**	**1.14[0.56,2.32]**
Total events: 18 (GnRH group), 16 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=2(P=0.83); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					



Analysis 1.9. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 9 Multiple pregnancy rate per woman randomised.

Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.9.1 Autologous cycles					
Babayof 2006	1/14	0/13		49.6%	3[0.11,80.39]
Papanikolaou 2010	1/18	0/17		50.4%	3[0.11,78.81]
Subtotal (95% CI)	**32**	**30**		**100%**	**3[0.3,30.47]**
Total events: 2 (GnRH agonist group), 0 (HCG group)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					
1.9.2 Donor cycles					
Acevedo 2006	3/30	4/30		29.26%	0.72[0.15,3.54]
Galindo 2009	16/106	7/106		48.31%	2.51[0.99,6.39]
Melo 2009	4/50	3/50		22.43%	1.36[0.29,6.43]
Subtotal (95% CI)	**186**	**186**		**100%**	**1.73[0.86,3.48]**
Total events: 23 (GnRH agonist group), 14 (HCG group)					



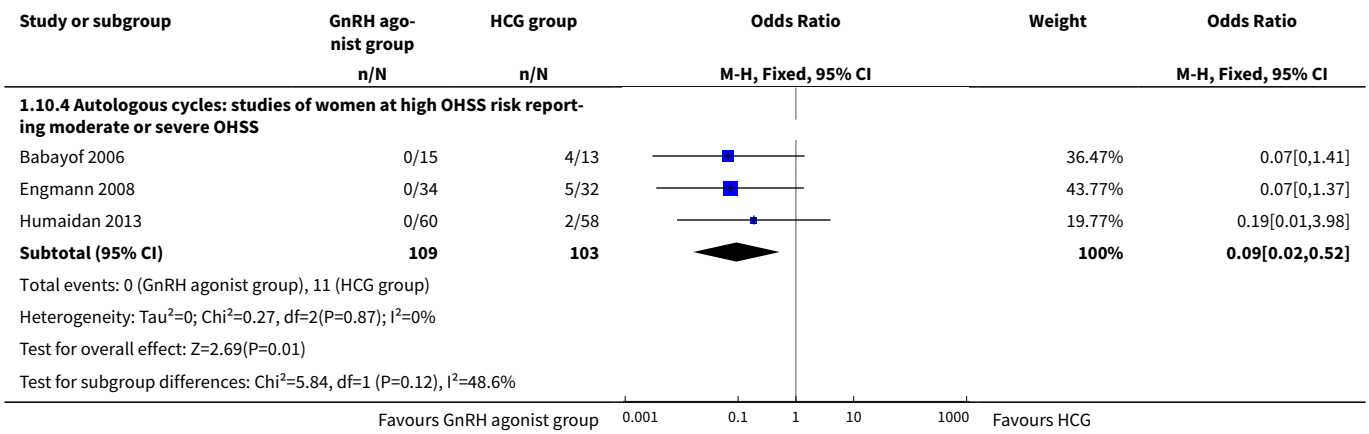
Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.87, df=2(P=0.39); I²=0%					
Test for overall effect: Z=1.54(P=0.12)					
Test for subgroup differences: Chi²=0.2, df=1 (P=0.66), I²=0%					

Favours GnRH agonist 0.001 0.1 1 10 1000 Favours HCG

Analysis 1.10. Comparison 1 GnRH agonist versus HCG for oocyte maturation triggering, Outcome 10 Subgroup and sensitivity analyses—OHSS incidence in autologous cycles: risk and severity.

Study or subgroup	GnRH agonist group n/N	HCG group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.10.1 Autologous cycles: studies of women at low OHSS risk reporting mild, moderate or severe OHSS					
Humaidan 2010	0/152	3/150		88.4%	0.14[0.01,2.7]
Humaidan 2006	0/30	0/15			Not estimable
Humaidan 2013	2/125	0/141		11.6%	5.73[0.27,120.47]
Kolibianakis 2005	0/52	0/54			Not estimable
Papanikolaou 2010	0/18	0/17			Not estimable
Pirard 2006	0/17	0/6			Not estimable
Subtotal (95% CI)	**394**	**383**		**100%**	**0.79[0.18,3.47]**
Total events: 2 (GnRH agonist group), 3 (HCG group)					
Heterogeneity: Tau²=0; Chi²=2.95, df=1(P=0.09); I²=66.08%					
Test for overall effect: Z=0.32(P=0.75)					
1.10.2 Autologous cycles: studies of women at high OHSS risk reporting mild, moderate or severe OHSS					
Babayof 2006	0/15	4/13		26.09%	0.07[0,1.41]
Engmann 2008	0/34	10/32		59.77%	0.03[0,0.56]
Humaidan 2013	0/60	2/58		14.14%	0.19[0.01,3.98]
Subtotal (95% CI)	**109**	**103**		**100%**	**0.06[0.01,0.34]**
Total events: 0 (GnRH agonist group), 16 (HCG group)					
Heterogeneity: Tau²=0; Chi²=0.72, df=2(P=0.7); I²=0%					
Test for overall effect: Z=3.22(P=0)					
1.10.3 Autologous cycles: all studies (women at high or low OHSS risk) reporting moderate or severe OHSS					
Babayof 2006	0/15	4/13		29.72%	0.07[0,1.41]
Engmann 2008	0/34	5/32		35.66%	0.07[0,1.37]
Humaidan 2010	0/152	3/150		22.44%	0.14[0.01,2.7]
Humaidan 2006	0/30	0/15			Not estimable
Humaidan 2013	2/185	2/199		12.18%	1.08[0.15,7.72]
Kolibianakis 2005	0/52	0/54			Not estimable
Papanikolaou 2010	0/18	0/17			Not estimable
Pirard 2006	0/17	0/6			Not estimable
Subtotal (95% CI)	**503**	**486**		**100%**	**0.21[0.07,0.66]**
Total events: 2 (GnRH agonist group), 14 (HCG group)					
Heterogeneity: Tau²=0; Chi²=3.76, df=3(P=0.29); I²=20.26%					
Test for overall effect: Z=2.67(P=0.01)					

Favours GnRH agonist group 0.001 0.1 1 10 1000 Favours HCG



APPENDICES

Appendix 1. MDSG specialised register search strategy

Keywords CONTAINS "GnRH a" or "GnRH agonist" or "GnRH agonists" or "GnRHa" or "GnRHa-gonadotropin" or "Gonadorelin" or "Gonadotrophin releasing agonist" or "gonadotropin releasing hormone agonist" or "Goserelin" or "goserelin acetate" or "Gosereline " or "buserelin" or "Buserelin Acetate" or "buserelin naferelin" or "busereline" or "Leuprolide" or "leuprolide acetate" or "leuprolin" or "leuprorelin" or "leuprorelin acetate" or "Nafarelin" or "triptoielin" or "triptorelin" or "triptoreline" or "triptoreline pamoat" or "triptorelyn" or "triptrolein" or "Lupron" or "deslorelin" or "Zoladex" or Title CONTAINS"GnRH a" or "GnRH agonist" or "GnRH agonists" or "GnRHa" or "GnRHa-gonadotropin"

AND

Keywords CONTAINS "trigger" or "triggered ovulation" or "*Ovulation Induction" or "ovulation trigger" or "oocyte maturation" or Title CONTAINS "trigger" or "triggered ovulation" or "*Ovulation Induction" or "ovulation trigger" or "oocyte maturation"

AND

Keywords CONTAINS "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "HCG" or "r-HCG" or "chorionic gonadotrophins" or Title CONTAINS "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "HCG" or "r-HCG" or "chorionic gonadotrophins"

Appendix 2. Cochrane Central Register of Controlled Trials

1 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (1664)
2 gonadotropin-releasing hormone$.tw. (656)
3 (buserelin or Suprefact).tw. (266)
4 (goserelin or Zoladex).tw. (445)
5 (leuprolide or lupron).tw. (391)
6 (nafarelin or Synarel).tw. (101)
7 (histrelin or Supprelin).tw. (0)
8 (deslorelin or Suprelorin or Ovuplant).tw. (8)
9 triptorelin$.tw. (171)
10 gonadotropin-releasing hormone agonist$.tw. (294)
11 gonadotrophin releasing hormone agonist$.tw. (130)
12 GnRH agonist$.tw. (611)
13 GnRH a.tw. (1025)
14 GnRHa.tw. (186)
15 or/1-14 (2712)
16 trigger$.tw. (1848)
17 (oocyte adj5 matur$).tw. (142)
18 (ovulat$ adj2 induc$).tw. (516)
19 or/16-18 (2452)
20 19 and 15 (246)

21 HCG$.tw. (909)
22 $HCG.tw. (903)
23 exp Chorionic Gonadotropin/ (560)
24 chorionic gonadotropin$.tw. (364)
25 chorionic gonadotrophin$.tw. (227)
26 or/21-25 (1215)
27 26 and 20 (138)

Appendix 3. MEDLINE

1 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (26342)
2 gonadotropin-releasing hormone$.tw. (9697)
3 (buserelin or Suprefact).tw. (1201)
4 (goserelin or Zoladex).tw. (887)
5 (leuprolide or lupron).tw. (1419)
6 (nafarelin or Synarel).tw. (251)
7 (histrelin or Supprelin).tw. (36)
8 (deslorelin or Suprelorin or Ovuplant).tw. (142)
9 triptorelin$.tw. (481)
10 gonadotropin-releasing hormone agonist$.tw. (1436)
11 gonadotrophin releasing hormone agonist$.tw. (400)
12 GnRH agonist$.tw. (2891)
13 GnRH a.tw. (822)
14 GnRHa.tw. (930)
15 or/1-14 (30322)
16 trigger$.tw. (124349)
17 (oocyte adj5 matur$).tw. (5092)
18 (ovulat$ adj2 induc$).tw. (6042)
19 or/16-18 (134873)
20 19 and 15 (1781)
21 HCG$.tw. (19418)
22 $HCG.tw. (19020)
23 exp Chorionic Gonadotropin/ (27317)
24 chorionic gonadotropin$.tw. (12107)
25 chorionic gonadotrophin$.tw. (3924)
26 or/21-25 (36144)
27 26 and 20 (549)
28 randomized controlled trial.pt. (300724)
29 controlled clinical trial.pt. (82572)
30 randomized.ab. (214782)
31 placebo.tw. (129299)
32 clinical trials as topic.sh. (151348)
33 randomly.ab. (158665)
34 trial.ti. (92324)
35 (crossover or cross-over or cross over).tw. (49488)
36 or/28-35 (730928)
37 exp animals/ not humans.sh. (3540159)
38 36 not 37 (676083)
39 27 and 38 (125)

Appendix 4. EMBASE

1 gonadorelin derivative/ or buserelin/ or buserelin acetate/ or deslorelin/ or folligen/ or exp gonadorelin/ or exp gonadorelin acetate/ or exp gonadorelin agonist/ or exp goserelin/ or exp histrelin/ or exp leuprorelin/ or exp lutrelin/ or exp nafarelin/ or exp nafarelin acetate/ or exp ovurelin/ or exp triptorelin/ (45421)
2 gonadorelin$.tw. (231)
3 gonadotropin-releasing hormone$.tw. (9950)
4 (buserelin or Suprefact).tw. (2053)
5 (goserelin or Zoladex).tw. (2250)
6 (leuprolide or lupron).tw. (2646)
7 (nafarelin or Synarel).tw. (540)
8 (histrelin or Supprelin).tw. (87)
9 (deslorelin or Suprelorin or Ovuplant).tw. (155)

10 triptorelin$.tw. (616)
11 gonadotropin-releasing hormone agonist$.tw. (1537)
12 gonadotrophin releasing hormone agonist$.tw. (443)
13 GnRH agonist$.tw. (3405)
14 GnRH a.tw. (908)
15 GnRHa.tw. (1065)
16 or/1-14 (47694)
17 trigger$.tw. (137076)
18 (oocyte adj5 matur$).tw. (5447)
19 (ovulat$ adj2 induc$).tw. (6441)
20 or/17-19 (148250)
21 20 and 16 (2510)
22 HCG$.tw. (20224)
23 $HCG.tw. (19726)
24 exp Chorionic Gonadotropin/ (32112)
25 chorionic gonadotropin$.tw. (11662)
26 chorionic gonadotrophin$.tw. (3838)
27 or/22-26 (41192)
28 27 and 21 (1052)
29 Clinical Trial/ (809202)
30 Randomized Controlled Trial/ (281780)
31 exp randomization/ (52523)
32 Single Blind Procedure/ (13353)
33 Double Blind Procedure/ (99325)
34 Crossover Procedure/ (29336)
35 Placebo/ (168562)
36 Randomi?ed controlled trial$.tw. (56492)
37 Rct.tw. (5973)
38 random allocation.tw. (989)
39 randomly allocated.tw. (14666)
40 allocated randomly.tw. (1671)
41 (allocated adj2 random).tw. (677)
42 Single blind$.tw. (10411)
43 Double blind$.tw. (113453)
44 ((treble or triple) adj blind$).tw. (225)
45 placebo$.tw. (150973)
46 prospective study/ (156030)
47 or/29-46 (1087729)
48 case study/ (10327)
49 case report.tw. (191485)
50 abstract report/ or letter/ (755276)
51 or/48-50 (953548)
52 47 not 51 (1056074)
53 28 and 52 (301)

Appendix 5. PsycINFO

1 exp Gonadotropic Hormones/ (3254)
2 gonadotropin-releasing hormone$.tw. (349)
3 (buserelin or Suprefact).tw. (4)
4 (goserelin or Zoladex).tw. (13)
5 (leuprolide or lupron).tw. (54)
6 (nafarelin or Synarel).tw. (0)
7 (histrelin or Supprelin).tw. (1)
8 (deslorelin or Suprelorin or Ovuplant).tw. (2)
9 triptorelin$.tw. (17)
10 gonadotropin-releasing hormone agonist$.tw. (41)
11 gonadotrophin releasing hormone agonist$.tw. (2)
12 GnRH agonist$.tw. (34)
13 GnRH a.tw. (7)
14 GnRHa.tw. (14)
15 or/1-14 (3390)

16 trigger$.tw. (13815)
17 (oocyte adj5 matur$).tw. (15)
18 (ovulat$ adj2 induc$).tw. (66)
19 or/16-18 (13890)
20 19 and 15 (50)
21 HCG$.tw. (61)
22 $HCG.tw. (55)
23 chorionic gonadotropin$.tw. (63)
24 chorionic gonadotrophin$.tw. (8)
25 or/21-24 (93)
26 20 and 25 (2)

Appendix 6. CINAHL

CINAHL search strategy for MM1690 29.05.14

#	Query	Results
S26	S11 AND S25	39
S25	S12 OR S13 or S14 or S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	892,353
S24	TX allocat* random*	3,910
S23	(MH "Quantitative Studies")	12,053
S22	(MH "Placebos")	8,750
S21	TX placebo*	31,617
S20	TX random* allocat*	3,910
S19	(MH "Random Assignment")	37,302
S18	TX randomi* control* trial*	73,175
S17	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	716,730
S16	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	105
S15	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	0
S14	TX clinic* n1 trial*	163,504
S13	PT Clinical trial	76,024
S12	(MH "Clinical Trials+")	175,230
S11	S6 AND S10	86
S10	S7 OR S8 OR S9	12,370
S9	TX (ovulat* N2 induc*)	516

(Continued)

S8	TX (oocyte N3 matur*)	42
S7	TX trigger*	11,843
S6	S1 OR S2 OR S3 OR S4 OR S5	1,298
S5	TX GnRHa	36
S4	TX GnRH	283
S3	TX gonadotrophin releasing hormone*	77
S2	TX gonadotropin-releasing hormone*	318
S1	(MH "Gonadorelin+")	1,061

WHAT'S NEW

Date	Event	Description
8 September 2014	New citation required but conclusions have not changed	6 new studies added (Engmann 2008; Humaidan 2013; Ossina 2004; Papanikolaou 2010; Peňa 2007; Segal 1992), but we have made no change to our conclusions
8 September 2014	New search has been performed	Updated. No change to conclusions

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 11, 2010

Date	Event	Description
16 November 2010	New citation required but conclusions have not changed	Two new authors added

CONTRIBUTIONS OF AUTHORS

Mohamed Youssef: developed and wrote the draft of the protocol, developed the title and intended methods of the review, entered the protocol and review into RevMan and responded to peer reviewers' comments.

Madelon van Wely: helped to develop the protocol, the title and the intended methods of the review; took part in writing the review and responding to peer reviewers' comments; and served as our consultant on statistical issues.

Monique Mochtar, Fulco van der Veen, Hesham Al-Inany and Georg Griesinger: helped to develop the protocol, took part in interpretation of the data and writing of the review and served as consultants on clinical issues.

Ismail Aboulfoutouh and Mohamed Nagi Mohesen: took part in interpretation of the data and writing of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Amsterdam, Netherlands.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, the following protocol changes were made.

- We conducted subgroup analyses of the studies on autologous cycle, grouped by baseline risk of OHSS (low or high).
- We conducted sensitivity analysis for the outcome of OHSS, including only studies of autologous cycles that reported moderate or severe OHSS as an outcome.
- We subgrouped studies with modified luteal phase support: luteal phase support with LH activity (single dose or two doses of HCG, recLH and repeated GnRH doses) and luteal phase support without LH activity (progesterone only or progesterone plus oestradiol).

Differences between original review and review update

The study by Engmann 2008 (excluded in the original review because of lack of standardisation between regimens of treatment in both groups in terms of dual pituitary suppression instead of the GnRH antagonist protocol for the control group and lack of E_2 supplementation in the control group) is now incorporated in the qualitative and quantitative analyses. Also, the studies of Ossina 2004, Peña 2007 and Segal 1992 were included in the section on studies awaiting classification; they have been moved to the section on included studies but because of lack of full publication were excluded from the qualitative analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fertilization in Vitro; *Sperm Injections, Intracytoplasmic; Chorionic Gonadotropin [*therapeutic use]; Gonadotropin-Releasing Hormone [*agonists]; Oocyte Donation [methods]; Oocytes [drug effects] [growth & development]; Ovarian Hyperstimulation Syndrome [epidemiology]; Ovulation Induction [*methods]; Pregnancy Rate; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy