

Gonadotrophin-releasing hormone antagonists for assisted reproductive technology (Review)

Al-Inany HG, Youssef MAFM, Aboulghar M, Broekmans FJ, Sterrenburg MD, Smit JG, Abou-Setta AM



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[Intervention Review]

Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

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ABSTRACT

Background

Gonadotrophin-releasing hormone (GnRH) antagonists can be used to prevent a luteinizing hormone (LH) surge during controlled ovarian hyperstimulation (COH) without the hypo-estrogenic side-effects, flare-up, or long down-regulation period associated with agonists. The antagonists directly and rapidly inhibit gonadotropin release within several hours through competitive binding to pituitary GnRH receptors. This property allows their use at any time during the follicular phase. Several different regimes have been described including multiple-dose fixed (0.25 mg daily from day six to seven of stimulation), multiple-dose flexible (0.25 mg daily when leading follicle is 14 to 15 mm), and single-dose (single administration of 3 mg on day 7 to 8 of stimulation) protocols, with or without the addition of an oral contraceptive pill. Further, women receiving antagonists have been shown to have a lower incidence of ovarian hyperstimulation syndrome (OHSS). Assuming comparable clinical outcomes for the antagonist and agonist protocols, these benefits would justify a change from the standard long agonist protocol to antagonist regimens. This is an update of a Cochrane review first published in 2001, and previously updated in 2006.

Objectives

To evaluate the effectiveness and safety of gonadotrophin-releasing hormone (GnRH) antagonists compared with the standard long protocol of GnRH agonists for controlled ovarian hyperstimulation in assisted conception cycle

Search strategy

We performed electronic searches of major databases, for example Cochrane Menstrual Disorders and Subfertility Group Specialised Register, CENTRAL, MEDLINE, EMBASE (from 1987 to April 2010); and handsearched bibliographies of relevant publications and reviews, and abstracts of major scientific meetings, for example the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM).

Selection criteria

Two review authors independently screened the relevant citations for randomised controlled trials (RCTs) comparing different agonist versus antagonist protocols in women undergoing IVF or ICSI.

Data collection and analysis

Two review authors independently assessed trial risk of bias and extracted data. If relevant data were missing or unclear, the authors were contacted for clarification.

Main results

Forty-five RCTs (n = 7511) comparing the antagonist to the long agonist protocols fulfilled the inclusion criteria. There was no evidence of a statistically significant difference in rates of live-births (9 RCTs; odds ratio (OR) 0.86, 95% CI 0.69 to 1.08). There was a statistically significant lower incidence of OHSS in the GnRH antagonist group (29 RCTs; OR 0.43, 95% CI 0.33 to 0.57).

Authors' conclusions

The use of antagonist compared with long GnRH agonist protocols was associated with a large reduction in OHSS and there was no evidence of a difference in live-birth rates.

PLAIN LANGUAGE SUMMARY

Gonadotrophin-releasing hormone antagonists in subfertile couples undergoing ovulation induction as part of an assisted conception program

Gonadotrophin-releasing hormone (GnRH) analogues are used during stimulation of ovulation in order to prevent cycle cancellation secondary to a premature luteinizing hormone (LH) surge. The two main categories of analogues are agonists and antagonists. Both are frequently used in assisted reproduction programs. This updated review evaluated the efficacy and safety of GnRH antagonists compared to the more widely used protocol of GnRH agonists (long protocol). Forty-five randomised controlled studies were included and the pooled data showed that GnRH antagonist use leads to similar live-birth rates but a markedly lower incidence of severe ovarian hyperstimulation syndrome.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Pregnancy outcomes related to GnRH antagonists for infertility treated with assisted reproductive technology.

Patient or population: patients with infertility treated with assisted reproductive technology

Settings: Fertility clinics

Intervention: GnRH antagonists

Comparison: Long GnRh agonists

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long GnRh agonists	GnRH antagonists				
Live birth rate per women randomised - All women	314 per 1000	282 per 1000 (240 to 331)	OR 0.86 (0.69 to 1.08)	1515 (9 studies)	⊕⊕⊕○ moderate ¹	
Ongoing pregnancy rate per women randomised - All women	303 per 1000	277 per 1000 (251 to 303)	OR 0.88 (0.77 to 1)	5014 (28 studies)	⊕⊕⊕○ moderate ¹	
Clinical pregnancy rate per women randomised - All women	315 per 1000	279 per 1000 (256 to 302)	OR 0.84 (0.75 to 0.94)	6571 (41 studies)	⊕⊕⊕○ moderate ¹	
OHSS incidence per women randomised - All women	66 per 1000	29 per 1000 (23 to 39)	OR 0.43 (0.33 to 0.57)	5417 (29 studies)	⊕⊕○○ low	
Miscarriage rate per clinical pregnancy rate	118 per 1000	114 per 1000 (86 to 149)	OR 0.96 (0.7 to 1.31)	1647 (27 studies)	⊕⊕○○ low ^{1,2}	

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

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Almost all of the included studies were not able to be blinded due to the nature of the treatment.

² The pooled estimate includes both the line of no effect and appreciable benefit or harm.

BACKGROUND

Description of the condition

Controlled ovarian hyperstimulation (COH) coupled with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was one of the major advances in the treatment of subfertility in the second half of the 20th century. One aspect of COH-IVF or ICSI that requires attention is the occurrence of a luteinizing hormone (LH) surge which may occur prematurely, before the leading follicle reaches the optimum diameter for triggering ovulation. Such premature LH surges prevent effective induction of multiple follicular maturation patterns for a significant number of women. Gonadotrophin-releasing hormone agonists (GnRHa) have played an important role in reducing the incidence of premature LH surges by reversibly blocking pituitary gonadotrophin secretion. As a result, the rate of cancellation of assisted conception cycles are decreased and pregnancy rates increased (Albano 1996; Hughes 1992). However, the use of GnRH agonists is not without disadvantages. Even though the standard long GnRHa protocol proved to be the most efficacious protocol (Daya 2000) for the use of GnRHa, it requires two to three weeks for desensitization with relatively high costs due to an increased requirement for gonadotrophin injections and the need for hormonal and ultrasonographic measurements (Olivennes 1994).

Description of the intervention

Gonadotrophin-releasing hormone antagonists have emerged as an alternative in preventing premature LH surges. In comparison with the GnRH agonists, the pharmacological mechanism by which GnRH antagonists suppress the release of gonadotrophins is completely different. While the agonists act by down-regulation of the pituitary GnRH receptors and desensitization of the gonadotrophic cells, the antagonists bind competitively to the receptors thereby preventing the endogenous GnRH from exerting its stimulatory effects on the pituitary cells. The competitive blockade of the receptors leads to an immediate arrest of gonadotrophin secretion. This mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonist and is highly dose dependent, in contrast with the agonists (Felberbaum 1995).

While the first generation of GnRH antagonists showed allergic side-effects due to an induced histamine release, which hampered the clinical development of these compounds, third generation GnRH antagonists such as ganirelix (NV Organon, Oss, the Netherlands) and cetrorelix (ASTA-Medica, Frankfurt am Main, Germany) have resolved these issues and are approved for clinical use (Olivennes 1998).

How the intervention might work

Applying GnRH antagonists for pituitary down-regulation during COH is expected to result in a dramatic reduction in the duration of GnRH analogue treatment and to reduce the amount of gonadotrophin needed for stimulation as compared with the long agonist protocol. Other potential benefits include a lower risk of developing severe ovarian hyperstimulation syndrome (OHSS) and avoidance of the oestrogen deprivation symptoms (for example hot flushes, sleep disturbances, headaches) frequently observed in the pre-stimulation phase of a long agonist protocol. Whether the previously mentioned benefits justify a change in routine treatment from the standard long GnRHa protocol to the GnRH antagonist regimen depends on whether the clinical outcomes using these protocols are similar.

Why it is important to do this review

The first Cochrane review on this topic was published in 2001 and was updated in 2006. As further RCTs have been published, this is a further update on the best available evidence comparing GnRH antagonist versus the long agonist protocol for women undergoing COH-IVF or ICSI.

OBJECTIVES

To evaluate the effectiveness and safety of gonadotrophin-releasing hormone (GnRH) antagonists compared with the standard long protocol of GnRH agonists for controlled ovarian hyperstimulation in assisted conception cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) with a parallel design were eligible for inclusion. Quasi-randomised trials were not included. If cross-over studies with cross-over occurring between cycles were available only inclusion of the first cycle, before the cross-over, would have been included.

Types of participants

Subfertile couples undergoing controlled ovarian hyperstimulation (COH) as part of an IVF or ICSI program using GnRH antagonists for the prevention of premature LH surges.

Types of interventions

Pituitary suppression with GnRH antagonist (for example cetrorelix, ganirelix) or long GnRHa together with ovarian stimulation with recombinant or urinary human follicle stimulating hormone (hFSH) or human menopausal gonadotrophin (hMG), or both, or clomiphene citrate as part of an IVF or ICSI treatment cycles. Further, the use of oral contraceptive pill pre-treatment did not constitute an inclusion or exclusion criterion but rather was a variation in the protocols used.

Types of outcome measures

Primary outcomes

- Live-birth rate (LBR) per randomised woman, defined as delivery of a live fetus after 20 completed weeks of gestation.
- Severe ovarian hyperstimulation syndrome (OHSS) rate per randomised woman, as detected by clinical grading of OHSS, laboratory investigations (e.g. haematocrit, haemoglobin, renal function) or imaging techniques (ovarian and abdominal ultrasound, chest X-ray), or both.

Secondary outcomes

- Ongoing pregnancy rate (OPR) per randomised woman, defined as a pregnancy beyond 12 weeks gestation.
- Clinical pregnancy rate (CPR) per randomised woman, defined as the presence of a gestational sac \pm fetal heart beat at transvaginal ultrasound.
- Miscarriage rate per randomised woman, defined as pregnancy loss before 20 weeks gestation.
- Number of cycles cancelled (note, new outcome added in the 2011 update).

Search methods for identification of studies

All published and unpublished RCTs of GnRH antagonist versus the long GnRH agonist protocol in women undergoing COH-IVF or ICSI were sought using the following search strategy, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator. The most recent searches were performed in April 2010.

Electronic searches

The following databases were searched (from their inception).

- Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library*) (updated search from 2006 to April 2010) ([Appendix 1](#)).
- Ovid MEDLINE (updated search from 2006 to April 2010) ([Appendix 2](#)). The MEDLINE search was combined with

the Cochrane highly sensitive search strategy (HSSS) for identifying randomised trials.

- EMBASE (updated search 2009 up to April 2010) ([Appendix 3](#)). EMBASE was only searched one year back as the UK Cochrane Centre has handsearched EMBASE from inception to this point and these trials are already available in CENTRAL. The EMBASE search was combined with the trial filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) (<http://www.sign.ac.uk/mehodology/filters.html#random>).
- Menstrual Disorders and Subfertility Group (MDSG) Specialised Register (updated search from 2006 to April 2010) ([Appendix 4](#)).
- PsycINFO (updated search from 2006 to April 2010) ([Appendix 4](#)). The PsycINFO search was combined with the trial filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) (<http://www.sign.ac.uk/mehodology/filters.html#random>).
- CINAHL (Cumulative Index to Nursing and Allied Health Literature).
- Trial registers for ongoing and registered trials: Current Controlled Trials (www.controlled-trials.com/), ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/home>), and the World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx).
- Citation indexes ([http://scientific.thomson.com/products/sci/Conference abstracts](http://scientific.thomson.com/products/sci/Conference%20abstracts)) on the ISI Web of Knowledge (<http://isiwebofknowledge.com/>).
- LILACS (Latin American and Caribbean Health Sciences) (<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F>).
- ClinicalStudyResults (www.clinicalstudyresults.org/).
- PubMed (www.ncbi.nlm.nih.gov/pubmed/). The PubMed search was combined with the random control filter for PubMed.
- Open SIGLE database for grey literature in Europe (<http://opensigle.inist.fr/>).

Searching other resources

The reference lists of all known primary studies, review articles, citation lists of relevant publications, abstracts of major scientific meetings (for example of the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM)). Known experts and personal contacts were contacted regarding any unpublished materials. In addition, we carried out the following.

- Handsearching of appropriate journals: the lists of journals are found in the MDSG Module. The Module is found in *The Cochrane Library* under BROWSE - 'By Review Group' - 'Cochrane Menstrual Disorders and Subfertility Group' - then 'about this group' at the top of this page. We liaised with the

MDSG Trials Search Co-ordinator to avoid duplication of handsearching.

Data collection and analysis

- Data collection and analysis were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. Included articles were screened for available information. Statistical analysis was performed in accordance with the statistical guidelines developed by the Cochrane MDSG.

- Two authors (HA and MY) independently extracted data and assessed the quality of trials using forms designed according to Cochrane guidelines. We sought additional information on trial methodology or actual original trial data from the authors of trials which appeared to meet the eligibility criteria but had aspects of methodology that were unclear, or where the data were in a form unsuitable for meta-analysis. We contacted trial authors to request additional information or data. We also received a response from the sponsoring pharmaceutical companies.

- We examined the heterogeneity between the results of different studies by inspecting the scatter in the data points, the overlap in their confidence intervals and more formally by checking results of Chi² tests. We had planned to look at the possible contribution of differences in trial design to any heterogeneity identified in this manner. Where possible, the outcomes were pooled statistically.

- Two independent authors (JS and FB) analysed possible explanations for the differences between antagonist and agonist stimulation regimens as well as possible differences between the present study outcomes compared to the previous update of this review in 2006. In this effort our focus was on LH instability.

Selection of studies

Titles and abstracts of studies were reviewed independently by two review authors (HA, MY or AMAS) using the a priori criteria for inclusion. The full manuscripts of studies were obtained for the short-listed papers considered potentially eligible for inclusion. Further information was sought from the authors of studies that did not contain sufficient information to make a decision about eligibility. Subsequently, a detailed 'Characteristics of excluded studies' table was constructed for those studies that did not satisfy the inclusion criteria. Included studies were independently critically appraised for their risk of bias by two review authors (HA, MY or AMAS) and any disagreements were resolved by referral to a third review author. A 'Characteristics of included studies' table was constructed.

Data extraction and management

A standardised data extraction form was developed and piloted for consistency and completeness. Data extraction was performed

independently by two review authors (HA, MY or AMAS) with discrepancies resolved by discussion. The data extraction forms included study demographics, patient characteristics and study risk of bias. This information was included in the review and presented in the tables 'Characteristics of included studies' and 'Characteristics of excluded studies' according to the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). The following data were extracted from each included trial.

Trial characteristics

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

Characteristics of the study participants

- Cause and duration of pre-existing subfertility
- Patient age
- Body mass index (BMI)
- Number of previous IVF-embryo transfer (ET) cycles
- Basal hormonal profile (FSH, LH)

Interventions used

- Types of ovarian hyperstimulation protocols used
- Types of pituitary down-regulation (GnRH agonist or antagonist)
- Types of luteal phase support: dose, duration and route of administration

Outcomes

- Live-birth rate, ongoing pregnancy and clinical pregnancy rates
- Incidence of ovarian hyperstimulation syndrome (OHSS)
- Miscarriage rate

Assessment of risk of bias in included studies

The risk of bias of the included trials was assessed using The Cochrane Collaboration's risk of bias (RoB) tool, a domain-based risk of bias assessment. The domains were: (1) sequence generation (for example: was the allocation sequence adequately generated?); (2) allocation concealment (for example was allocation adequately concealed?); (3) blinding of participants, personnel and outcome assessors (for example: was knowledge of the allocated

intervention adequately prevented during the study?); (4) incomplete outcome data (for example: were incomplete outcome data adequately addressed?); (5) selective outcome reporting (for example: were reports of the study free of suggestion of selective outcome reporting?); and (6) other sources of bias (for example: was the study apparently free of other problems that could put it at a high risk of bias?). Other sources of bias included baseline imbalances, source of funding, early stopping for benefit, and appropriateness of cross-over design. See the [Characteristics of included studies](#) table.

Measures of treatment effect

For dichotomous data (for example live-birth rates), the numbers of events in the control and intervention groups of each study were used to calculate the odds ratio (OR) with 95% confidence interval (CI) for each individual trial. The continuous data for each study were expressed as mean differences with 95% CIs.

Unit of analysis issues

The primary analysis was per woman randomised, determined as the number of women achieving an event divided by the number of women randomised. Data per cycle were not included in the analysis as they potentially lead to a unit-of-analysis error.

Dealing with missing data

The data have been analysed on an intention-to-treat basis. Authors of trials were contacted for missing information.

Assessment of heterogeneity

Presence of statistical heterogeneity of treatment effect among studies was determined by visual inspection of the outcome tables and by using the Breslow-Day χ^2 test for heterogeneity with a 10% level of statistical significance. Additionally, the I^2 test was used to quantify any noticeable heterogeneity. The following broad classifications of heterogeneity were used:

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

Assessment of reporting biases

If the study protocol was available then this was used to check for possible reporting bias. If not, then we used the outcomes identified in the methods section of each trial to compare to the outcomes reported in the results section.

Data synthesis

The data from primary studies were combined using the Peto-modified Mantel-Haenszel method for dichotomous outcomes; and using the inverse variance method for continuous outcomes. All analyses were performed using Review Manager software (RevMan 5, The Cochrane Collaboration, Oxford, UK).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was performed for the following categories:

- 1) GnRH antagonist regimen (fixed or flexible).
- 2) GnRH antagonist type (cetorelix or ganirelix).
- 3) GnRH antagonist plus pre-treatment with oral contraceptive pill (OCP).
- 4) Patient characteristics (polycystic ovary syndrome (PCOS); poor responders).
- 5) Patients undergoing mild ovarian stimulation.

Sensitivity analysis

Sensitivity analysis was performed for the outcomes LBR and OPR, after exclusion of studies with a higher risk of bias. Such studies provided no clear information on the mode of randomisation or used inadequate allocation concealment ([Moher 1999](#)).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

See the table '[Characteristics of included studies](#)'.

Results of the search

Forty-five randomised controlled studies, involving 7511 randomised women, met the inclusion criteria and were fully reviewed ([Characteristics of included studies](#)). A date limited search of two data bases from April 2010 to April 2011 was run. Nineteen studies have been entered into the Classification pending references section of this update. These studies will be appraised for inclusion or exclusion in the next update of this review, due April 2012.

Included studies

Study characteristics

1. Twelve studies were multi-centre ([Albano 2000](#); [Baart 2007](#); [Barmat 2005](#); [Euro Midd East 2001](#); [Euro Orgalutran](#)

2000; Fluker 2001; Heijnen 2007; Hurine 2006; Kim 2009; Olivennes 2000; Rombauts 2006; Sauer 2004) while the remaining 33 studies were single-centre trials.

2. Sample size calculations were considered to be appropriate when the authors of the studies pre-calculated the number needed in each arm prior to starting the trial. This helps to prevent the occurrence of type II errors. Twelve studies performed a priori sample size calculations (Hwang 2004; Baart 2007; Engmann 2008 a; Heijnen 2007; Hurine 2006; Kurzawa 2008; Lainas 2010; Sbarcia 2009; Tehraninejad 2010; Lin 2006; Depalo 2009; Tazegul 2008); 22 studies reported that a sample size calculation had not been performed; and it was not clear if sample size calculations were performed in the remaining 11 studies.

3. Intention-to-treat analysis was performed in 17 studies (Badrawy 2005; Depalo 2009; Engmann 2008 a; Euro Midd East 2001; Euro Orgalutran 2000; Fluker 2001; Heijnen 2007; Hurine 2006; Hwang 2004; Kim 2004; Lin 2006; Loutradis 2004; Marci 2005; Rombauts 2006; Sauer 2004; Serafini 2003; Xavier 2005); 16 studies reported that the original analyses did not use the intention-to-treat principle (Albano 2000; Baart 2007; Bahceci 2005; Cheung 2005; El Sahwi 2005; Firouzabadi 2010; Hohmann 2003; Inza 2004; Kurzawa 2008; Kyono 2005; Lee 2005; Olivennes 2000; Sbarcia 2009; Tazegul 2008; Tehraninejad 2010; Ye 2009); it was not reported clearly in the rest of the studies.

Participants

1. Baseline characteristics were comparable between groups (Characteristics of included studies table).

2. Of the 46 included studies, 31 trials involved an unspecified population of infertile couples while the remaining trials were performed in specific infertile populations. These populations were 'poor responders' (Inza 2004; Cheung 2005; Marci 2005; Kim 2009; Sbarcia 2009; Tazegul 2008) or had polycystic ovary syndrome (Bahceci 2005; Engmann 2008 a; Hwang 2004; Kim 2004; Kurzawa 2008; Lainas 2007; Lainas 2010; Moshin 2007; Tehraninejad 2010).

3. The number of randomised patients ranged from 20 (Franco 2003) to 730 (Euro Orgalutran 2000), including both the GnRH agonist and antagonist groups.

4. Six studies included more than 300 participants (Euro Midd East 2001; Euro Orgalutran 2000; Heijnen 2007; Martinez 2008; Rombauts 2006; Sbarcia 2009). There were 16 studies with less than 100 study cases (Barmat 2005; Check 2004; Cheung 2004; Engmann 2008; Franco 2003; Friedler 2003; Hwang 2004; Inza 2004; Kim 2004; Kim 2009; Kurzawa 2008; Lainas 2007; Lee 2005; Marci 2005; Moraloglu 2008; Moshin 2007; Sauer 2004; Serafini 2003; Tazegul 2008; Tehraninejad 2010).

5. Five studies were published before 2002. There were 25 studies published between 2002 and 2006 and 13 studies

published between 2007 and 2010.

Intervention

1. All included studies compared GnRH antagonist with long GnRH agonist protocols in women undergoing IVF or ICSI cycles.

2. Three types of antagonist protocols were identified: (1) single, long-acting administration (Hsieh 2008; Lee 2005; Moshin 2007; Olivennes 2000); (2) fixed, daily administration (Albano 2000; Cheung 2005; Euro Midd East 2001; Euro Orgalutran 2000; Firouzabadi 2010; Fluker 2001; Hsieh 2008; Hurine 2006; Hwang 2004; Martinez 2008; Moshin 2007; Sauer 2004); and (3) flexible daily administration (Baart 2007; Badrawy 2005; Bahceci 2005; Barmat 2005; Brelik 2004; Check 2004; Depalo 2009; El Sahwi 2005; Engmann 2008 a; Franco 2003; Hohmann 2003; Karimzadeh 2010; Kim 2004; Kim 2009; Kurzawa 2008; Lainas 2007; Lainas 2010; Lee 2005; Lin 2006; Loutradis 2004; Marci 2005; Moraloglu 2008; Rombauts 2006; Sbarcia 2009; Serafini 2003; Tazegul 2008; Tehraninejad 2010; Ye 2009; Xavier 2005). In the fixed daily protocol, in most of the studies GnRH antagonist was begun on day six of FSH treatment regardless of follicle size. In the flexible daily protocol, GnRH antagonist was administered according to the lead follicle size and not the cycle date nor the day of FSH administration.

3. In 24 included trials, the antagonist cetrorelix was administered (Albano 2000; Bahceci 2005; Brelik 2004; Cheung 2005; Hohmann 2003; Hsieh 2008; Hurine 2006; Hwang 2004; Kim 2004; Kim 2009; Kurzawa 2008; Kyono 2005; Lainas 2010; Lee 2005; Loutradis 2004; Marci 2005; Moraloglu 2008; Moshin 2007; Olivennes 2000; Sauer 2004; Sbarcia 2009; Tehraninejad 2010; Xavier 2005; Ye 2009). In 14 trials, the antagonist ganirelix was administered (Euro Orgalutran 2000; Euro Midd East 2001; Fluker 2001; Franco 2003; Badrawy 2005; Barmat 2005; Baart 2007; Engmann 2008 a; Firouzabadi 2010; Karimzadeh 2010; Lainas 2007; Martinez 2008; Check 2004; Rombauts 2006). One trial used both cetrorelix and ganirelix (Tazegul 2008) and in four included trials the type of antagonist used was unclear (Inza 2004; Friedler 2003; Kyono 2005; Heijnen 2007).

4. Oral contraceptive pill pre-treatment was used in 14 studies (Barmat 2005; Cheung 2005; Engmann 2008 a; Hurine 2006; Kim 2004; Kim 2009; Kurzawa 2008; Kyono 2005; Lainas 2007; Lainas 2010; Moraloglu 2008; Rombauts 2006; Sauer 2004; Tehraninejad 2010). Further single trials used Diane (Hwang 2004), estradiol in the luteal phase (Franco 2003), and vaginal Nuvaring (Martinez 2008).

5. Patients randomised to treatment with GnRH antagonist started ovarian stimulation on day two to three of the menstrual cycle. The GnRH antagonist was started on stimulation day six by daily subcutaneous administration up to and including the day of human chorionic gonadotrophin (hCG) administration in the fixed protocol or depending on the dominant follicle size in

the flexible protocol. The GnRH long agonist reference treatment was started in the mid-luteal phase (cycle day 21 to 24) by either daily intranasal or subcutaneous administration.

6. Ovarian stimulation was started after two weeks if pituitary down-regulation was established (serum estradiol level < 50 pg/ml). In both treatment groups, ovarian stimulation was started with a fixed daily dose of 150 or 225 IU recombinant follicle stimulating hormone (rFSH) or human menopausal gonadotrophin (hMG) for the first five stimulation days. Thereafter, the dose of FSH was adapted depending on the ovarian response, as monitored via ultrasonography (US). Triggering of ovulation was induced with hCG (10,000 IU) if at least three follicles that were > 17 mm in diameter were observed by US.

Outcomes

1. Study participant follow up: the optimum follow up would be to report on the number of single, healthy babies going home with their parents (for example single, live, take-home baby rate). If unavailable, other follow ups were assessed including the live-birth (LBR) and ongoing pregnancy rates (OPR). None of the included trials described the single, live, take-home baby rate or the take-home baby rate. Nine studies reported on the LBR

(Albano 2000; Baart 2007; Barmat 2005; Heijnen 2007; Kim 2009; Kurzawa 2008; Lin 2006; Marci 2005; Ye 2009). Further, 28 trials reported the OPR and 41 studies reported the clinical pregnancy rate (CPR).

2. Twenty-nine studies reported OHSS incidence (Albano 2000; Badrawy 2005; Bahceci 2005; Barmat 2005; Engmann 2008 a; Euro Midd East 2001; Euro Orgalutran 2000; Firouzabadi 2010; Fluker 2001; Heijnen 2007; Hohmann 2003; Hsieh 2008; Hurine 2006; Hwang 2004; Karimzadeh 2010; Kurzawa 2008; Kyono 2005; Lainas 2007; Lainas 2010; Lee 2005; Lin 2006; Moraloglu 2008; Moshin 2007; Olivennes 2000; Rombauts 2006; Serafini 2003; Tehraninejad 2010; Xavier 2005; Ye 2009).

Excluded studies

Thirty-three studies were excluded for various reasons (see table [Characteristics of excluded studies](#)).

Risk of bias in included studies

For the risk of bias (ROB) of the included trials, please see [Figure 1](#) and [Figure 2](#).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

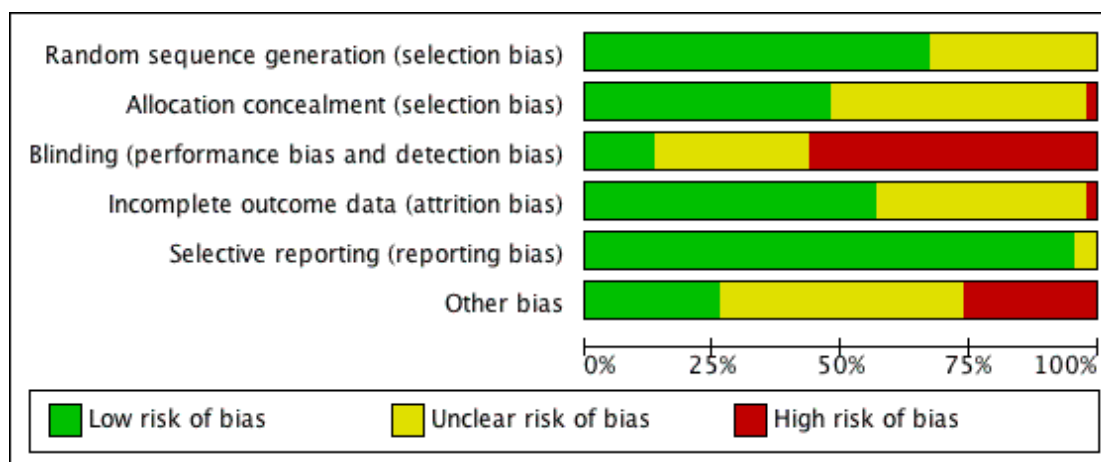


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Albano 2000	?	?	?	?	?	?
Baart 2007	?	?	?	?	?	?
Badrawy 2005	?	?	?	?	?	?
Bahceci 2005	?	?	?	?	?	?
Barmat 2005	?	?	?	?	?	?
Brelik 2004	?	?	?	?	?	?
Check 2004	?	?	?	?	?	?
Cheung 2005	?	?	?	?	?	?
Depalo 2009	?	?	?	?	?	?
El Sahwi 2005	?	?	?	?	?	?
Engmann 2008 a	?	?	?	?	?	?
Euro Midd East 2001	?	?	?	?	?	?
Euro Orglutran 2000	?	?	?	?	?	?
Firouzabadi 2010	?	?	?	?	?	?
Fluker 2001	?	?	?	?	?	?
Franco 2003	?	?	?	?	?	?
Friedler 2003	?	?	?	?	?	?
Heijnen 2007	?	?	?	?	?	?
Hohmann 2003	?	?	?	?	?	?
Hsieh 2008	?	?	?	?	?	?
Hurine 2006	?	?	?	?	?	?
Hwang 2004	?	?	?	?	?	?
Inza 2004	?	?	?	?	?	?
Karimzadeh 2010	?	?	?	?	?	?
Kim 2004	?	?	?	?	?	?
Kim 2009	?	?	?	?	?	?
Kurzawa 2008	?	?	?	?	?	?
Kyono 2005	?	?	?	?	?	?
Lainas 2007	?	?	?	?	?	?
Lainas 2010	?	?	?	?	?	?
Lee 2005	?	?	?	?	?	?
Lin 2006	?	?	?	?	?	?
Loutradis 2004	?	?	?	?	?	?
Marci 2005	?	?	?	?	?	?
Martinez 2008	?	?	?	?	?	?
Moraloglu 2008	?	?	?	?	?	?
Moshin 2007	?	?	?	?	?	?
Olivennes 2000	?	?	?	?	?	?
Rombauts 2006	?	?	?	?	?	?
Sauer 2004	?	?	?	?	?	?
Sbarcia 2009	?	?	?	?	?	?
Serafini 2003	?	?	?	?	?	?
Tazegul 2008	?	?	?	?	?	?
Tehranejad 2010	?	?	?	?	?	?
Xavier 2005	?	?	?	?	?	?
Ye 2009	?	?	?	?	?	?

Allocation

- Randomisation was done at the time of recruitment of participants.
- All trials had a parallel design and proper randomisation was carried out by 31 studies by using: interactive voice response systems (Albano 2000; Euro Midd East 2001; Euro Orgalutran 2000; Rombauts 2006); stratified randomisation (Fluker 2001); computer-generated random number tables with or without sealed envelopes for allocation concealment (Baart 2007; Badrawy 2005; Barmat 2005; Depalo 2009; Engmann 2008 a; Firouzabadi 2010; Heijnen 2007; Hohmann 2003; Hurine 2006; Hwang 2004; Karimzadeh 2010; Kim 2009; Kurzawa 2008; Lainas 2007; Lainas 2010; Loutradis 2004; Martinez 2008; Moraloglu 2008; Sauer 2004; Sbarcia 2009; Tazegul 2008; Tehraninejad 2010; Ye 2009; Xavier 2005); or random number table (Bahceci 2005; Cheung 2005).
- Allocation concealment was properly performed by a nurse (Lainas 2007) or by an interactive telephone system (Martinez 2008).
- The methods of sequence generation and allocation concealment were not clearly reported in the remaining trials (Bahceci 2005; Brelik 2004; Check 2004; Friedler 2003; Inza 2004; Kim 2004; Kyono 2005; Lee 2005; Marci 2005; Moshin 2007; Olivennes 2000; Serafini 2003).

Blinding

- Blinding was examined with regards to who was blinded in the trials. All levels were sought and categorized as follows: (i) double blind (neither the investigator nor the participants knew of the allocation); (ii) single blind (the investigator only knew of the allocation); (iii) no blinding (both investigator and participants knew the allocated treatment); (iv) unclear.
- Since it was impossible to administer the different medications (that is long agonist and antagonist) according to one standard protocol without the use of a double dummy, almost all the studies were open-label (that is no blinding). One study (Cheung 2005) blinded the clinicians and embryologists from the treatment allocation by using a nurse practitioner to administer the medications. The embryologist scoring the embryos or the researcher was blinded to the study groups in four trials (Baart 2007; Depalo 2009; Hwang 2004; Martinez 2008) and one study (El Sahwi 2005) reported that it was blinded.
- None of the trials were reported as being double blinded, with 27 trials reporting no blinding (Albano 2000; Badrawy 2005; Bahceci 2005; Barmat 2005; Check 2004; Engmann 2008 a; Euro Midd East 2001; Euro Orgalutran 2000; Firouzabadi

2010; Fluker 2001; Franco 2003; Friedler 2003; Heijnen 2007; Hohmann 2003; Kurzawa 2008; Kyono 2005; Lainas 2007; Lainas 2010; Loutradis 2004; Marci 2005; Olivennes 2000; Rombauts 2006; Sauer 2004; Tazegul 2008; Tehraninejad 2010; Xavier 2005; Ye 2009). The remaining trials did not clearly report if blinding was performed.

Incomplete outcome data

Live-birth rate was reported in only nine trials (Albano 2000; Barmat 2005; Heijnen 2007; Hurine 2006; Kim 2009; Kurzawa 2008; Lin 2006; Marci 2005; Ye 2009).

Selective reporting

All studies reported their outcome measures in a pre-specified manner.

Other potential sources of bias

Commercial funding

Twelve studies received commercial funding (Albano 2000; Barmat 2005; Cheung 2005; Euro Midd East 2001; Euro Orgalutran 2000; Fluker 2001; Hohmann 2003; Hurine 2006; Kurzawa 2008; Lee 2005; Olivennes 2000; Rombauts 2006). Thirteen studies reported no conflict of interest or commercial support (Bahceci 2005; Brelik 2004; El Sahwi 2005; Heijnen 2007; Inza 2004; Kim 2004; Kim 2009; Kyono 2005; Loutradis 2004; Marci 2005; Sbarcia 2009; Serafini 2003; Tehraninejad 2010). The other studies did not clearly report funding.

Effects of interventions

See: [Summary of findings for the main comparison](#) Pregnancy outcomes related to GnRH antagonists for infertility treated with assisted reproductive technology.

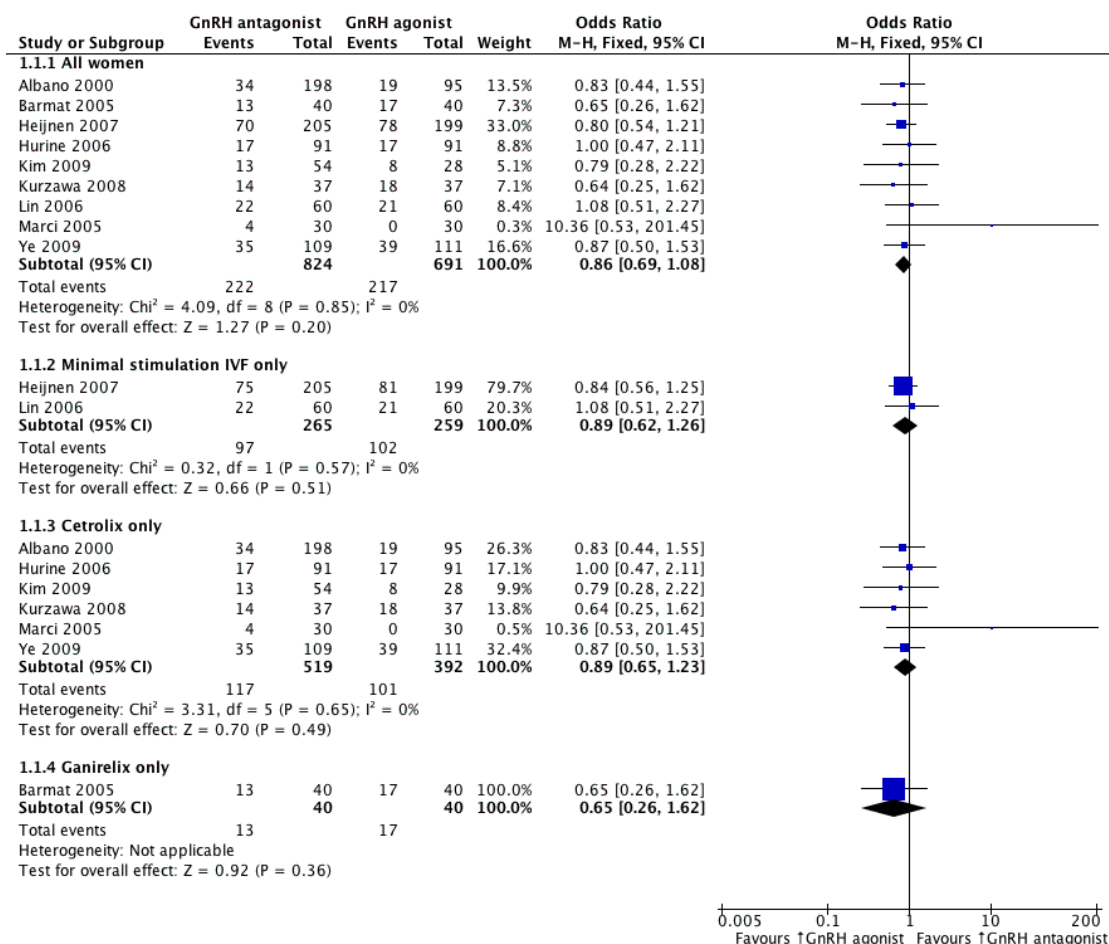
The included studies enrolled a total of 7511 participants who were randomised, although the sample size varied across the trials. The analyses were performed on the number of women randomised and not on the number of participants treated.

1.1 Live birth rate per women randomised

1.1.1 All women

Nine trials reported live birth rates in 1515 women (Figure 3). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.86, 95% CI = 0.69 to 1.08; $p = 0.20$; $I^2 = 0.00\%$, 95% CI = 0.00% to 31.62%).

Figure 3. Forest plot of comparison: I GnRH antagonist versus long course GnRH agonist, outcome: I.1 Live birth rate per women randomised.



1.1.2 Minimal stimulation IVF only

In a subgroup analysis, two trials reported live birth rates in 524 women undergoing minimal stimulation IVF (Figure 3). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.89, 95% CI = 0.62 to 1.26; p = 0.51; I² = 0.00%).

1.1.3 Cetrolix only

In a subgroup analysis, six trials reported live birth rates in 911 women receiving cetrolix (Figure 3). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.89, 95% CI = 0.65 to 1.23; p = 0.49; I² = 0.00%, 95% CI = 0.00% to 62.74%).

1.1.4 Ganirelix only

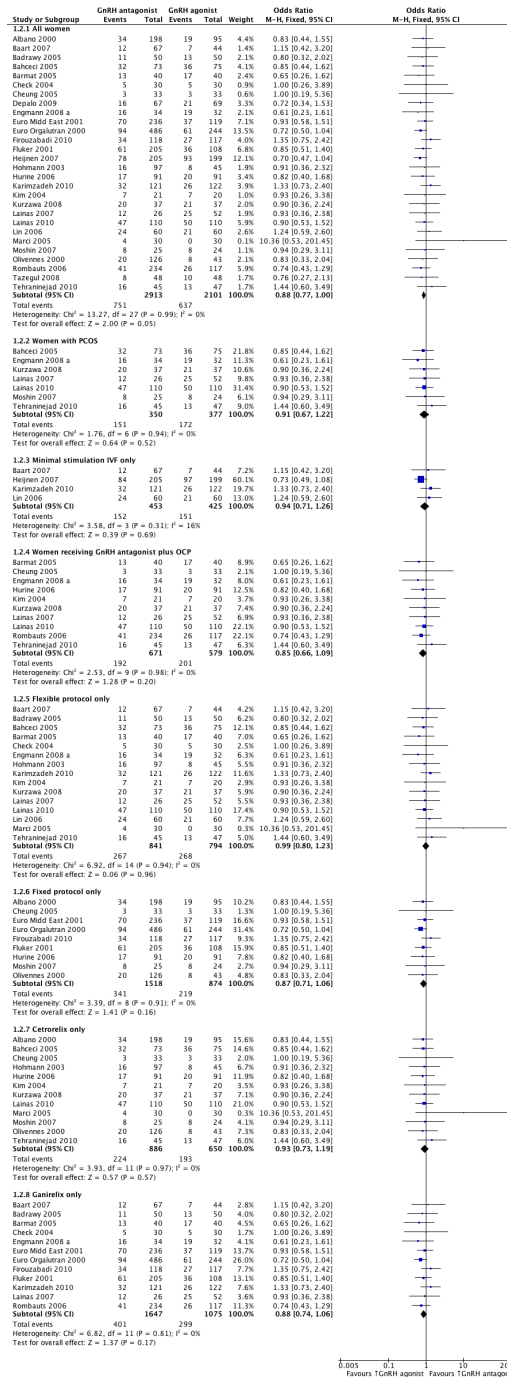
In a subgroup analysis, one trial reported live birth rates in 80 women receiving ganirelix (Figure 3). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.65, 95% CI = 0.26 to 1.62; p = 0.36).

1.2 Ongoing pregnancy rate per women randomised

1.2.1 All women

Twenty-eight trials reported ongoing pregnancy rates in 5014 women (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.88, 95% CI = 0.77 to 1.00; p = 0.05; I² = 0.00%, 95% CI = 0.00% to 0.00%).

Figure 4. Forest plot of comparison: 1 GnRH antagonist versus long course GnRH agonist, outcome: 1.2 Ongoing pregnancy rate per women randomised.



1.2.2 Women with PCOS

In a subgroup analysis, seven trials reported ongoing pregnancy rates in 727 women with PCOS (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.91, 95% CI = 0.67 to 1.22; $p = 0.52$; $I^2 = 0.00\%$, 95% CI = 0.00% to 2.07%).

1.2.3 Minimal stimulation IVF only

In a subgroup analysis, four trials reported ongoing pregnancy rates in 878 women undergoing minimal stimulation IVF (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.94, 95% CI = 0.71 to 1.26; $p = 0.69$; $I^2 = 16.12\%$, 95% CI = 0.00% to 89.17%).

1.2.4 Women receiving GnRH antagonist plus OCP

In a subgroup analysis, ten trials reported ongoing pregnancy rates in 1250 women receiving GnRH antagonist plus OCP (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.85, 95% CI = 0.66 to 1.09; $p = 0.20$; $I^2 = 0.00\%$, 95% CI = 0.00% to 0.00%).

1.2.5 Flexible protocol only

In a subgroup analysis, fifteen trials reported ongoing pregnancy rates in 1635 women receiving the flexible GnRH antagonist protocol (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.99, 95% CI = 0.80 to 1.23; $p = 0.96$; $I^2 = 0.00\%$, 95% CI = 0.00% to 6.33%).

1.2.6 Fixed protocol only

In a subgroup analysis, nine trials reported ongoing pregnancy rates in 2392 women receiving the fixed antagonist protocol (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.87, 95% CI = 0.71 to 1.06; $p = 0.16$; $I^2 = 0.00\%$, 95% CI = 0.00% to 17.45%).

1.2.7 Cetrorelix only

In a subgroup analysis, twelve trials reported ongoing pregnancy rates in 1536 women receiving cetrorelix (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.93, 95% CI = 0.73 to 1.19; $p = 0.57$; $I^2 = 0.00\%$, 95% CI = 0.00% to 0.00%).

1.2.8 Ganirelix only

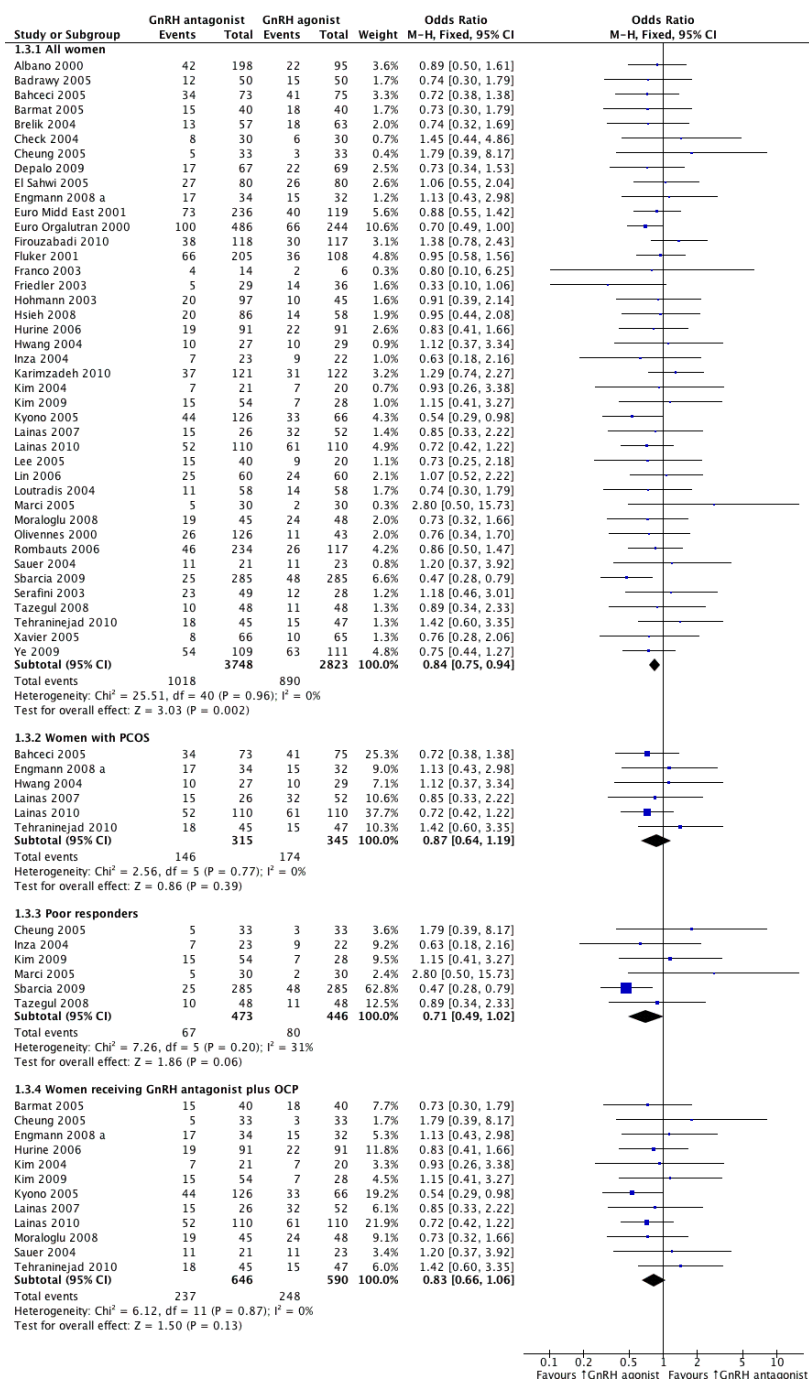
In a subgroup analysis, twelve trials reported ongoing pregnancy rates in 2722 women receiving ganirelix (Figure 4). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.88, 95% CI = 0.74 to 1.06; $p = 0.17$; $I^2 = 0.00\%$, 95% CI = 0.00% to 32.93%).

1.3 Clinical pregnancy rate per women randomised

1.3.1 All women

Forty-one trials reported clinical pregnancy rates in 6571 women (Figure 5). There was a significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.84, 95% CI = 0.75 to 0.94; $p = 0.002$; $I^2 = 0.00\%$, 95% CI = 0.00% to 0.00%).

Figure 5. Forest plot of comparison: 1 GnRH antagonist versus long course GnRH agonist, outcome: 1.3 Clinical pregnancy rate per women randomised.



1.3.2 Women with PCOS

In a subgroup analysis, six trials reported clinical pregnancy rates in 660 women with PCOS (Figure 5). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.87, 95% CI = 0.64 to 1.19; p = 0.39; I² = 0.00%, 95% CI = 0.00% to 51.88%).

1.3.3 Poor responders

In a subgroup analysis, six trials reported clinical pregnancy rates in 919 poor responders (Figure 5). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.71, 95% CI = 0.49 to 1.02; p = 0.06; I² = 31.10%, 95% CI = 0.00% to 72.03%).

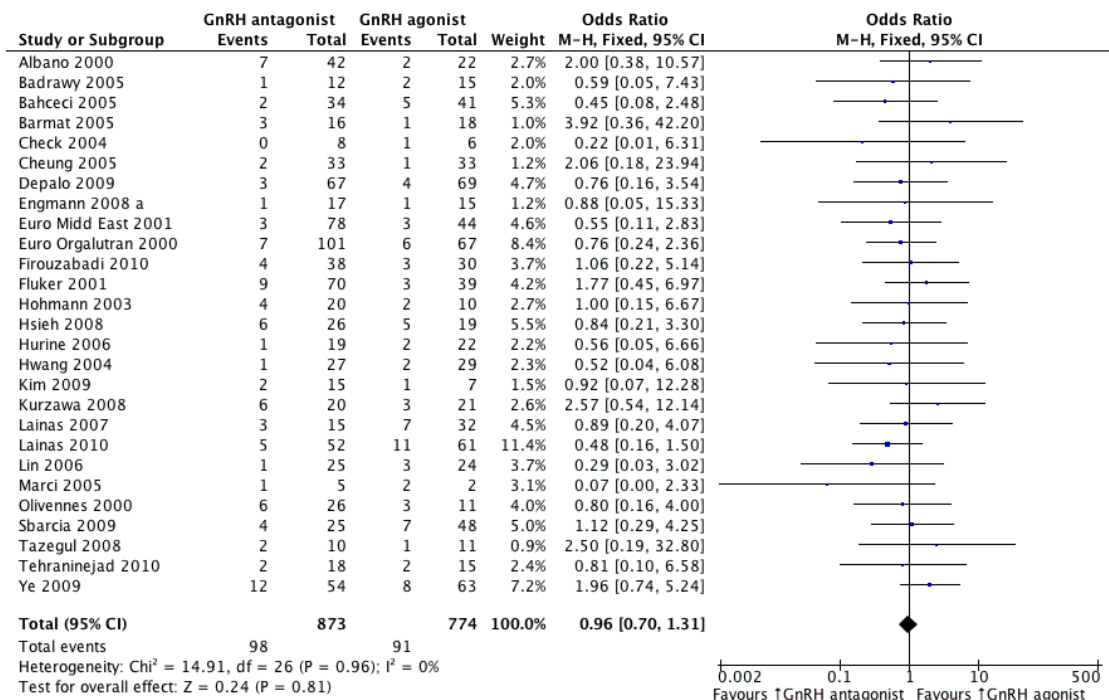
1.3.4 Women receiving GnRH antagonist plus OCP

In a subgroup analysis, twelve trials reported clinical pregnancy rates in 1236 women receiving GnRH antagonist plus OCP (Figure 5). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.83, 95% CI = 0.66 to 1.06; p = 0.13; I² = 0.00%, 95% CI = 0.00% to 25.27%).

1.4 Miscarriage rate per clinical pregnancy rate

Twenty-seven trials reported miscarriage rates per clinical pregnancy rates in 1647 women (Figure 6). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.96, 95% CI = 0.70 to 1.31; p = 0.81; I² = 0.00%, 95% CI = 0.00% to 0.00%).

Figure 6. Forest plot of comparison: I GnRH antagonist versus long course GnRH agonist, outcome: I.4 Miscarriage rate per clinical pregnancy rate.

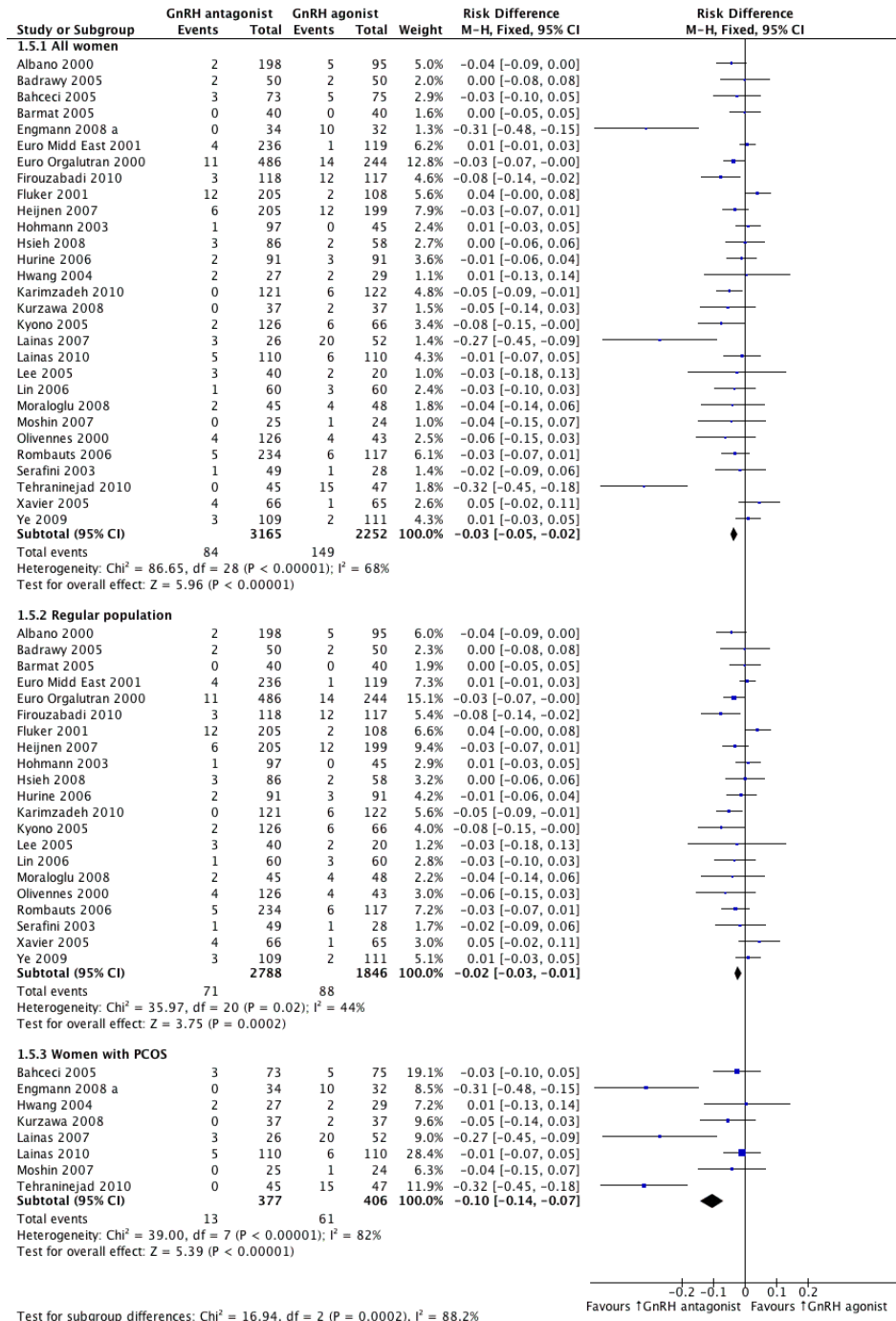


1.5 Ovarian hyperstimulation per woman randomised

1.5.1 All women

Twenty-nine trials reported ovarian hyperstimulation rates in 5417 women (Figure 7). There was a significant difference favouring GnRH antagonist compared with GnRH agonist (R.D = -0.03, 95% CI = -0.05 to -0.02; $p < 0.00001$; $I^2 = 67,68\%$, 95% CI = 52.50% to 78.02%).

Figure 7. Forest plot of comparison: I GnRH antagonist versus long course GnRH agonist, outcome: I.5 Ovarian hyperstimulation per woman randomised.



1.5.2 Regular population

Twenty-one trials reported ovarian hyperstimulation rates in 4634 women without PCOS (Figure 7). There was a significant difference favouring GnRH antagonist compared with GnRH agonist (R.D = -0.02, 95% CI = -0.03 to -0.01; p = 0.002; I² = 44.40%, 95% CI: 7.01% to 66.76%).

1.5.3 Women with PCOS

Eight trials reported ovarian hyperstimulation rates in 783 women with PCOS (Figure 7). There was a significant difference favouring

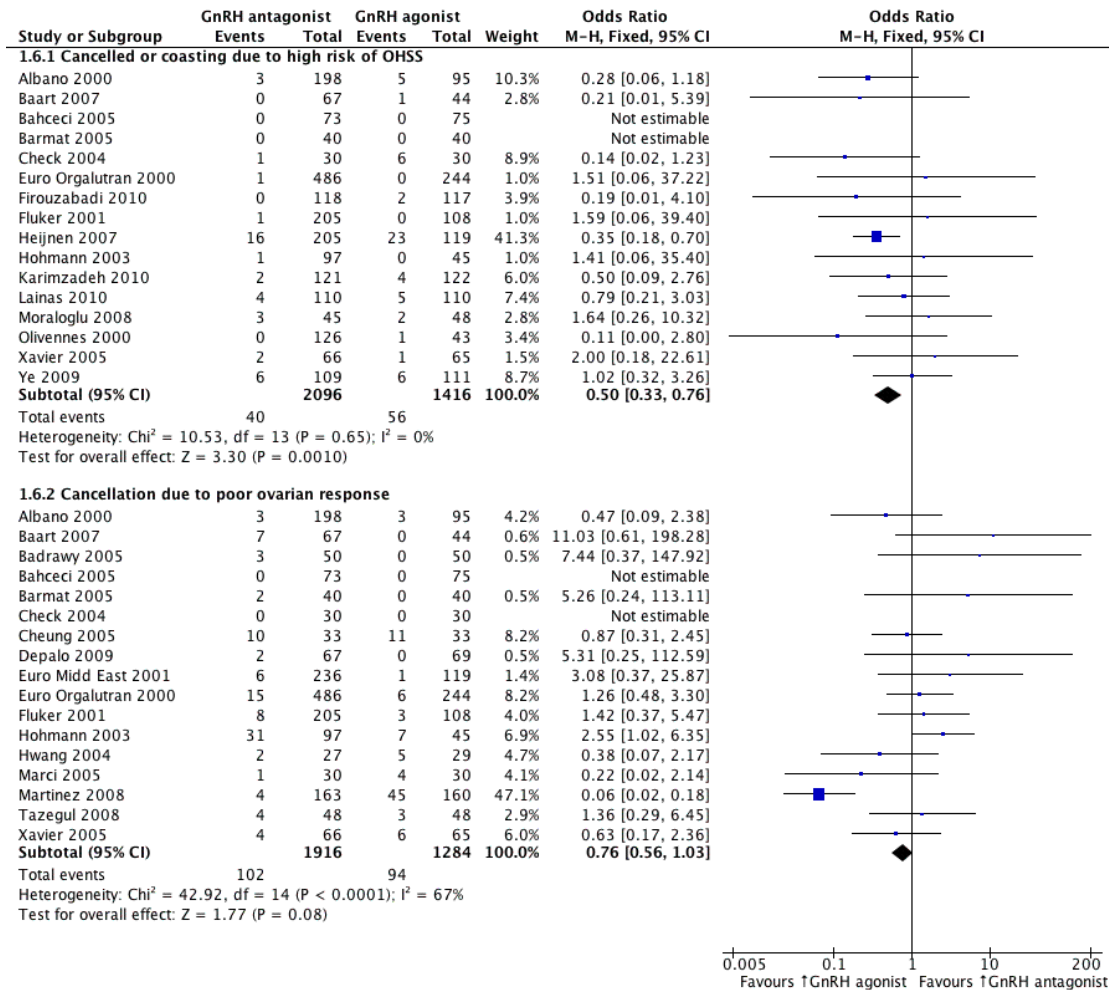
GnRH antagonist compared with GnRH agonist (R.D = -0.10, 95% CI = -0.14 to -0.07; p < 0.00001; I² = 82.05%, 95% CI = 65.82% to 90.57%).

1.6 Cycle cancellation

1.6.1 Cancelled or coasting due to high risk of OHSS

Sixteen trials reported rates of cycle cancellation or coasting due to high risk of OHSS in 3512 women (Figure 8). There was a significant difference favouring the GnRH antagonist compared with the GnRH agonist (O.R = 0.50, 95% CI = 0.33 to 0.76; p = 0.001; I² = 0.00%, 95% CI = 0.00% to 44.61%).

Figure 8. Forest plot of comparison: I GnRH antagonist versus long course GnRH agonist, outcome: I.6 Cycle cancellation.



1.6.2 Cancellation due to poor ovarian response

Seventeen trials reported rates of cancellation due to poor ovarian response in 3200 women (Figure 8). There was no significant difference following GnRH antagonist compared with GnRH agonist (O.R = 0.76, 95% CI = 0.56 to 1.03; $p = 0.08$; $I^2 = 67.38\%$, 95% CI = 44.05% to 80.99%).

DISCUSSION

Summary of main results

The previous version of this systematic review included 27 studies, while this updated version includes 45 RCTs and 7511 randomised women. To our knowledge this systematic review and meta-analysis is the most recent and largest amount of evidence comparing the use of GnRH antagonist with long GnRH agonist protocols in IVF or ICSI treatment cycles.

In this updated version of the review we focused on the efficacy and safety of GnRH antagonist compared to GnRH agonist cycles in ART. Regarding efficacy, no significant differences in live birth rate and ongoing pregnancy rate were demonstrated between GnRH agonist and GnRH antagonist down-regulation protocols.

With regard to safety, GnRH antagonists significantly reduced the incidence of OHSS with 60%. For the overall population from assembled studies, the absolute risk reduction was 4% (95% CI 3 to 5), with a corresponding number needed to harm (NNH) of 25 (95% CI 19 to 36). If studies on PCOS cases were excluded, the risk reduction was 2% (95% CI 1 to 3), corresponding to a 45% relative reduction and a NNH of 45. This means that for every 45 women undergoing down-regulation by a GnRH agonist, one more case of OHSS can be expected for the general ART population. In addition, with GnRH antagonist treatment the chance of cancellation or coasting due to a high risk of developing OHSS was only half of that with GnRH agonist treatment (reduction 53%; 95% CI 36, 78). This means that the potential harm from the agonist treatment scheme may even be higher than expressed by the absolute risk reduction. In summary, GnRH antagonists have now demonstrated comparable efficacy and better safety than GnRH agonists. These findings together may have major implications for clinical practice as they would justify a change from standard long agonist treatment to antagonist cycles.

Previous versions of this systematic review have shown significantly lower clinical and ongoing pregnancy rates for the GnRH antagonist protocol. Changes in findings in the present review and meta-analysis compared to the preceding version in 2006 can possibly be explained by factors which might have changed over time, such as the type of GnRH antagonist protocols used, the incidence of LH instability and OCP pretreatment. Two earlier meta-analyses of studies, comparing fixed and flexible GnRH antagonist protocols directly, demonstrated a trend towards higher pregnancy rates when using the fixed protocol, possibly explained by better LH

control (Al-Inany 2005, Kolibianakis 2006). The improved performance of antagonist cycles in the present update, however, can not be explained by the relative use of fixed protocols, as relatively few new fixed protocols were included. Moreover, subgroup analysis according to GnRH antagonist protocol used did not yield obvious differences in live birth rates.

Several studies have suggested that LH-instability decreases the probability of pregnancy in antagonist cycles (Bosch 2003, Kolibianakis 2003, Shoham 2002, Seow 2010). LH-instability is defined as any fluctuation in LH level, either a LH surge or rise in LH concentration, in the course of ovarian hyperstimulation. A decrease in the relative incidence of LH instability in the current review can possibly have improved pregnancy outcomes in antagonist cycles, although the mechanism for such change is yet unclear. Further studies are needed to investigate the possible role of LH-instability in improvement of pregnancy outcomes of GnRH-antagonist cycles.

Increased pregnancy rates of the GnRH-antagonist may also be the result of an improved learning curve with the relatively new GnRH antagonist over the last 10 years. Extensive experience with GnRH antagonist protocols in large studies, leading to more favourable study outcomes, may have positively influenced pregnancy outcomes of antagonist cycles. However, the relative inclusion of small and large studies in this systematic review has not changed compared to preceding versions. Finally, changes in the use of OCP pretreatment (Griesinger 2008), scheduling of hCG for final oocyte maturation (Kolibianakis 2004, Tremellen 2010, Orvieto 2008) or patient selection (Sbarcia 2009) may all have contributed to the optimisation of the use of antagonist cycles in ART.

Previous work on the role of OCP pretreatment in direct comparison studies has indicated that OCP pretreatment leads to a longer duration of stimulation, higher oocyte yield but reduced ongoing pregnancy rate (Smulders 2010). Also a trend towards lower pregnancy rates when using OCP pretreatment has been observed in a separate meta-analysis (Griesinger 2008). As such, it has been recommended that OCP pretreatment does not seem to be the regimen of choice for GnRH antagonist cycles. In the present review, however, a subgroup analysis of studies that used OCP pretreatment revealed no significant difference between the agonist and antagonist groups for ongoing or clinical pregnancy rates. The percentage of patients receiving OCP pretreatment in this update equates with the preceding version in 2006.

We could not evaluate the economic differences between the two protocols. Even so, we may assume that the significant reduction of OHSS with GnRH antagonist treatment could have a direct impact on reduction of the cost of the cycle. However, it should be noted that cost effectiveness should be estimated by cost per pregnancy rather than cost per cycle. One should also keep in mind the indirect costs, for example absence from work (both partners), productivity loss and other indirect costs due to differences in treatment duration.

Overall completeness and applicability of evidence

Overall, the data demonstrate that GnRH antagonist is useful in women undergoing IVF or ICSI, especially women at high risk of OHSS, because it significantly reduces the occurrence of OHSS by 60% compared to agonist cycles. Moreover, the use of antagonists has been proposed to benefit poor responders because it reduces suppression of endogenous gonadotrophins (Nikolettos 2001). Our findings suggest that GnRH antagonist leads to comparable pregnancy rates, but large studies that report on live birth rates are needed.

A long GnRH agonist protocol with maximum ovarian stimulation has been the standard protocol for many decades. However, it is relatively complex and expensive, requires long treatment cycles, intensive monitoring and leads to an abnormal hormonal environment in women. There is now an eager desire to shift to more patient friendly mild ovarian stimulation regimens in which GnRH antagonist may be a suitable solution because its use is associated with comparable pregnancy outcomes and shorter duration of treatment.

A GnRH antagonist regimen with OCP pre-treatment offers a simple alternative for achieving gonadotrophin suppression during the early follicular phase. This regimen can be used to improve synchronization of the follicular development and scheduling of IVF or ICSI treatment cycles by inducing a withdrawal bleeding so that the start time of controlled ovarian stimulation can be planned. Several studies reported that OCP pre-treatment was associated with a longer stimulation period, greater gonadotrophin use and a lower pregnancy rate (Griesinger 2008). Conversely we did not observe significant differences with respect to the pregnancy rates.

Quality of the evidence

- While a number of conclusions can be drawn from the meta-analyses of the 45 included RCTs, many studies do not report live birth rates which limits their usefulness.
- Overall, the methodological quality of the trials was good, with the trials published as a full manuscript or abstract in a peer-reviewed journal.
- The method of allocation using computer-generated randomisation and sealed envelopes was reported in 34 studies. Blinding was difficult to perform due to the clear differences in GnRH analogue regimens. Six of the included studies reported on blinding. Sample size calculations and intention-to-treat analyses were performed in 12 and 18 studies respectively. Thirty-seven studies were conducted in a single centre and 12 were multi-centre studies.

Potential biases in the review process

- Patient heterogeneity is well recognised. In addition, the definitions of PCOS, poor response and mild stimulation are not universally agreed upon, with variations between the trials. There was also some variation in the treatment regimens being administered but the principles and protocols of treatment were similar. In many studies only a limited number of the outcomes of interest were reported.

Agreements and disagreements with other studies or reviews

- There is a systematic review and meta-analysis that included 22 RCTs (n = 3176) to compare GnRH antagonists and GnRH agonists. The reported outcome measure, clinical pregnancy or ongoing pregnancy, was converted to live-births in 12 studies using the published data. No significant difference was detected in the probability of a live-birth between the two GnRH analogues (OR 0.86, 95% CI 0.72 to 1.02). The result remained stable in a subgroup analysis that ordered the studies by type of population studied, gonadotrophin type used for stimulation, type of agonist protocol used, type of agonist used, type of antagonist protocol used, type of antagonist used, presence of allocation concealment, presence of co-intervention and the way the information on live-births was retrieved (Kolibianakis 2006).
- A systematic review and meta-analysis evaluated the efficacy of gonadotrophin antagonist versus GnRH agonist in poor ovarian responders in IVF and ICSI cycles. Six RCTs were included that compared GnRH antagonist to long or short GnRH agonist. There was no difference between GnRH antagonist and GnRH agonist (long and flare-up protocols) with respect to cycle cancellation rate, number of mature oocytes and clinical pregnancy rate per cycle initiated, per oocyte retrieval and per embryo transfer. When the meta-analysis was applied to the two trials that had used GnRH antagonist versus long protocols of GnRH agonist, a significantly higher number of retrieved oocytes was observed in the GnRH antagonist protocols (MD 1.12, 95% CI 0.18 to 2.05; P = 0.018) (Franco 2006).
- In another systematic review and meta-analysis of four RCTs (n = 874) ongoing pregnancy rate was the main outcome. There was no evidence of a statistically significant difference between patients with and without OCP pre-treatment (OR 0.74, 95% CI 0.53 to 1.03). Duration of gonadotrophin stimulation (1.41 days, 95% CI 1.13 to 1.68) and gonadotrophin consumption (542 IU, 95% CI 127 to 956) were significantly increased after OCP pre-treatment. No significant differences were observed regarding the number of retrieved oocytes (Griesinger 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The GnRH antagonist protocol is a short and simple protocol with a comparable live-birth rate to longer protocols with GnRH agonists. It is associated with a highly significant reduction in the incidence of the ovarian hyperstimulation syndrome compared to the GnRH agonist long protocol and therefore justifies a move away from the standard GnRH agonist long protocol to a GnRH antagonist protocol.

Implications for research

- Further studies are needed to assess this new strategy, in poor and high responders.

- Patient satisfaction survey should be undertaken.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Albano 2000

Methods	RCT, open-label parallel design, multi-centre (7 centres), multi-national	
Participants	293 Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI Inclusion criteria: with no more than three previous IVF-ET attempt with all causes of infertility (except polycystic ovary and moderate or severe endometriosis) Baseline characteristics: Age 31.9±3.7 versus 31.6±3.8, Duration of infertility: not stated, FSH: not stated, BMI not stated	
Interventions	<p>Group I (n=198): hMG (menogon, humegon, pergonal) was started at 2 or 3 ampoules for 4 days and the dose was adjusted according to response+ multiple dose regimen of 0.25 mg of GnRH antagonist (Cetrorelix) was administered SC starting from day 6 of hMG treatment to 115 participants up to and including day of hCG administration (Fixed)</p> <p>GnRH agonist (n=95): mid luteal GnRH analogue (Buserlin 150ug four times daily intranasally)+ hMG (menogon, humegon,pergonal) was started at 2 or 3 ampoules for 4 days and the dose was adjusted according to response</p> <p>Luteal phase support: daily vaginal progesterone or HCG injections</p>	
Outcomes	Premature LH surge defined as (LH >10IU/L) and progesterone level>1ng/L. Stimulation length, no. of hMG ampoules. E2 on hCG, no of oocytes retrieved, clinical pregnancy/OPU, clinical pregnancy/ET. Miscarriage Ectopic. OHSS moderate or severe OHSS. Clinical pregnancy was defined as fetal heart beat on ultrasonography. Ongoing pregnancy was defined as pregnancy ongoing after 12 weeks of amenorrhoea	
Notes	<ul style="list-style-type: none"> Number of ICSI cases was not stated in the cetrorelix group and in the buserlin group. Implantation rate was not mentioned as an outcome variable also, no of embryos obtained and no of embryos transferred was not stated Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text. Tolerability was not mentioned Centre adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome 	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only reported as a randomised trial with no further details of how randomisation was performed
Allocation concealment (selection bias)	Low risk	Concealed; Central telephone, 2:1 randomisation ratio

Albano 2000 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Supported by pharmaceutical company, the study appears to be free from other sources of bias

Baart 2007

Methods	RCT, two-centre trial
Participants	<p>111 infertile women undergoing IVF/ ICSI</p> <p>Inclusion criteria: were not at an a priori increased risk for chromosomally abnormal embryos. < 38 years of age, regular indication for IVF and with a partner with a sperm count > 5 million progressively motile sperm per millilitre, regular menstrual cycles (ranging from 25 to 35 days), BMI 19 - 29 kg m², no known chromosomal abnormalities, no relevant systemic disease or uterine and ovarian abnormalities, no history of recurrent miscarriage, and no previous IVF cycles not resulting in an embryo transfer</p> <p>Baseline characteristics: Female age (years) 34.1 (28-37) vs 33.2 (22-37), basal FSH 8.1 (4.4-13.8) vs 7.6 (5.5-18.4), Inhibin B level on cycle Day 3 or 4 : 86 (2-1056) vs 88 (15-593)</p>
Interventions	<p>Group I (n=67):150 IU FSH on 2nd day of the cycles (fixed) + 0.25 mg sc of GnRH antagonist co-treatment (orgalutran) administered when at least one follicle measuring > 14 mm (flexible protocol)</p> <p>GnRH agonist (n= 44): 225 IU rFSH (fixed) + long GnRH agonist , 0.1 mg triptorelin (Long GnRH agonist protocol)</p> <p>Oocyte maturation triggering: 10 000 IU sc hCG (Pregnyl) when one follicle > 18 mm plus 2 follicles > 15 mm</p> <p>Oocyte retrieval: 35 hours later, followed by IVF/ ICSI.</p> <p>Maximum of embryo transferred: 2</p> <p>Follow up: OPR was confirmed by vaginal ultrasound scan at 12 weeks of gestation</p>
Outcomes	<p>Primary outcome measures: ovarian response, as assessed by the number of oocytes obtained and the proportion of chromosomally abnormal embryos per patient. This was expressed as the ratio of abnormal embryos on the number of embryos diagnosed per patient.</p> <p>Secondary outcome measures: proportion of fertilized oocytes, the proportion of embryos with normal morphology and the proportion of embryos biopsied and diagnosed</p>

Baart 2007 (Continued)

Notes	<ul style="list-style-type: none"> • Drop out: 27 out of 67 (40%) patients were either lost before oocyte retrieval, fertilization or embryo biopsy in mild group. 11 out of 44 (25%) patients did not reach PGS analysis after conventional stimulation • The study was terminated prematurely, after an unplanned interim analysis (which included 61% of the planned number of patients) found a lower embryo aneuploidy rate following mild stimulation 	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule in a ratio of 4:6 (conventional group: mild group)
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes. After the patient agreed to participate, the next available numbered envelope on entry into the study was opened by the treating physician during the preparatory IVF consultation
Blinding (performance bias and detection bias) All outcomes	Low risk	Embryologist
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Funding was provided by university and non-governmental organization Early stopping due for benefit occurred. "The proportion of chromosomally abnormal embryos per patient was found to be significantly reduced after mild ovarian stimulation (P ¼ 0.02, which is below the Pocock critical bound of 0.0354 for a single interim analysis after 61% (111 of 181) of patients had been included (Pocock, 1977)) and the study was terminated."

Badrawy 2005

Methods	RCT, single-centre, open-label, parallel design
Participants	100 infertile women undergoing ICSI Inclusion criteria: primary infertility patients, 18-39 years old, with regular menstrual cycle and FSH levels < 10 IU/L done at cycle day 3 and ultrasound examination showed normal uterus

Badrawy 2005 (Continued)

	<p>Exclusion criteria: women with severe endometriosis (American Fertility Society stage III and IV), and azoospermic males were excluded from the study</p> <p>Baseline characteristics: age 30.8± 4.8 vs 30.28 ± 5.9 years</p>
Interventions	<p>GnRH antagonist (n =50): 225 IU Menogon hMG (menogon, humegon, pergonal) was started at 2 or 3 ampoules for 4 days (adjusted) + 0.25 mg of GnRH antagonist s.c ganirelix started from day 6 of hMG treatment/lead follicle measures 14 mm (Flexible multiple dose GnRH antagonist)</p> <p>GnRH agonist (n =50): mid-luteal GnRH analogue, buserlin 150ug four times daily intranasally (Suprefact) + 225 IU hMG (menogon, humegon, pergonal) was started at 2 or 3 ampoules for 4 days and the dose was adjusted according to response (Long GnRH agonist)</p> <p>Oocyte maturation triggering: hCG 10,000 IU (Chorimon) was administered deeply IM when the leading follicle reached 20mm in mean diameter with at least three follicles >18 mm</p> <p>Oocyte retrieval: 34-36 hours</p> <p>Embryo transfer: 2-3 days after OPU</p> <p>Luteal phase support : Cyclogest (Shire Pharmaceuticals Ltd., Andover, UK) vaginal pessaries, 400mg twice a day continued for 2 weeks. B-HCG was done 2 weeks following embryo transfer and if negative Cyclogest is stopped. If, however, pregnancy test (B-HCG) was positive, Cyclogest is continued until 12 weeks gestation</p>
Outcomes	<p>Female partner age</p> <p>Infertility duration years</p> <p>Baseline FSH mIU/ml</p> <p>Day 3 LH mIU/ml</p> <p>Day14 E2 pg/ml</p> <p>E2 pg/ml on day of HCG</p> <p>hMG ampoule</p> <p>Stimulation duration</p> <p>Number of follicles</p> <p>Size of follicles (mm)</p> <p>Endometrial thickness</p> <p>Number of oocytes retrieved</p> <p>Number of MII oocytes</p> <p>Number of oocytes fertilized</p> <p>Fertilization rate</p> <p>Embryos</p> <p>No of transferred embryos</p> <p>Pregnancy rate/ET</p> <p>Abortion rate</p> <p>OHSS</p>
Notes	<p>Number of participants at randomisation: 100 (ganirelix 50/ Superfact 50)</p> <p>Number of participants at stimulation: 100 (ganirelix 50/ Superfact 50)</p> <p>Number of participants at OPU: 95 (ganirelix 47/ Superfact 50)</p>
Risk of bias	

Badrawy 2005 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation stated to be using sealed envelopes without any further details
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, LBR was not reported
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias. Funding source not stated

Bahceci 2005

Methods	RCT, single-centre, open-label, parallel design, randomisation: 1:1 (cetorelix: leuprolide acetate) ratio
Participants	148 patients with PCOD , no previous ART or had hyperprolactinaemia or thyroid abnormalities
Interventions	GnRH antagonist (n= 75): antagonist protocol: cetorelix 0.25 mg/d subcutaneously started when the leading follicle reached 14 mm. HCG 10,000 IU administered when at least 2 follicles reached 18mm (Flexible) GnRH agonist (n= 70): agonist protocol: L.A. 0.5 mg, on day 14 of the cycle. Daily administration of gonadotropins, 2 or 3 ampoules initiated on the third day of the antecedent menstrual period (Long GnRH agonist protocol) Oocyte maturation triggering: HCG 10,000 IU administered when at least 2 follicles reached 18mm
Outcomes	Days of analogue treatment Number of patients who reached the day of hCG (%) Number of HMG ampoules Days of HMG treatment Number of follicles on the day of HCG injection No. of patients with oocyte retrieval No. of patients with ovum retrieval No. of patients with 1 or more fertilized oocytes No. of COC

Bahceci 2005 (Continued)

	No. of 2PN oocytes No. of embryo transfers No. of clinical pregnancies	
Notes	Number of participants at randomisation: 148 (cetrorelix:75/leuprolide acetate:73) Number of participants at stimulation: 129 (cetrorelix:59/leuprolide acetate:70) Number of participants at OPU: 129 (cetrorelix:59/leuprolide acetate:70)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number table
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, LBR did not reported
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias. The sources of funding not declared

Barmat 2005

Methods	RCT, multi-centre (4 US centres), open-label, parallel design
Participants	80 women undergoing IVF/ICSI Inclusion criteria: < 39 years of age, day-3 FSH level of =10, E2 level of <60 pg/mL, AFC >5 with a menstrual cycle range of 26 - 34 days, and no more than one previous failed IVF or IVF/ICSI cycle. BMI 19 - 32 kg/m ² no hydrosalpinx present by hysterosalpingogram, laparoscopy, or ultrasound within the past year. Male factor infertility cases could be included (ICSI and/or frozen sperm) with the exception of nonobstructive azoospermia. Only one study cycle was allowed Exclusion criteria: history of previous poor response (<4 follicles and/or an E2 level of <500 pg/mL on the day of hCG), had taken infertility medications (clomiphene and/or gonadotropins) within the past month, or had failed to consent to taking OCs, GnRH-analogues, or

	gonadotropins
Interventions	<p>GnRH antagonist (n= 40): OC (Desogen; Organon USA) on cycle days 2 to 4 for 14 to 28 days + 300 IU/day r FSH SC (adjusted) + 250 µg ganirelix was initiated when a lead follicle obtained a mean diameter of 12 to 14 mm (flexible)</p> <p>GnRH agonist (n= 40): leuprolide (GnRH-agonist group), 0.5 mg per day during the mid luteal phase with approximately a 5-day overlap with the OCs. Once adequate pituitary desensitization is achieved the dose of GnRH-agonist was reduced to 0.25 mg per day.+ 300 IU/day r FSH SC (adjusted)</p> <p>Oocyte maturation triggering: at follicular diameter 16 - 18 mm, 5000 to 10,000 IU of hCG (Pregnyl), In cases at risk of ovarian hyperstimulation syndrome, the physician could give a dose of 5000 IU of hCG</p> <p>Oocyte retrieval: 35 to 36 hours later</p> <p>Embryo transfer: 3 or 5 day</p> <p>Luteal phase support: Progesterone, one centre treated patients with P, 25 mg IM, on the day of retrieval, followed by P, 50 mg IM daily, with some patients being supplemented with hCG 2,500 IU on days 3 and 6 after retrieval. The other centre's prescribed luteal support with a daily dose of P (50 mg IM)</p>
Outcomes	<p>Patients to oocyte retrieval (n = 77)</p> <p>Days from OCP to oocyte retrieval</p> <p>Days on OC</p> <p>Stimulation day-1 E2 (pg/mL)</p> <p>Recombinant FSH (IU)</p> <p>Days of recombinant FSH</p> <p>Stimulation day of ganirelix start</p> <p>Days of leuprolide or ganirelix</p> <p>LHday hCG (IU/L)</p> <p>E2day hCG (pg/mL)</p> <p>P4day hCG (pg/mL)</p> <p>No of follicles</p> <p>Follicle sizes</p> <p>No. of oocytes retrieved</p> <p>No. of mature oocytes</p> <p>No. of 2PN embryos</p> <p>No. of embryos transferred</p> <p>Percentage of patients with cryopreservation</p> <p>Embryos cryopreserved/patient with cryopreservation</p> <p>No. of pregnancies/embryos transferred (%)</p> <p>No. of pregnancies/cycle started (%)</p> <p>No. of ongoing pregnancies/embryos transferred (%)</p> <p>No. of ongoing pregnancies/cycle started (%)</p> <p>No. of implanted embryos (%)</p> <p>No. of ongoing twin gestations (%)</p> <p>Delivered pregnancies</p>

Barmat 2005 (Continued)

Notes	<ul style="list-style-type: none"> • Patients who continued to have elevated E2 levels (>60 pg/mL) and a cyst were removed from the study. If the E2 level was <60 pg/mL and the cyst was still present, it could be aspirated and the patient would remain enrolled in the study and begin their recombinant FSH administration on Friday, along with a reduction of the GnRH-agonist dose to 0.25 mg per day. • Patients who had a serum E2 level of >60 pg/mL or a cyst >20 mm were continued on the same leuprolide dose for another week. • In patients randomised to the GnRH-antagonist group who had an E2 level of <60 pg/mL, they could begin recombinant FSH on that Friday (5th day after OC). If they had a cyst >20 mm, they were cancelled from the study. • Number of participants at randomisation: 80 (ganirelix: 40/leuprolide acetate: 40) • Number of participants at stimulation: 79 (ganirelix: 38/leuprolide acetate: 41) • Number of participants at OPU: 129 (ganirelix: 36/leuprolide acetate: 41)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dark sealed envelopes (true), randomisation:1:1 (ganirelix acetate: leuprolide acetate) ratio
Allocation concealment (selection bias)	Low risk	Dark sealed envelopes (true)
Blinding (performance bias and detection bias) All outcomes	High risk	Did not reported clearly
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Support: Pharmaceutical company, the study appears to be free from other sources of bias

Brelik 2004

Methods	RCT, single-centre, parallel design, randomization:1:1 (cetorelix: triptorelin) ratio
Participants	<p>120 infertile women undergoing IVF/ICSI</p> <p>Inclusion/ Exclusion criteria: Infertile patients undergoing IVF regardless the indications or pre-stimulatory LH levels</p>

Brelik 2004 (Continued)

Interventions	GnRH antagonist (n= 57): in the antagonist arm, rFSH from day 2 of the cycle, and when the leading follicle reached 13 mm cetorelix 0.25 mg (Cetrotide; Serono) was started. The LH levels were checked on the day, when the leading follicle reached 13 mm (LH1) and 21 mm (LH2) (Flexible) GnRH agonist (n= 63): in the agonist arm, triptorelin 3,75 (Diphereline SR 3,75; Beaufour Ipsen) was administered on day 20 of the preceding cycle and 14 days later if E2<30pg/mL, stimulation with rFSH (Gonal-F; Serono) was initiated
Outcomes	Number of FSH ampoules used Number of oocytes retrieved Fertilization rate (%) of all retrieved oocytes Early cleavage rate (%) Grade A embryos rate (%) Number of embryos transferred Clinical pregnancy rate (%) LH levels
Notes	Number of participants at randomisation:120 (cetorelix:57/ triptorelin:63) Number of participants at stimulation: 120 (cetorelix:57/ triptorelin:63) Number of participants at OPU: 120 (cetorelix:57/ triptorelin:63)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported clearly
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported clearly
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, LBR not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias. Study funding not declared

Check 2004

Methods	RCT, single-centre, open-label, parallel design, randomisation:1:1 (ganirelix: leuprolide) ratio
Participants	Couples requiring IVF or intracytoplasmic sperm injection (ICSI)
Interventions	Agonist regimen: leuprolide acetate 0.5mg qd for 10 days from mid-luteal phase Antagonist regimen: 250µg ganirelix when dominant follicle is at least 14 mm and estradiol is at least 1000 pg/ml (flexible)
Outcomes	Clinical pregnancy, viable pregnancy, implantation rate
Notes	Number of participants at randomisation: 60 (ganirelix: 30/ leuprolide: 30) Number of participants at stimulation: 54 (ganirelix: 24/ leuprolide: 30) Number of participants at OPU: 54 (ganirelix: 24/ leuprolide: 30)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was not used and drop-out rate was above 10% with reasons provided
Selective reporting (reporting bias)	Low risk	Protocol not available but materials match results
Other bias	Unclear risk	Study funding not reported.

Cheung 2005

Methods	RCT, single-centre, parallel design
Participants	66 infertile women undergoing IVF/ICSI Inclusion/ Exclusion criteria: Poor responders were classified as patients who had exhibited a poor ovarian response with <3 mature follicles on a long GnRH agonist protocol in their previous IVF cycles, or those with repeated high basal levels of FSH >10 IU/l. Patients with polycystic ovaries were excluded from the study

Interventions	<p>GnRH antagonist (n= 33): OCP (Nordette) 30 µg of ethinyl estradiol and 150 µg of levonorgestrel for 21 days+ 300 IU daily rFSH (Gonal-F) + 0.25 mg sc. cetorelix (Cetrotide) fixed, multi-dose GnRH antagonist protocol starting on day 6 of the stimulation (fixed)</p> <p>GnRH agonist (n= 33): long GnRH agonist protocol, buserelin acetate nasal spray (Suprecur) daily dose of 600 µg starting at the mid-luteal phase of the preceding cycle+ 300 IU daily rFSH (Gonal-F) (long GnRH agonist)</p> <p>Oocyte maturation triggering: 10 000 IU of i.m. HCG (Profasi) when the leading follicles reached 18-20 mm together with at least three mature follicles >16 mm</p> <p>Oocyte retrieval: 36 hrs later. ICSI was performed only in cases with severe male factor or previous fertilization failure</p> <p>Maximum number of embryo transfer: Depending on the number of embryos available, up to three embryos were transferred on day 3 after oocyte retrieval</p> <p>Luteal phase support: i.m. hCG (Profasi) 2000 IU given every 3 days for four doses starting on the day of oocyte retrieval</p> <p>A clinical pregnancy was established when there was a gestational sac seen on ultrasonography</p>	
Outcomes	<p>The main outcome measures were duration of stimulation, consumption of gonadotrophins, cycle cancellation rate, and the number of mature follicles recruited and total oocytes retrieved. The hormone levels throughout the cycle, laboratory outcomes and clinical pregnancy rates were also reviewed</p>	
Notes	<ul style="list-style-type: none"> • Number of participants at randomisation: 66 (cetorelix: 33/ buserlin acetate: 33) • Number of participants at stimulation: 63 (cetorelix: 31/ buserlin acetate: 32) • Number of participants at OPU: 40 (cetorelix: 19/ buserlin acetate: 21) • Cycles in which <3 mature follicles developed, or if the ovaries failed to respond after 10 days of stimulation, were either cancelled or converted to intra-uterine insemination in patients with patent tube(s). 	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number table (true), randomisation:1:1 (cetorelix: buserlin acetate) ratio
Allocation concealment (selection bias)	Low risk	Performed
Blinding (performance bias and detection bias) All outcomes	Low risk	Blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected

Cheung 2005 (Continued)

		outcomes
Other bias	High risk	Pharmaceutical company supported, the study appears to be free from other sources of bias

Depalo 2009

Methods	RCT, single-centre study	
Participants	<p>136 consecutive patients undergoing ICSI</p> <p>Inclusion criteria: age 24 - 42 years, baseline FSH level < 10 IU/ml, absence of uterine or ovarian abnormalities or severe endometriosis or polycystic ovary syndrome, no more than three previous IVF attempts and, no oral contraceptive pills taken before the stimulation cycle. Male factor infertility cases, such as number of spermatozoa < 5.0 million/ml and < 30% motility were included. Criteria for cycle cancellation were as follows: 53 follicles with diameter 14 mm after 8- 10 days of stimulation</p> <p>Baseline characteristics: age 34.4±4 vs 34±3.9 yrs. Basal FSH (mIU/ml) 6.4±2.4 vs 5.7±2. Basal E2 (pg/ml) 21.71±3 vs 16.7±9.4. BMI (kg/m²) 23.7± 4.1 vs 22.7±3.4</p>	
Interventions	<p>GnRH antagonist (n= 67): a daily dose of cetrorelix 0.25 mg (Cetrotide) was when a leading follicle reached a diameter of 12-14 mm + rFSH (Gonal F) starting on cycle day 2-3 at a dose of 225 UI/daily, for the first 5 days (adjusted) (Flexible protocol)</p> <p>GnRH agonist (n= 69): 0.1 mg triptorelin (Decapeptyl 0.1 mg) were administered subcutaneously daily, starting in the late luteal phase (day 21) of the previous cycle + rFSH starting on cycle day 2-3 at a dose of 225 UI/daily, for the first 5 days (adjusted)</p> <p>Final oocyte maturation: was achieved with 6500 UI of hCG (Ovitrelle) when two or more follicles reached a diameter 18 mm.</p> <p>Oocyte retrieval: 35-36 hrs after hCG administration.</p> <p>Embryo transfer: 3 embryos on day 2</p> <p>Luteal phase support: was supplemented with progesterone in oil, 50 mg/ day (Pronogest) starting the day after oocyte retrieval and continuing until 12 weeks's gestation if pregnancy was achieved</p>	
Outcomes	Oocyte and embryo grading, implantation rate, clinical pregnancy and ongoing rates	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list at initiation of stimulation, to receive GnRH antagonist or agonist, by using a free Internet software for randomisation (Graphpad Software Quick-Calcs)
Allocation concealment (selection bias)	Unclear risk	Not reported

Depalo 2009 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	The embryologist scoring the embryos was blinded to the study groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	Outcomes were reported in a pre-specified manner
Other bias	Unclear risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes. Study funding not reported

El Sahwi 2005

Methods	RCT, single-centre, parallel design, randomisation:1:1	
Participants	160 patients scheduled for ICSI	
Interventions	Agonist group were treated with buserelin/HMG stimulation (long luteal protocol) while the antagonist group were treated with cetrorelix/hMG stimulation (flexible protocol).	
Outcomes	The treatment period number of hMG ampoules used number of abandoned cycles number of oocytes retrieved fertilization rate implantation rate clinical pregnancy rate the occurrence of hyperstimulation syndrome (OHSS) the convenience and compliance of patients	
Notes	Number of participants at randomisation: 160 (cetrorelix: 80/ buserelin: 80) Number of participants at stimulation: 160 (cetrorelix: 80/ buserelin: 80) Number of participants at OPU: 142 (cetrorelix: 74/ buserelin: 68)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as randomisation using opaque envelopes without any further details
Allocation concealment (selection bias)	Low risk	Opaque envelopes

El Sahwi 2005 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, LBR/OPR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias. Study funding not reported

Engmann 2008 a

Methods	RCT, single-centre
Participants	60 women (high responders), aged 20-39 years, normal basal FSH concentration ≤ 10.0 IU/L), and undergoing their first cycle of IVF with either PCOS or PCOM (defined according to the Rotterdam consensus guidelines) or undergoing a subsequent cycle with a history of high response in a previous IVF cycle. Patients were recruited for the trial for only one cycle Exclusion criteria: Women with hypogonadotropic hypogonadism were excluded Baseline characteristics: Age (yrs) 32.0 ± 3.7 vs 33.1 ± 3.6 , BMI (kg/m ²) 28.3 ± 7.1 vs 30.7 ± 6.4 , Baseline serum FSH (IU/L) 5.4 ± 1.8 vs 5.3 ± 1.2
Interventions	Study group: OCPs for 21 days + 112-225 IU/day rFSH + ganirelix acetate when the dominant follicle ≥ 14 mm (Flexible multiple dose protocol) Control group: OCP for 25 days overlapping with 1 mg leuprolide acetate (Lupron), then reduced to 0.5 mg once down regulation was achieved (Low dose long GnRH agonist protocol) + 112-225 IU/day rFSH Oocyte maturation triggering: when 2-3 leading follicles were >18 mm in diameter study group: GnRH agonist, 1mg approximately 12 hours after the last dose of ganirelix control group: 3300 to 10,000 IU hCG (Profasi) Oocyte retrieval: 35 hours later, followed by IVF/ ICSI. Maximum of embryo transferred: 3 Luteal phase support: Study group: 50 mg IM P in oil daily + 0.1 mg transdermal E2 patches every other day Control group: 50 mg IM P in oil daily Follow up: an ultrasound scan was carried out 5 to 6 weeks after oocyte retrieval to determine the viability of the pregnancy. A second ultrasound was performed at 12 weeks' gestation to confirm any ongoing pregnancy (+ve heart beat)
Outcomes	OHSS, implantation rate, number of oocytes retrieved, proportion of mature oocytes retrieved, fertilization rate, mid-luteal phase mean ovarian volume (MOV), clinical and ongoing pregnancy rates, and luteal phase serum E2 and P levels

Engmann 2008 a (Continued)

Notes	The diagnosis of OHSS was based on the criteria by Golan et al	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers. To ensure similar distribution of previous high response in the two groups, separate randomisation schedules were drawn up for women undergoing their 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 used a series of consecutively numbered sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, LBR did not address by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias. Study funding not reported

Euro Midd East 2001

Methods	RCT, multi-centre (12 centres, 9 countries), Europe-middle east multi-national, open-label, parallel
Participants	321 Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI with all causes of infertility Age ? Duration of infertility: ganirelix 4.3, triptorelin 4.1 FSH: ganirelix 5.8 iu/ml, triptorelin 2.8 BMI ?
Interventions	GnRH antagonist (n= 215): 150 IU rFSH (Puregon) (adjusted) + multiple dose regimen of 0.25 mg of GnRH antagonist (ganirelix) was administered SC starting from day 6 of stimulation (fixed) GnRH agonist (n=106): mid-luteal GnRH analogue (triptorelin 0.1mg sc) + 150 IU rFSH (Puregon) (adjusted) Luteal phase support was done according to the centre routine practice

Outcomes	<p>Premature LH surge defined as (LH >10IU/L) and progesterone level >1ng/L Ganirelix group 1 versus triptorelin group 0 Stimulation length ganirelix group 9 versus triptorelin group 26 rFSH: ganirelix group 1350iu versus triptorelin group 1800IU E2 on hCGG ganirelix group 1090pg/ml versus triptorelin group 1370pg/ml no of oocytes retrieved ganirelix group 7.9±5.1 versus triptorelin group 9.6±6.8 no of embryos obtained ganirelix group 4.0±3.0 versus triptorelin group 4.7±3.0 no of embryos transferred: not mentioned Implantation rate ganirelix group 22.9 versus triptorelin group 22.9 clinical preg/cycle ganirelix group 32.3 versus triptorelin group 37.8 clinical preg/ET ganirelix group 35.8 versus triptorelin group 41.7 Ongoing pregnancy rate ganirelix group 31.4 versus triptorelin group 33.9 Cancellation ganirelix group 22 versus triptorelin group 15 Miscarriage ganirelix group 10.3 versus triptorelin group 11.4 Ectopic ganirelix group 2 versus triptorelin group 0 OHSS ganirelix group 4 versus triptorelin group 1 severe OHSS: only one case ganirelix group Local reaction ganirelix group 11.9 versus triptorelin group 24.1</p>	
Notes	<ul style="list-style-type: none"> • Number of participants at randomisation: 355 (ganirelix 236 / triptorelin 119) • Number of participants at stimulation: (ganirelix 226 / triptorelin 108) • Number of participants at OPU: (ganirelix 214 / triptorelin 105) • Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text <ul style="list-style-type: none"> • The authors used the estimated difference of ganirelix and buserelin in ongoing pregnancy rate was compared with the margin of 5%. And for cumulus-oocyte complexes, the estimated treatment difference was compared with the equivalence margin of 3 oocytes • Center adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome 	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive response voice system, stratified randomisation, 2:1 randomisation ratio
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, LBR did not addressed by the study

Euro Midd East 2001 (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Supported by pharmaceutical company

Euro Orgalutran 2000

Methods	RCT, multi-centre (20 centres), open-label, parallel design
Participants	730 Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI with all causes of infertility Baseline characteristics: Age ganirelix 31.9 ± 3.6, buserlin 31.9 ± 3.8, Duration of infertility: ganirelix 4.5± 2.7, buserlin 4.4 ±2.7, FSH: ganirelix 7.7, buserlin 8.4, BMI ganirelix 23 ± 2.9, buserlin 23 ± 2.7
Interventions	GnRH antagonist (n= 486): rFSH (Puregon) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted according to response + multiple dose regimen of 0.25 mg of GnRH antagonist (ganirelix) was administered SC starting from day 6 of hMG treatment (fixed) GnRH agonist (n= 244): mid-luteal GnRH analogue (buserlin 0.6 or 1.2mg four times daily intranasally) + rFSH (Puregon) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted according to response IVF was done in 357 cases and ICSI was done in 291 cases and 10 cases had both IVF and ICSI Luteal phase support: was done according to the centre routine practice
Outcomes	Premature LH surge defined as (LH >10IU/L) and progesterone level>1ng/L Stimulation length no. of hMG ampoules E2 on hCG no of oocytes retrieved no of embryos obtained no of embryos transferred Implantation rate Clinical preg/OPU Clinical preg/ET Miscarriage Ectopic OHSS moderate or severe OHSS
Notes	<ul style="list-style-type: none"> • Number of participants at randomisation: 730 (ganirelix 486 / buserlin 244) • Number of participants at stimulation: 701 (ganirelix 463 / buserlin 238) • Number of participants at OPU: (ganirelix 440 / buserlin 221) • Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text

Euro Orgalutran 2000 (Continued)

	<ul style="list-style-type: none"> • Tolerability was not mentioned in the table of outcomes but stated in the text • The authors used the estimated difference of ganirelix and buserelin in ongoing pregnancy rate was compared with the margin of -5%. And for cumulus-oocyte complexes, the estimated treatment difference was compared with the equivalence margin of -3 oocytes • Centre adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive response voice system (true), 2:1 randomisation ratio
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, LBR did not addressed by the study
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Supported by pharmaceutical company, the study appears to be free from other sources of bias

Firouzabadi 2010

Methods	RCT, single-centre
Participants	<p>235 infertile women undergoing IVF/ICSI</p> <p>Inclusion criteria: first cycle of the ART, age <35 years, and basal FSH <10 IU/L.</p> <p>Exclusion criteria: previous IVF or ICSI, hyperprolactinaemia, hyperthyroidism, hypothyroidism, uterine abnormality, severe endometriosis, or solitary ovary</p> <p>Baseline characteristics: Age (years) 28.71 ± 2.8 vs 28.36 ± 3.1, BMI (kg/m²) 28.1 ± 3.4 vs 27.54 ± 4.3, Basal FSH (IU/L) 5.77 ± 1.2 vs 5.54 ± 1.1</p>
Interventions	<p>GnRH antagonist (n=118): 225 IU rFSH on 2nd day of the cycles (adjusted) + HMG+ 0.25 mg sc of ganirelix took place on the 6th day of the stimulation (fixed protocol)</p> <p>GnRH agonist (n= 117): 150-225 IU r FSH (adjusted) + long GnRH agonist , 500 µg buserelin</p>

	<p>per day (Suprefact) (SC), during menstrual cycle 21 and onwards, once down-regulation was achieved, the dose of buserelin has been reduced to 250 µg (low dose GnRH agonist protocol)</p> <p>Oocyte maturation triggering: hCG 10,000 IU (Profasi) was administered intramuscularly (IM) when at least two follicles were 18 mm</p> <p>Oocyte retrieval: 36 hours later, followed by IVF/ ICSI</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: 800 mg daily cyclogest suppository (Aburaihan, Iran) was started on the day of oocyte collection to provide luteal phase support, and it continued until the fetal heart activity was documented by ultrasonography.</p> <p>Follow up: the serum hCG level on day 16 after the oocyte recovery was tested to determine chemical pregnancy, if any; a vaginal ultrasonography has been carried out on day 35 following the oocyte recovery for documentation of fetal heart activity and confirmation of a clinical pregnancy</p>	
Outcomes	<p>Primary outcome measures: clinical pregnancy rate per cycle and ongoing pregnancy, which later were defined as pregnancy proceeding beyond the 12th gestational week</p> <p>Secondary outcome measures: OHSS, defined by ≥ 15 follicles with a mean diameter ≥ 14 mm per each ovary at the end of the follicular phase of stimulation and/or E2 levels on the day of hCG administration $>3,000$ pg/mL and/or presence of ascites after hCG administration in ultrasonography</p>	
Notes	<p>Drop out: GnRH antagonist group: 6, GnRH agonist: 9 8 cycles of ET cancelled (due to poor quality of embryos in GnRH antagonist group</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedules
Allocation concealment (selection bias)	Low risk	Sealed in envelopes and handed to patients
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, LBR did not address by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Fluker 2001

Methods	RCT, multi-centre (11 centres, United States and Canada), open-label, parallel design
Participants	313 Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI with all causes of infertility Baseline characteristics: Age: ganirelix 33.0 ± 3.4 vs leuprolide 32.8 ± 4.0. Duration of infertility: ganirelix 4.1 ± 3.0 vs leuprolide 3.8 ± 2.6. FSH: ganirelix 7.9 iu/ml vs leuprolide 3.3 iu/ml. BMI: ganirelix 23.0 ± 3.0 vs leuprolide 23.0 ± 3.0
Interventions	GnRH antagonist (n= 205): A multiple dose regimen of 0.25 mg of GnRH antagonist (Ganirelix) was administered SC starting from day 6 of rec FSH treatment up to and including day of hCG administration (Fixed)+ rFSH (Follistim) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted according to response GnRH agonist (n= 108): mid-luteal GnRH analogue (leuprolide 1.0mg sc) to 99 participants of the control group + rFSH (Follistim) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted according to response Luteal phase support was done according to the centre routine practice
Outcomes	Premature LH surge defined as (LH >10IU/L) and progesterone level >1ng/L Ganirelix group versus leuprolide group Stimulation length ganirelix group versus leuprolide group rFSH: ganirelix group iu versus leuprolide group IU E2 on hCG ganirelix group pg/ml versus leuprolide group pg/ml no of oocytes retrieved ganirelix group ± versus leuprolide group ± no of embryos obtained ganirelix group ± versus leuprolide group ± no of embryos transferred: Implantation rate ganirelix group versus leuprolide group clinical preg/cycle ganirelix group versus leuprolide group clinical preg/ET ganirelix group versus leuprolide group Ongoing pregnancy rate ganirelix group versus leuprolide group Cancellation ganirelix group versus leuprolide group Miscarriage ganirelix group versus leuprolide group Ectopic ganirelix group versus leuprolide group OHSS ganirelix group 4 versus leuprolide group 1 Severe OHSS: ganirelix 3 case, leuprolide 2 Local reaction ganirelix group 11.9 versus leuprolide group 24.1
Notes	<ul style="list-style-type: none"> • Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text. • The authors used the estimated difference of ganirelix and leuprolide in ongoing pregnancy rate was compared with the margin of 5%. • And for cumulus -oocyte complexes, the estimated treatment difference was compared with the equivalence margin of 3 oocytes. • Number of participants at randomisation: 313 (ganirelix 208 / leuprolide 105) • Number of participants at stimulation: (ganirelix 198 / leuprolide 99) • Number of participants at OPU: (ganirelix 186 / leuprolide 95) • Centre adjusted analysis: not mentioned
<i>Risk of bias</i>	

Fluker 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive response voice system (true), 2:1 randomisation ratio, stratified randomisation
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Supported by pharmaceutical company, the study appears to be free from other sources of bias. Study funding not reported

Franco 2003

Methods	RCT, open-label, parallel design, single-centre
Participants	20 patients without specific ovulatory dysfunction aged ≤ 37 , that would be submitted to ovarian stimulation
Interventions	<p>Group A (n = 14): 4mg/day of estradiol valerate was started and continued for 14 days + rFSH (Puregon) was started one day after the end of estradiol valerate in a fixed dose of 150-300 UI + ganirelix (Organolutran, Organon) was taken in a dose of 0.25 mg/day when the follicular diameter was ≥ 15 mm, and continued until the day of the hCG administration (Flexible)</p> <p>Group B (n = 6): In the 21st day of the menstrual cycle, a dose of 200 μg of nafarelin acetate was taken through nasal twice a day. After 14 days of administration of the agonist, with the blockage established (menstruation), the administration of recombinant FSH was started in a fixed dose of 150-300 IU for a period of 5 days</p> <p>Oocyte maturation triggering: 5-10 000 IU uhCG at least two follicles ≥ 17 mm</p> <p>Maximum number of embryos transferred: 2-3</p> <p>Luteal phase support: not reported</p>
Outcomes	No of oocytes retrieved Fertilization rate Implantation rate Pregnancy rate

Franco 2003 (Continued)

Notes	Number of participants at randomisation: 20 (ganirelix: 14/ nafarelin: 6) Number of participants at stimulation: N/A Number of participants at OPU: N/A	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list, randomisation:2:1 (ganirelix: nafarelin) ratio
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Friedler 2003

Methods	RCT, open-label, parallel design, single-centre
Participants	<40 years old undergoing IVF due to male or tubal infertility
Interventions	All patients received vaginal micronized progesterone (300 mg/day) as luteal supplementation. LP characteristics were compared between the two groups and between the conception and non conception cycles. Estradiol (E2), progesterone and LH levels were measured on the day of HCG administration (day 0), days +5, +8, +11 and +16. (Unclear)
Outcomes	E2 and progesterone levels Clinical pregnancy rate Implantation rates
Notes	Power calculation: No power calculation Number of participants at randomisation: N/A Number of participants at stimulation: N/A Number of participants at OPU: N/A

Friedler 2003 (Continued)

	Type of antagonist protocol:N/A	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Patients not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Protocol is not available but the methods and results match
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis was not used but the drop-out rate was less than 10%
Other bias	Unclear risk	Baseline characteristics are similar but no reporting of study funding

Heijnen 2007

Methods	RCT, two centres, parallel-group randomised, open-label, non-inferiority effectiveness trial
Participants	404 infertile women undergoing IVF/ICSI Inclusion criteria: no previous IVF treatment or had borne a healthy child after previous IVF treatment, were aged younger than 38 years, and had a menstrual cycle length of 25-35 days and a body-mass index of 18-28 kg/m ² Baseline characteristics: Age of women (years) 32.9 (3.1) vs 32.8 (3.2), BMI (kg/m ²) 23.0 (2.6) vs 23.2 (2.5), Duration of infertility (years) 3.6 (1.9) vs 3.6 (2.1)
Interventions	GnRH antagonist (n= 205): mild ovarian stimulation with gonadotropin-releasing hormone [GnRH] antagonist co treatment combined with single embryo transfer(mild protocol) GnRH agonist (n= 199): (stimulation with a GnRH agonist long protocol and transfer of two embryos (long GnRH agonist protocol))
Outcomes	Primary outcome measures: pregnancy and term live-birth within 1 year of randomisation; total costs per couple and child up to 6 weeks after expected delivery; and patients' discomfort

Heijnen 2007 (Continued)

Notes	<p>Supernumerary high-quality embryos: cryopreserved and thawed for transfer in a subsequent un stimulated cycle before the start of a new IVF treatment cycle. These frozen-thawed embryo-transfer cycles were treated as a part of the previous IVF cycle. In both groups either one or two cryopreserved embryos were transferred, according to the patient's preference</p> <p>Fund: ZonMw (Netherlands), programme Doelmatigheidsonderzoek.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random blocks of size four and six were stratified by centre
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes and made available at each centre; envelopes were sequentially allocated to consecutive patients and opened by treating physicians at IVF planning consultations
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free of other source of bias. Study funding by non-governmental organization

Hohmann 2003

Methods	RCT, university-affiliated IVF centre, open-label, parallel design, randomization: 2:1 (cetorelix: triptoreline) ratio T
Participants	<p>142 infertile women undergoing IVF/ICSI</p> <p>Inclusion criteria: age between 20 to 38 yr; 2) body mass index (body weight divided by the square of body height) between 19 to 29 kg/m²; 3) history of regular menstrual cycles, ranging from 25 to 35 d; 4) no relevant systemic disease, severe endometriosis, or uterine and ovarian abnormalities; 5) no more than three previous IVF cycles; and 6) no previous IVF cycle with a poor response or ovarian hyperstimulation syndrome</p>

Interventions	<p>Group A: GnRH agonist triptoreline (Decapeptyl) 1 mg/d, sc starting 1 wk before the expected menses (usually cycle day 21) + fixed daily dose of 150 IU rFSH sc (Gonal-F)</p> <p>Groups B and C: GnRH antagonist cetrorelix (Cetrotide) 0.25 mg/d, sc commencing when the largest follicle had reached a diameter of 14 mm + rFSH was initiated on cycle day 2 (group B) or 5 (group C). (Flexible)</p> <p>Oocyte maturation triggering: when the leading follicle had reached a diameter of 18 mm or more and at least three follicles had reached a diameter of 15 mm or more, 10,000 IU hCG (Pregnyl) was administered</p> <p>Embryo transfer: 35 hrs before the planned time of oocyte retrieval followed by IVF with or without ICSI</p> <p>Maximum number of embryo transferred: 2 embryos were transferred 3-5 d</p> <p>Luteal support: intravaginal progesterone (P; Progestan, Organon; 200 mg, three times daily) was given from the day of oocyte retrieval until a urine pregnancy test was performed 17 d later</p>	
Outcomes	<p>Included patients (n 142)</p> <p>Age (yr)</p> <p>Body mass index (kg/m²)</p> <p>FSH day 2/3 (IU/litre)</p> <p>Inhibin Bday 2/3 (ng/litre)</p> <p>Patients undergoing oocyte retrieval (n 104)</p> <p>n (% per started cycle)</p> <p>Cycle day start cetrorelix</p> <p>Day hCG</p> <p>FSH (IU/litre)</p> <p>LH (IU/litre)</p> <p>E2 (n mol/litre)</p> <p>P (n mol/litre)</p> <p>No. of follicles (10 mm)day hCG</p> <p>No. of follicles (15 mm)day hCG</p> <p>No. of oocytes retrieved</p> <p>No. of embryos</p> <p>Fertilization rate per subject (%)</p> <p>No. of pregnancies (%)</p> <p>No. of ongoing pregnancies (%)d</p> <p>No. of twin pregnancies (%)e</p>	
Notes	<p>Number of participants at randomisation: 169 (cetrorelix: NA/ triptoreline: NA)</p> <p>Number of participants at stimulation: 142 (cetrorelix: 45/ triptoreline: 97)</p> <p>Number of participants at OPU: 104 (cetrorelix: 38/ triptoreline: 66)</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation

Hohmann 2003 (Continued)

Allocation concealment (selection bias)	Low risk	Schedule assigned via numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Support: Pharmaceutical Company, the study appears to be free from other sources of bias

Hsieh 2008

Methods	RCT phase III, open-label, single-centre study
Participants	251 infertile women undergoing IVF/ICSI inclusion criteria: age at least 18 years but not older than 39 years; and body weight of 40-70 kg Baseline characteristics: Age (yr) 33.9 ± 4.4 vs 32.3 ± 2.1 vs 31.6 ± 2.4 vs 30.9 ± 2.5 vs 32.1 ± 2.7 BMI (kg/m ²) 20.6 ± 1.4 vs 19.0 ± 1.0 vs 19.5 ± 1.1 vs 20.7 ± 2.1 vs 21.1 ± 1.8, Baseline FSH (IU/L) 4.0 ± 1.8 vs 3.7 ± 1.6 vs 3.9 ± 1.3 vs 3.8 ± 1.4 vs 3.6 ± 1.8
Interventions	Down regulation Group 1 (n = 86): cetrorelix 0.25 mg/day, cetrorelix was administered from menstrual day 8 until the day of hCG administration. (Fixed) Group 2 (n= 28): cetrorelix 0.2 mg/day, Group 3 (n= 30): cetrorelix 0.15 mg/day Group 4 (n= 58): LA 0.5 mg/day, administered on days 21-23 of the previous menstrual cycle Group 5 (n= 49): LA depot 1.88 mg .Single dose LA depot subcutaneous COH: 150-225 IU/day rFSH (Gonal-F) in women < 34 years old, 225-300 IU rFSH in women > 34 years Final oocyte maturation triggering: 5000 IU hCG were given when at least three mature ≥18 mm follicles were obtained Oocytes retrievals: 36 hrs later. Maximum embryo transfer: 6 embryos were transferred at 72 hrs after IVF/ ICSI injection. Luteal phase support: hCG (2,000 IU/day) on days 1, 4 and 7 post-ET and progesterone (400 mg/day; Utrogeston) from day 1 post-ET Follow up: Clinical pregnancy was determined by visualization of a gestational sac, and fetal viability

Hsieh 2008 (Continued)

	by ultrasound 4 weeks post-ET	
Outcomes	Gn dosage, and serum concentration of LH and E2 on the day of hCG administration, retrieved oocyte and embryo numbers, development of OHSS, embryo quality, and pregnancy rate (PR), implantation rate (IR) and abortion rate (AR)	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	Study funding not reported.

Hurine 2006

Methods	RCT, multi-centre (eight European IVF centres), phase IIIb study
Participants	182 infertile women undergoing IVF/ICSI Inclusion criteria: patients needed to have a regular IVF/ICSI indication, a male partner with viable sperm in the ejaculate (testicular biopsy or epididymal sperm was not allowed) , aged between 18 and 39 Exclusion criteria: patients with any previous assisted reproduction treatment cycles with less than three oocytes or three or more consecutive ART cycles without a clinical pregnancy or patients with any contraindication to ART, gonadotrophins or OC pills . Patients with a significant systemic disease Baseline characteristics: Age (years) 32.8 ± 3.8 vs 32.2 ± 4.2. Body mass index (kg/m2) 23.7 ± 4.0 vs 22.6 ± 3.5. FSH (IU/l) on CD2 or 3 7.2 ± 2.2 vs 7.4 ± 3.3 0. Estradiol (pmol/l) on CD2 or 3 138 ± 55, 148 ± 103

Interventions	<p>GnRH antagonist (n= 91): daily OC pills (30 µg ethinyl E2 and 150 µg levonorgestrel) for 21- 28 days + r-hFSH 150-225 IU (Gonal-F) according to the study centre's standard practice (adjusted) + daily cetrorelix 0.25 mg subcutaneously started on stimulation day 6 and continued up to and including the day of r-hCG administration. (Fixed)</p> <p>Group 2 (n= 91): daily buserelin, 500 µg, subcutaneously at the mid-luteal phase of a natural for at least 10 days until down-regulation was achieved, after which the dose was reduced to 200 µg/day + r-hFSH 150-225 IU(Gonal-F) , according to the study centre's standard practice (adjusted)</p> <p>Final oocyte triggering: r-hCG 250 µg (=6500 IU) (Ovitrelle) was injected as soon as the largest follicle reached a mean diameter ≥ 18 mm and at least two other follicles of a mean diameter ≥ 16 mm</p> <p>Oocyte retrieval: 34-38 hrs after r-hCG administration under ultrasound guidance, followed by a standard IVF or ICSI procedure</p> <p>Maximum number of embryo transfer: no more than 2-3 embryos were replaced either 2-3 days or 5-6 (blastocyst transfer) days</p> <p>Luteal phase support: intravaginal natural progesterone (three times daily 200 mg Progestan®, Organon, Oss, The Netherlands) was started as luteal support. This was continued up to a negative pregnancy test or during the first 3 weeks of pregnancy</p>
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Outcomes	<p>Number of oocytes retrieved in IVF/ICSI patients.</p> <p>Pregnancy was defined as continuing increase in serum hCG. In that case, 4 and 10 weeks after embryo transfer, ultrasound was performed to assess the number of fetal sacs and heart activity. Clinical pregnancy was defined as the presence of a fetal sac, with or without heart activity. Ongoing pregnancy as a positive heart activity at a gestational age of 12 weeks</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated concealed randomisation list. Randomisation was performed by centre
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes

Hurine 2006 (Continued)

Other bias	High risk	Supported by Serono pharmaceutical, however the study appears to be free from other sources of bias
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Hwang 2004

Methods	RCT, single-centre Part II trial
Participants	<p>60 PCOS infertile women undergoing IVF/ICSI</p> <p>Inclusion criteria: PCOS included: (i) chronic anovulation manifested by the symptoms of oligomenorrhoea (.40 days per cycle), amenorrhoea or irregular menstrual cycle and confirmed by a basal body temperature chart or serum progesterone determination; (ii) ultrasonographic evidence of polycystic ovaries an enlarged ovary with >.10 peripherally located follicles of 3-8mm diameter around a dense central stroma; and (iii) at least one of the two hormonal abnormalities (a) normal FSH concentration (3-10 mIU/ml) and elevated LH concentration (.10 mIU/ml) or LH /FSH ratio .2; and (b) hyperandrogenaemia (serum testosterone concentrations .0.8 ng/ml). A diagnosis of congenital adrenal hyperplasia, Cushing's syndrome, androgen-producing tumours, hyperprolactinaemia and thyroid dysfunction were all excluded</p> <p>Exclusion criteria: patients older than 38 years or with serum FSH levels .12 mIU/ml</p> <p>Baseline characteristics: Age (years) 31.4 ± 3.5 vs 31.7 ± 3.7 Duration of infertility (years) 4.4 ± 1.9 4.4 ± 1.6. Body mass index (kg/m2) 23.2 ± 2.8 23.4 ± 2.9 . Baseline FSH 5.8 ± 1.2 vs 5.4 ± 1.7</p>
Interventions	<p>GnRH antagonist: Diane-35 / day from day 5 of the cycle for 21 days + cetorelix acetate was then initiated with a single dose of 0.25 mg administered sc + From day 4 to day 9, cetorelix acetate was reduced to 0.125 mg/day + 150 IU of hMG (Pergonal) every day. The dose of cetorelix acetate was increased to 0.25 mg/day from day 10 until the day before hCG (Pregnyl; NY Organon) injection, and the dose of HMG (Fixed)</p> <p>GnRH agonist :GnRH agonist long protocol. A GnRH agonist, buserelin acetate (Supremon), 500mg/day was administrated from day 3 of induced or spontaneous menstruation. After 14 days of buserelin injection, buserelin was continued until the day of HCG injection, while the dosage was decreased to 250 mg/day at the beginning of hMG administration + 150 IU/day hMG was prescribed for 6 days beginning from the day of ensuing pituitary down-regulation</p> <p>Oocyte maturation triggering: hCG, 10 000 IU, was administered i.m. when at least two follicles reached 18mm in diameter with adequate E2 response</p> <p>Oocyte retrieval: was performed 36 hrs later</p> <p>Embryo transfer: was performed 3 days after oocyte recovery.</p> <p>luteal phase support: 600 mg of vaginally administered micronized progesterone (Utrogestan) daily starting from the day after oocyte retrieval</p> <p>Follow up: clinical pregnancy was defined as a visible fetal heart beat on ultrasonography at 7 weeks of gestation</p>
Outcomes	<p>The primary outcome measures: fertilization, pregnancy and implantation rates.</p> <p>The secondary outcome measures: serum LH and testosterone status upon starting and during HMG administration, and the total days of injection</p>

Hwang 2004 (Continued)

Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation numbers with a block size of 10
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	The laboratory staff were blinded to the stimulation protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, however LBR did not address by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Inza 2004

Methods	RCT, single-centre, parallel design
Participants	Patients < 40, with FSH levels on day 3 < 12 IU/ml
Interventions	GnRH agonist long protocol versus GnRH antagonist protocol (type of antagonist protocol: N/A) (unknown)
Outcomes	Number and quality of retrieved oocytes Amount of gonadotropins used Days of stimulation Final estradiol levels Fertilization rate Number and quality of embryos transferred Pregnancy rate Implantation rate
Notes	Number of participants at randomisation: 45 (Antagonist: 23/ Agonist: 22) Number of participants at stimulation: 45 (Antagonist: 23/ Agonist: 22) Number of participants at OPU: 45 (Antagonist: 23/ Agonist: 22)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Karimzadeh 2010

Methods	RCT, single-centre trial
Participants	<p>243 patients who were candidate for ART</p> <p>Inclusion criteria: age 18-35 years, presence of a regular and proven ovulatory menstruation cycle with a length of 26 to 35 days, basal FSH <10 IU/L, body mass index (BMI) of 18-30 kg/m² and first IVF attempt. Indication for IVF were unexplained infertility, male factor, tubal factor, early stage endometriosis and cervical factor</p> <p>Baseline characteristics: Age (years) 30.0 ± 2.3 vs 29.4 ± 2.4, BMI (kg/m²) 25.9 ± 2.3 vs 25.3 ± 1.9. Basal FSH (IU/L) 6.5 ± 1.2 vs 5.9 ± 1</p>
Interventions	<p>GnRH antagonist (n= 121): clomiphene citrate 100 mg from cycle day three through seven + rFSH 75 IU daily from cycle day 5 + 0.25 mg GnRH antagonist (ganirelix) daily was started with dominant follicle ≥12 mm and in this day 75 IU human menopausal gonadotropin (hMG) (Menogon) increased to the initial gonadotropin. (mild Flexible GnRH antagonist protocol)</p> <p>GnRH agonist (n= 122): buserelin (suprefact) 500 lg subcutaneously (S.C.) everyday for menstrual cycle 21, once down regulation had been achieved, then the dose of buserelin would be reduced to 250 lg + 150-225 IU rFSH (Gonal F) S.C.</p> <p>Oocyte maturation triggering: Human chorionic gonadotropin 10,000 IU (Pregnyl) was given when one to three follicles reached 18 mm</p> <p>Oocyte retrieval: 34 to 36 hrs after HCG and IVF or ICSI was performed</p> <p>ET: on the day 2 or 3, under ultrasound guidance,</p> <p>Luteal support: progesterone in oil 100 mg daily IM was started on the day of oocyte retrieval and continued until the documentation of fetal heart activity on ultrasound.</p> <p>Follow up: pregnancy was confirmed by measuring serum β-hCG levels 12 days after</p>

Karimzadeh 2010 (Continued)

	ET. Clinical pregnancy was considered as the presence of gestational sac with fetal heart activity by TVS that performed 3 weeks after positive β -hCG
Outcomes	Primary outcome measures: clinical pregnancy rate per cycle and ongoing pregnancy; later were defined as pregnancy proceeding beyond the 12th gestational week Secondary outcome: OHSS, defined by ≥ 15 follicles with a mean diameter ≥ 14 mm per each ovary at the end of the follicular phase of stimulation, and/or E2 levels on the day of hCG administration [3,000 pg/mL and/or presence of ascites after hCG administration in ultrasonography
Notes	In control group (GnRH agonist/gonadotropin) 6 were excluded, and 13 patients did not come back, and follow up in 3 patients lost. In study group (CC/gonadotropin/ antagonist) 2 were excluded, and 12 patients did not come back, and follow up in 7 lost

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcome data, however the study did not address live birth rate
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Kim 2004

Methods	RCT, single-centre, parallel design
Participants	41 women undergoing IVF/ICSI Inclusion/ Exclusion criteria: Not stated
Interventions	GnRH antagonist: OCP+ cetrorelix 0.125 mg/day, was administered on day 1 and 2 of COH with recombinant FSH (rFSH), and cetrorelix 0.25 mg/day was restarted when the leading follicle reached a mean diameter of 13 mm and continued to the day of hCG injection. (Flexible)

Kim 2004 (Continued)

	GnRH agonist: No details are available for the agonist group, except that they were down-regulated with triptorelin (triptorelin 0.1 mg/day)
Outcomes	Number of retrieved oocytes Number of MII oocytes Number of embryos transferred Fertilization rate Ongoing pregnancy rate
Notes	Number of participants at randomisation: 41 (cetorelix: 21/ triptorelin: 20) Number of participants at stimulation: 41 (cetorelix: 21/ triptorelin: 20) Number of participants at OPU: 41 (cetorelix: 21/ triptorelin: 20)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	Declared no financial support

Kim 2009

Methods	RCT, two centres
Participants	82 low responders , aged 28 to 41 years, who were defined as patients with repeated day 3 levels of FSH >8.5 mIU/mL, and/or antral follicle count %5 and were eligible to undergo IVF/ICSI Baseline characteristics: there were no significant differences in average age, body mass index, proportion of patients with high basal FSH or small number of basal antral follicle, and basal endocrine profile among three groups(data not given)

Interventions	<p>Group A (n=27): ethinyl estradiol 0.03 mg and levonorgestrel 0.15 (21days) + 225 IU/day rhFSH (Gonal-F) + 0.25 GnRH antagonist (Cetrotide) when the leading follicle \approx 14 mm (flexible multiple-dose protocol)</p> <p>Group B (n=27): 225 IU/day rhFSH (Gonal-F) + 0.25 GnRH antagonist (Cetrotide) when the leading follicle \approx 14 mm (multiple-dose protocol)</p> <p>Group C (n= 28): decapeptyl 0.1 mg GnRH agonist luteal low-dose long protocol, The dose of GnRHα was then reduced to 0.05 mg/day + 225 IU/day rhFSH (Gonal-F) (Low dose GnRH agonist protocol)</p> <p>Oocyte maturation triggering: rhCG (Ovidrel) of 250 mg, when one or more follicles \geq 18 mm</p> <p>Oocyte retrieval: 35-36 hours later, followed by IVF/ ICSI.</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: intravaginal progesterone gel (Crinone 8%)</p> <p>Follow up: up to live birth</p>	
Outcomes	<p>Total dose of rhFSH (IU)</p> <p>Days of rhFSH administration</p> <p>No. of follicles \geq14 mm on hCG day</p> <p>Endometrial thickness on hCG day (mm)</p> <p>No. of cycle with premature LH surge</p> <p>No. of cycles with ICSI</p> <p>No. of oocytes retrieved</p> <p>No. of mature oocytes</p> <p>No. of fertilized oocytes</p> <p>No. of grade I, II embryos</p> <p>No. of embryos frozen</p> <p>No. of embryos transferred</p> <p>Clinical pregnancy rate per cycle (%)</p> <p>Implantation rate (%)</p> <p>Miscarriage rate per clinical pregnancy (%)</p> <p>Live birth rate per cycle (%)</p> <p>Twin pregnancy rate per clinical pregnancy (%)</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported

Kim 2009 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	Reported nothing to disclose

Kurzawa 2008

Methods	RCT, single-centre trial
Participants	<p>74 PCOS meeting Rotterdam criteria undergoing ICSI</p> <p>Inclusion criteria: male factor subfertility, several unsuccessful intrauterine inseminations, previous ineffective IVF (none or <30% of fertilizations), age ≤35 years, BMI <26 kg/m², basal FSH <12 mIU/ml, negative HBV and HCV virus infection and HIV</p> <p>Exclusion criteria: ≥2 miscarriages, ≥3 unsuccessful IVF/ICSI cycles, anatomical abnormalities of the uterus on laparoscopy or hysteroscopy and existence of ovarian cysts</p> <p>Baseline characteristics: Age (years) 31.33±3.91 vs 30.36±3.40, BMI (kg/m²) 23.1±1.3 vs 22.3±1.6</p>
Interventions	<p>GnRH antagonist (n=37): OCO (Cilest)+ 150 IU rFSH on 2nd day of the cycles (adjusted) + 0.25 mg sc of cetrorelix acetate (Cetrotide) administered when follicles reached a diameter of 14 mm (flexible protocol)</p> <p>GnRH agonist (n= 37): OCP (Cilest) + 150 IU rFSH (adjusted) + long GnRH agonist triptorelin (Diphereline SR 3.75) (Depot GnRH agonist protocol)</p> <p>Oocyte maturation triggering: 10,000 IU hCG or subcutaneous injection of 250 µg hCG when the dominant follicle reached ≥18 mm with the following two ≥16 mm and estradiol level between 1000 and 4000 pg/mL.</p> <p>Oocyte retrieval: 36 hours later, followed by ICSI.</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: oral 30 mg/day of dydrogesterone (Duphaston), and intravaginal 150 mg/day of progesterone</p> <p>Follow up: Pregnancy was checked by pregnancy test in serum 14 days after ET and confirmed by vaginal ultrasound scan at 12 weeks of gestation</p>
Outcomes	<p>Primary endpoints</p> <p>Embryological:</p> <p>Matured oocytes (M2) rate, defined as proportion of metaphase II to total number of retrieved oocytes</p> <p>Fertilization rate, defined as proportion of two pronuclei oocytes to number of injected oocytes</p> <p>Quality of zygotes on the first day of culture</p> <p>Quality of embryos on the third day of culture</p> <p>Secondary endpoints</p> <p>Clinical:</p>

Kurzawa 2008 (Continued)

	<p>Delivery per attempt, defined as a live birth after 32 weeks of gestation Clinical pregnancy per attempt, defined as an ongoing pregnancy at 12 weeks of gestation Implantation rate; defined as gestational sacs per number of transferred embryos Multiple pregnancy per viable pregnancy Miscarriage per intrauterine pregnancy, defined as a miscarriage of an ongoing pregnancy after 12 weeks of gestation Occurrence of severe OHSS Number of days of gonadotropin treatment Gonadotropin consumption Correlation between serum LH level and IVF outcome</p>
Notes	Financial support-grant number KBN 2 P05E 034 28 from State Committee for Scientific Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random letters (A for GnRH antagonists protocol or B for GnRH agonists protocol).
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	Financial support from State Committee for Scientific Research, the study appears to be free from other sources of bias

Kyono 2005

Methods	RCT, open-label, parallel design, single-centre
Participants	Women under the age of 40 yrs with previous cycles <3 times, and BMI < 27 kg/m ² underwent COH for ART
Interventions	Patients were treated with GnRH agonist long protocol, GnRH antagonist protocol, and GnRH antagonist with hCG 200IU protocol following contraceptive pills for 2 - 3 weeks as pretreatment.(Unknown)

Kyono 2005 (Continued)

Outcomes	Total amount of FSH dosage, Blood E2 level at hCG injection, the number of oocytes, small follicle (< 10mm) counts at OPU, day 3 embryo high quality rate, clinical pregnancy rate, and severe OHSS rate	
Notes	Number of participants at randomisation: 192 (cetorelix: 126/ buserelin: 66) Number of participants at stimulation: N/A Number of participants at OPU: N/A	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Lainas 2007

Methods	RCT, single-centre
Participants	78 infertile women with PCOS women undergoing IVF/ICSI Inclusion criteria: PCOS (presence of oligo-ovulation/anovulation and polycystic ovaries), age 18-39 years, less than three previous IVF/ICSI, attempts, no endometriotic cyst present as assessed by transvaginal, ultrasound examination and basal hormonal levels of FSH in the early follicular phase of 10 IU l21. Exclusion criteria: patients with known previous poor ovarian response Baseline characteristics: Age (years) 32.0 (14) vs 30.5 (16), BMI (kg m ²) 23.2 (20.9) vs 23.6 (18.9), FSH (IU l21) 6.3 (1.7) vs 5.8 (2.6)
Interventions	GnRH antagonist (n=26): OCP + 150 IU rFSH on 2nd day of the cycles (adjusted) + 0.25 mg sc of ganirelix (Orgalutran) administered on day 2 of menses/day 1 of stimulation (flexible protocol) GnRH agonist (n= 52): OCP + 150 IU rFSH (adjusted) + long GnRH agonist , 0.1

Lainas 2007 (Continued)

	<p>mg triptorelin 3 days before discontinuation of the OCP, once down-regulation was achieved, the dose of GnRH agonist was decreased on that day to 0.05 mg/day (low dose GnRH agonist protocol)</p> <p>Oocyte maturation triggering: 3 follicles > 17 mm, i0000 IU of hCG was administered</p> <p>Oocyte retrieval: 35 - 36 hours later, followed by IVF/ ICSI</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: 600 mg of micronized progesterone was initiated 2 days after oocyte retrieval</p> <p>Follow up: OPR was confirmed by vaginal ultrasound scan at 12 weeks of gestation</p>	
Outcomes	<p>Primary outcome measure: E2 levels on Day 5 of stimulation</p> <p>Secondary outcome measures: follicular development, LH and progesterone levels</p>	
Notes	<ul style="list-style-type: none"> • In cases of excessive ovarian response that could lead to life threatening OHSS (Navot et al 1992), elective cryopreservation was performed. • Excessive ovarian response was defined by the following criteria: high E2 levels (.4000 pg ml²¹) and more than 35 follicles on the day of hCG (Navot et al 1992), haematocrit >.45, white blood cell count >15 000, ovarian size >12 cm 3 days after oocyte retrieval (Navot et al 1992; Brinsden et al 1995). A modified system of OHSS classification previously described was adopted (Rizk and Aboulghar 1993) 	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list in a 1:2 ratio
Allocation concealment (selection bias)	Low risk	By a study nurse, the responsible physicians (investigators) were not involved in the randomisation process,
Blinding (performance bias and detection bias) All outcomes	High risk	Neither patients nor doctors were blinded to the treatment assigned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not address by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Lainas 2010

Methods	RCT, single-centre	
Participants	<p>220 PCOS women undergoing ICSI</p> <p>Inclusion criteria: PCOS (presence of oligo-ovulation/anovulation) and polycystic ovaries, age 18-39 years, no endometriotic cyst present, as assessed by transvaginal ultrasound examination, basal FSH 10 IU/ml</p> <p>Exclusion criteria: Patients with known previous poor ovarian response</p> <p>Baseline characteristics: Age (years) 32 (29-35) vs 31 (28-35), BMI (kg/m²) 23.2 (20.9-25.8) vs 24.6 (20.9-29.3), FSH (IU/l) 6.0 (4.3-6.9) vs 6.2 (4.8-7.5), LH (IU/l) vs 5.9 (3.4-7.6) 5.3 (4.0-7.5)</p>	
Interventions	<p>GnRH antagonist (n=110): OCP + 150 IU FSH on 2nd day of the cycles (adjusted) + 0.25 mg sc of cetrorelix acetate (Cetrotide) administered when at least one of the following criteria were fulfilled, the presence of at least one follicle measuring > 14 mm, serum E2 levels > 600 pg/ml; and serum LH levels >10 IU/l (flexible protocol)</p> <p>GnRH agonist (n= 110): OCP (Cilest) + 150 IU r FSH (adjusted) + long GnRH agonist , 0.1 mg triptorelin 3 days before discontinuation of the OCP, once down regulation was achieved, the dose of GnRH agonist was decreased on that day to 0.05 mg/day (low dose GnRH agonist protocol)</p> <p>Oocyte maturation triggering: 3 follicles > 17 mm, 5000 IU of hCG was administrated</p> <p>Oocyte retrieval: 35 - 36 hours later, followed by IVF/ ICSI.</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: 600 mg of micronized progesterone was initiated 2 days after oocyte retrieval.</p> <p>Follow up: OPR was confirmed by vaginal ultrasound scan at 12 weeks of gestation</p>	
Outcomes	<p>The primary outcome measure: ongoing pregnancy rate per patient randomized. Ongoing pregnancy and clinical pregnancy were defined as the presence of gestational sac with fetal heart beat detection at 12 weeks and at 6-7 weeks of gestation, respectively.</p> <p>Secondary outcome measures: OHSS incidence, duration of r FSH stimulation, total dose of r FSH, E2 and progesterone concentration on the day of hCG administration, cycle cancellation rate, number of cumulus-oocyte complexes (COCs) retrieved, number of metaphase II oocytes and fertilization rates</p>	
Notes	<p>OHSS classification:a modified classification system based on combined criteria previously reported (Golan et al 1989; Navot et al 1992; Rizk and Aboulghar 1999) was used in the current study</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list, in a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Not reported

Lainas 2010 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Neither patients nor doctors were blinded to the treatment assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data, however LBR did not address by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Lee 2005

Methods	RCT, single-centre, university hospital, tertiary medical centre, parallel design
Participants	61 infertile women undergoing IVF/ICSI Inclusion criteria: were no more than 39 years of age, a history of regular menstruation cycles (menstrual cycle length 26-33 days), body mass index 18-29 kg/m ² , no history of poor ovarian response or reserve (less than three oocytes in a previous IVF cycle), baseline FSH levels <11 IU/L, normal results for serum liver and renal function testing, presence of two ovaries, and no pill or hormone pretreatment within recent three months prior to stimulation cycle Exclusion criteria: ovarian-factor or uterine-factor infertility, or those suffering ovarian cysts, as determined by the use of ultrasound at the commencement of a stimulation cycle
Interventions	COS with either a multiple-dose (MD) or a single-dose (SD) protocol for GnRH antagonist (cetrotrelix) administration (Flexible), or with a long protocol (LP) for GnRH agonist (buserelin) administration, followed by oocyte retrieval, IVF/ICSI, and embryo transfer
Outcomes	Amount of hMG administered (ampoules) Period of hMG stimulation (days) Serum E2 level on day of hCG administration (pg/mL) Numbers of follicles (size 10 mm) on day of hCG administration Thickness of endometrium (mm) on day of hCG administration Number of oocytes retrieved Fertilization rate (%) Number of zygotes Number of transferred embryos Number of frozen embryos Implantation rated Pregnancy rated

Lee 2005 (Continued)

Notes	Number of participants at randomisation: 61 (cetorelix: 41/ buserlin: 20) Number of participants at stimulation: 60 (cetorelix: 40/ buserlin: 20) Number of participants at OPU: 60 (cetorelix: 40/ buserlin: 20)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Did not reported clearly
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Did not reported clearly
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	University grant, the study appears to be free from other sources of bias

Lin 2006

Methods	RCT, single-centre trial
Participants	120 infertile women undergoing ICSI Inclusion criteria: age 20-38 years with regular cycles, normal basal FSH<10 mIU/ml, LH <10 mIU/ml and E2<60 pg/ml), BMI 18.5 - 24.9 kg/m ² , male-factor infertility Exclusion criteria: endometriosis, anovulation, PCOS and hydrosalpinx Baseline characteristics: age (years) 31.3±4.4 vs 30.7±4.4, Weight (kg) 53.5±8.2 vs 55.2±8.2, Day-3 FSH level (mIU/ml) 5.12±1.76 vs 5.28±1.44, Day-3 LH level (mIU/ml) 4.75±2.19 vs 4.31±2.39
Interventions	GnRH antagonist (n= 60): 100 mg/day CC cd 3 to 7 + 2-4 ampoules hMG was given on days 4, 6,8 and 9 + 2.5 mg cetorelix acetate (Cetrotide1) when the leading follicle had reached 14 mm (Flexible) GnRH agonist (n=60): 0.5 mg/day buserelin GnRH agonist (GnRH _a) long protocol + 2-4 ampoules of hMG (Pergonal) or FSH (Metrodin) Oocyte maturation triggering: 10,000 IU hCG (Pregnyl1), when at least two follicles had reached 18 mm Oocyte retrieval: 34-36 hrs, followed by ICSI Maximum embryo transfer:

Lin 2006 (Continued)

	Luteal phase support: 600 mg/day vaginally of micronized progesterone (Utrogestan) starting from the day after oocyte retrieval Follow up: up to live birth	
Outcomes	Primary outcome measure: amount of gonadotrophin used Secondary outcome measures: endometrial thickness, number of oocytes and MII oocytes recovered, as well as rates of fertilization and pregnancy	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation
Allocation concealment (selection bias)	Low risk	Sealed in envelopes and the physicians were not aware of the allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	The study appears to be free from other sources of bias

Loutradis 2004

Methods	RCT, university-affiliated IVF centre, open-label, parallel design
Participants	[1] Age between 20 and 38 years, [2] no low response in a previous treatment cycle, [3] no uterine or ovarian anomalies, and [4] history of regular menstrual cycles ranging from 25 to 35 days
Interventions	GnRH antagonist: started ovarian stimulation on day 3 of the cycle with the administration of 225 IU of r FSH. Group B was treated with the GnRH antagonist cetrorelix (0.25mg/day, SC; Cetrotide) (Flexible), commencing when the largest follicle had reached a diameter of 14 mm, and simultaneous augmentation of 75 IU of FSH was initiated up to and including the day of hCG administration GnRH agonist: was treated with the GnRH agonist triptoreline (1 mg/day SC; Decapeptyl) starting 1 week before the expected menses. After down-regulation was achieved (serum E2 <50 pg), ovarian stimulation was commenced with a fixed daily dose of 225

Loutradis 2004 (Continued)

	IU of recombinant FSH (r FSH). Oocyte maturation triggering: When the leading follicle had reached a diameter of 18 mm in group A and 20 mm in group B and at least two follicles had reached 15 mm or more, r FSH was discontinued and a single 10,000 IU hCG dose (Pregnyl) was administered	
Outcomes	Peak E2 (pg/mL) Total dosage of gonadotropins (IU) Duration of gonadotropin administration (d) No. of oocytes retrieved Total no. of good-quality embryos No. of ETs Clinical pregnancy rates Implantation rates No. of cryopreserved embryos	
Notes	Number of participants at randomisation: 116 (cetorelix: 58/ triptoreline: 58) Number of participants at stimulation: 116 (cetorelix: 58/ triptoreline: 58) Number of participants at OPU: 116 (cetorelix: 58/ triptoreline: 58)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table, Randomisation:1:1 (cetorelix: triptoreline) ratio
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Marci 2005

Methods	RCT, single-centre, open-label, parallel design
Participants	60 infertile women (poor responders) undergoing IVF/ICSI Inclusion criteria: estradiol concentrations <600 pg/ml concentration on the day of HCG administration and a poor response (number of oocyte retrieved <3) after a previous standard long protocol using analogues for down regulation and recombinant gonadotrophin at a dose of 225 IU for stimulation (r-FSH, Gonal-F)
Interventions	GnRH antagonist (n= 30): 375 IU rFSH (Gonal-F) from cd2 + GnRH antagonist cetrorelix 0.25 mg per day was then administered from when the two lead follicles had reached 14 mm diameter, irrespective of the day of the cycle until the day of HCG injection. (Flexible) GnRH agonist (n= 30): by analogues (GnRHa) from day 23 of the cycle (Enantone 3.75 mg) + 375 IU daily , sc, rFSH, (Gonal-F) from day 3 of the next cycle at a dose of. In group B (n = 30), ovarian stimulation started at day 2 with rFSH at a dose of 375 IU (Gonal-F) Oocyte maturation triggering: hCG (Profasi; Serono) 10,000 IU was administered intramuscularly (IM) 24 hrs after the last r-FSH injection when at least two follicles had reached a diameter of 17 mm Oocyte retrieval: 36 hrs after HCG administration followed by IVF/ICSI Embryo transfers: were performed 48 hrs after oocyte retrieval Luteal phase: 2 × 200 mg/day of micronized vaginal progesterone (Prometrium) Follow up: serum HCG concentrations were measured 14 days after embryo transfer. Clinical pregnancies were confirmed 28-35 days after embryo transfer by the presence of a gestational sac under ultrasound
Outcomes	Age (years) Initiated cycles Stopped cycles Cycles with oocyte retrieval Stimulation duration (days) Number of ampoules Follicles >15 mm Oocytes retrieved Oocytes fertilized Cycles with transfers Embryos transferred Endometrial thickness (mm) Clinical pregnancies
Notes	Number of participants at randomisation: 60 (cetrorelix: 30/ enantone: 30) Number of participants at stimulation: 60 (cetrorelix: 30/ enantone: 30) Number of participants at OPU: 55 (cetrorelix: 29/ enantone: 26)
Risk of bias	
Bias	Authors' judgement Support for judgement

Marci 2005 (Continued)

Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Martinez 2008

Methods	RCT, single-centre, donor-recipient cycle
Participants	323 Donors: < 35 years, baseline FSH <10 U, BMI < 30 kg.m2, no history of hereditary disease Baseline characteristics: Age (years) 27.2+4.7 vs 26.5+4.7, BMI (kg/m2) 23.0+3.5 vs 23.1+3.0, Baseline FSH (IU/ml) 7.0+2.3 vs 6.5+2.1
Interventions	GnRH antagonist: vaginal contraceptive (Nuvaring) + leuprorelin acetate, 3.75 mg + 2-3 ampoules per day of hMG GnRH agonist: vaginal contraceptive (Nuvaring) + rFSH 150-200 U/day + ganirelix (Orgalutran) 0.25 mg/day, from day 6 of stimulation (Fixed) Oocyte maturation triggering: 10,000 U of hCG when at least three follicles > 20 mm in diameter Oocyte retrieval: 35-36 hours later, followed by IVF/ ICSI Follow up: 10-14 days after puncture
Outcomes	Clinical pregnancy rate (confirmed by the presence of a gestational sac in the ultrasound examination carried out 4-5 weeks after transfer) The implantation rate was calculated by dividing the number of gestational sacs by the number of embryos transferred Other secondary results were the total number of OCCs retrieved, the number of days and total dose of gonadotropin stimulation, and plasma estradiol levels on the day of hCG administration
Notes	
Risk of bias	

Martinez 2008 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table
Allocation concealment (selection bias)	Low risk	Telephone call
Blinding (performance bias and detection bias) All outcomes	Low risk	Researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Moraloglu 2008

Methods	RCT, single-centre
Participants	<p>93 patients undergoing IVF/ICSI between May 2005 and August 2006, Age: 25-38 years.</p> <p>Exclusion criteria: history of previous poor response (<4 follicles and/or serum estradiol (E2) level <500 pg/ml on the day of hCG), ≥ previous IVF cycles, PCOS or azoospermia, were aged over 38 years, had a body mass index ≥30 kg/m² and basal follicle-stimulating hormone (FSH) measurement ≥10 IU/ml, and those with relevant systemic disease, severe endometriosis or uterine and ovarian abnormalities</p> <p>Baseline characteristics: Age: 30.91±5.52 vs 30.25±4.94. BMI: 29.36±4.45 vs 26.58±3.32. Basal E2: 6.63±1.33 vs 6.32±1.77. AFC: 5.02±2.56 vs 8.02±2.95</p>
Interventions	<p>GnRH antagonist (n=45): OC (Desogesteral+ 225 IU FSH + 0.25 mg sc of cetrorelix acetate (Cetrotide) administered when follicles reached a diameter of ≥14 mm (flexible protocol)</p> <p>GnRH agonist (n= 48): OCP (Desogesteral+ 225 IU FSH + long GnRHa leuprolide acetate 1 mg/day sc (Lupron) 1 week before the expected menses with approximately a 5-day overlap with the OC, The dose of GnRHa was then reduced to 0.5 mg/day, (Low dose GnRH agonist protocol)</p> <p>Oocyte maturation triggering: hCG 5000 IU (Profai) sc, > 3 follicles of 18 mm in diameter</p> <p>Oocyte retrieval: 36 hours later, followed by IVF/ ICSI.</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: intravaginal progesterone gel (Crinone 8%) and was started no later than the day of ET until a urine pregnancy test was performed 12 days later.</p>

Moraloglu 2008 (Continued)

	Follow up: An ultrasound scan was carried out 5 to 6 weeks after oocyte retrieval to determine the viability of the pregnancy. A second ultrasound was performed at 12 weeks' gestation to confirm any ongoing pregnancy (+ ve heart beat)	
Outcomes	Antral follicle numbers Total stimulation duration, days Total gonadotropin consumption, IU/l Serum E2 value on day of hCG Cycles cancelled for premature LH surge (%) Cycles cancelled for fertilisation failure (%) No. of oocytes per retrieval No. of mature oocytes (M2) No. of fertilised oocytes, fertilization rate (%) Total embryos obtained No. of embryos transferred Clinical pregnancy per cycle initiated (%) No. of cycles with OHSS (%) Clinical pregnancy per transfer	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data , however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Not reported

Moshin 2007

Methods	RCT, single-centre trial
Participants	49 PCOS infertile women undergoing IVF/ICSI
Interventions	GnRH antagonist (n=25): 225 IU FSH on 2nd day of the cycles (fixed) + 0.25 mg sc of GnRH antagonist cetrorelix (Cetrotide, Serono International, Switzerland) started on the 6th day of stimulation (fixed protocol) GnRH agonist (n=24): 225 IU rFSH (fixed) + long GnRH agonist, 3.75 mg of triptorelin (Dipherelin) in the mild-luteal phase of the preceding cycle (long depot GnRH agonist protocol) Oocyte maturation triggering: 10,000 IU sc hCG (Pregnyl) when one follicle 18 -20 mm Oocyte retrieval: 35 hours later, followed by IVF/ ICSI.
Outcomes	Duration of stimulation, number of ampoules of FSH, fertilization rate, implantation rate, ongoing pregnancy rate, OHSS incidence
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data , however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	Study funding not reported.

Olivennes 2000

Methods	RCT, multi-centre (9 centres), open-label, parallel design
Participants	169 infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI Inclusion criteria: with no more than three previous IVF-ET attempt with all causes of infertility (except polycystic ovary and moderate or severe endometriosis) Baseline characteristics: Age cetrorelix 31.4 ± 3.7, decapeptyl 31.8 ± 3.8. Duration

Olivennes 2000 (Continued)

	of infertility: cetrorelix 59.3 ± 35, decapeptyl 55.3 ± 38.1. FSH: cetrorelix 6.3 ± 2, decapeptyl 6.3 ± 1.9. BMI cetrorelix 22.4, decapeptyl 22.8
Interventions	A single dose of 3 mg of GnRH antagonist (cetrorelix) (Depot) was administered SC to 115 participants On day 7 of hMG mid-luteal GnRH analogue (decapeptyl 3.75) Ovarian suppression was confirmed by E2 >50pg/ml / FSH and LH <10IU/L, P <1 µg/ml Then hMG (menogon) was started at 2 or 3 ampoules for 4 days and the dose was adjusted according to response Luteal phase support using daily vaginal progesterone ICSI was done in 12 cases in the cetrorelix group and 5 patients in the decapeptyl group
Outcomes	Premature LH surge defined as (LH >10IU/L) and progesterone level >1ng/L Stimulation length no. of hMG ampoules E2 on hCG no of oocytes retrieved no of embryos obtained no of embryos transferred Clinical preg/OPU Clinical preg/ET Miscarriage Ectopic OHSS Moderate or severe OHSS Clinical pregnancy was defined as fetal heart beat on ultrasonography Ongoing pregnancy was defined as pregnancy ongoing after 12 weeks of amenorrhoea
Notes	<ul style="list-style-type: none"> • Number of participants at randomisation: 169 (cetrorelix 126/ decapeptyl 43). Number of participants at stimulation: 154 (cetrorelix 115 / decapeptyl 39). Number of participants at OPU: 149 (cetrorelix 113 / decapeptyl 36) • When triggering of ovulation was not done within 4 days of administration of the 3mg dose of cetrorelix, a daily injection of 0.25mg was given to 11 cases until hCG administration <ul style="list-style-type: none"> • Implantation rate was not mentioned as an outcome variable • Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text • Tolerability was not mentioned in the table of outcomes but stated in the text regarding the cetrorelix group only. No mention of itching or redness in the decapeptyl group • Although power calculation was not done, the authors were concerned with the response to cetrorelix so they assumed 107 patients will be enough number to obtain 95% response rate with a CI width of 5% • Centre adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome
<i>Risk of bias</i>	

Olivennes 2000 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not address by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Supported by pharmaceutical company, however the study appears to be free from other sources of bias

Rombauts 2006

Methods	RCT, 10 IVF centres, open-label, parallel design
Participants	351 infertile women undergoing IVF/ICSI Inclusion criteria: healthy females of infertile couples, age at time of screening between 18 and 39 years, body mass index between 18 and 29 kg/m ² , body weight <90 kg, a normal menstrual cycle with a range of 24-35 days and an intra-individual variation of ± 3 days, and willingness to give written informed consent Exclusion criteria: included contraindications for the use of gonadotrophins, endocrine abnormalities (e.g. polycystic ovary syndrome), more than three unsuccessful controlled ovarian stimulation cycles, a history of low or no ovarian response during FSH/HMG treatment, and clinically relevant abnormal laboratory values (including hormones) or medical examination findings
Interventions	GnRH antagonist: treatment with the GnRH antagonist ganirelix (0.25 mg, Orgalutran) was started on day 5/6 of rFSH treatment. If no follicles 14 mm were observed by ultrasonography on that day, the start of ganirelix was delayed. Injections containing 0.25 mg ganirelix per 0.5 ml were administered sc in the thigh, once daily in the morning, until and including the day of HCG administration. (Flexible) GnRH agonist: in the OC-scheduled group, women started taking a combined OC pill (30 µg ethinyl oestradiol/150 µg desogestrel) Marvelon® (NV Organon) on day 1 of the menstrual cycle. They took it daily for between 14 and 28 days, depending on the planned start of rFSH treatment Women in the nafarelin group started pretreatment with the GnRH agonist nafarelin (Synarel®; Pharmacia, Australia) on day 21-24 of the preceding cycle. Nafarelin was

	<p>administered intranasally at a daily dose of 0.8 mg until and including the day of hCG administration</p> <p>In all three groups ovarian stimulation was performed with rFSH (follitropin beta, Puregon®; NV Organon, The Netherlands), which was administered sc once daily in the morning at a fixed dose of 200 IU during the first 5-6 days. After this period the dosage of rFSH could be adjusted depending on the ovarian response as assessed by ultrasound. Treatment was continued until (and including) the day of HCG administration. In the OC-scheduled ganirelix group, stimulation with rFSH was started 2 days after discontinuation of the OC (irrespective of whether or not menses had started), in the non-scheduled group on day 2-3 of the menstrual cycle and in the nafarelin group after 2-4 weeks of nafarelin treatment [as soon as pituitary down-regulation had been achieved (i.e. serum estradiol 50 pg/ml or 200 pmol/l); if this stage was not achieved after 4 weeks of nafarelin treatment, the subject discontinued]</p> <p>HCG, 10 000 IU in 1 ml saline (Pregnyl®, NV Organon, the Netherlands), was administered, either sc or i.m., when at least three follicles 17 mm or at least one follicle 20 mm were observed on ultrasound. In case of risk of ovarian hyperstimulation syndrome (OHSS), the HCG dose was reduced to 5000 IU. Oocyte retrieval was performed 30-36 hrs after hCG administration, followed by IVF or ICSI. No more than three embryos were transferred 2-3 days after oocyte retrieval. Progesterone for luteal support was given daily (doses and administration form as per usual protocol of the participating centre), starting at the latest on the day of embryo transfer, for 2 weeks or up to menses</p> <p>The study was approved by the Ethics Committee of each participating centre. All women gave written informed consent. The study was performed according to the principles of the Declaration of Helsinki, and the ICH/Good Clinical Practice guidelines. The study was monitored by uniformly trained Clinical Research Associates of Organon with assistance of a contract research organization for the clinics in Perth and Adelaide</p>
<p>Outcomes</p>	<p>Prior to the start of treatment, a physical and gynaecological examination was performed to exclude any abnormality. Blood samples were taken for routine biochemistry, haematology, and hormonal parameters. A pregnancy test (urinary hCG) was performed. Blood samples for hormone assessments were taken just before the first rFSH injection (treatment day 1) and at least once every 2 days from day 5/6 of rFSH treatment (in the antagonist groups just before ganirelix injection) up to and including the day of HCG. Serum FSH, LH, estradiol, and progesterone values were determined by means of the automated Wallac AutoDelfia Fluoroimmunoassay system (PerkinElmer Inc., Wellesley MA, USA) at a central laboratory (ABL BV, Assen, The Netherlands). The maximum intra-assay and inter-assay coefficients of variation were 3.3% for FSH, 3.4% for LH, 4.9% for estradiol, and 4.3% for progesterone. To measure follicular development, ultrasonography was performed at least once every two days from day 5/6 of rFSH treatment up to and including the day of HCG. Other parameters assessed were treatment failure (defined as the number of women who did not have an HCG injection or who received an hCG injection because of premature luteinization), number of LH rises (LH =10 IU/l), number of oocytes retrieved, number of good quality embryos (grade 1 (defined as excellent: no fragmentation) and grade 2 (defined as good: 1-20% fragmentation)), fertilization rate, implantation rate, and ongoing pregnancy rate (assessed by ultrasound =12-16 weeks after embryo transfer)</p>
<p>Notes</p>	<p>Number of participants at randomisation: 351 (ganirelix: 234/ nafarelin: 117) Number of participants at stimulation: 332 (ganirelix: 221/ nafarelin: 111)</p>

Rombauts 2006 (Continued)

	Number of participants at OPU: 313 (ganirelix: 212/ nafarelin: 101)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Pharmaceutical company support, however the study appears to be free from other sources of bias

Sauer 2004

Methods	RCT, open-label, multi-centre study. Phase III trial
Participants	74 infertile women (aged 18-39 years) undergoing ICSI Inclusion criteria: regular menstrual cycles, BMI <35 kg/m ² . both ovaries present, no clinical signs of pelvic or uterine abnormalities, normal cervical cytology, wash-out period completed for any previous IVF drug protocols and FSH concentrations in the normal range. All women were also required to be willing and able to comply with the study protocol Baseline characteristics: Mean age (±SD) of the ITT population was 32.6 ± 4.0 years. The age range was broad (22-39 years) and there were no significant differences between the three treatment groups. Mean BMI was 24.2 ± 4.5 g/m ² . again with no significant differences between groups. Fifty-one of the 73 women in the ITT population (69.99%) were Caucasian and the proportion of Caucasians did not differ between treatment groups
Interventions	GnRH antagonist: OCP pretreatment for 14-18 days, followed by cetrorelix (3 mg), starting on day 7 + rFSH 225 IU, starting on day 5 after OCP/dose adjustments after day 6 GnRH agonist: leuprorelin (0.5 mg/ day reduced to 0.25 mg/day after down regulation

Sauer 2004 (Continued)

	<p>was achieved),long luteal, overlapping with OCP pretreatment for 7 days + rFSH 225 IU, starting on day 5 after OCP/dose adjustments after day 6 GnRH antagonistII: OCP + cetrorelix and r-FSH together with mid-cycle r-LH</p> <p>Oocyte maturation: hCG rhCG 250 μg When at least one follicle was \geq 18 mm and at least two follicles were \geq 16 mm and E2 within acceptable range Embryo transfer: no more than three embryos were to be replaced: two if transferred at blastocyst stage Luteal phase support: Micronized progesterone according to centres' practice</p>	
Outcomes	<p>The primary efficacy end-point: the number of metaphase II oocytes retrieved per patient Secondary efficacy: end-points were the duration and total dose of r-hFSH therapy, the total number of follicles > 14 mm on the day of r-HCG administration, oocyte and embryo quality and development, the number of patients with at least one embryo considered viable for cryopreservation, oestradiol concentration per follicle >10 mm, total number of oocytes, implantation rates per-embryos transferred and pregnancy rates (biochemical and clinical)</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, Internet-based system. randomisation 1:1:1
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	High risk	Supported by pharmaceutical company, however the study appears to be free from other sources of bias

Sbarcia 2009

Methods	RCT, single-centre	
Participants	<p>564 low responders, undergoing their first IVF cycle were eligible for the study</p> <p>Inclusion criteria: age 40 years or older and no previous IVF cycle, and the exclusion criteria were FSH >10 IU/ mL, a previous IVF cycle, and age 45 years or older</p> <p>Exclusion criteria: PCOS</p> <p>Baseline characteristics:</p> <p>Maternal age, years 42.3 1.4 vs 42.1 1.5, Body mass index 25.1 2.6 vs 24.8 2.4, Basal FSH levels, IU/L 7.0 2.5 vs 6.9 2.4</p>	
Interventions	<p>Group A (n= 285): 300 IU/day rhFSH (Gonal-F) + 0.25 GnRH antagonist (Cetrotide) when the leading follicle \approx 14 mm or the E2 plasma levels were 600 pg/mL (flexible multiple-dose protocol)</p> <p>Group C (n= 285): busarelin 0.4 mg/day long GnRH agonist + 225 IU/day rhFSH (Gonal-F) (GnRH agonist protocol)</p> <p>Oocyte maturation triggering: 10,000 IU of IM hCG when plasma E2 between 800 and 3500 pg/mL and at least three follicles >16 mm in mean diameter</p> <p>Oocyte retrieval: 36 hours later, followed by ICSI</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: 50 mg daily of P (Prontogest) IM from the day of replacement</p> <p>Follow up: pregnancies were confirmed by a rising titre of serum b-hCG 12 days after ET and ultrasound demonstration of the gestation sac 4 weeks after the transfer</p>	
Outcomes	<p>Primary outcomes: clinical pregnancy rate per cycle started and per transfer</p> <p>Secondary outcomes: days of stimulation, E2 at the day of hCG, amount of FSH administered, number of oocytes yielded, number of embryos transferred, implantation rate, and abortion rate</p>	
Notes	Drop out: four women in the cetrorelix group and two in the control group	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation number sequence at the time that their cycle was scheduled
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcome data, however, LBR, OPR were not addressed by the study

Sbarcia 2009 (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Low risk	authors declared have nothing to disclose

Serafini 2003

Methods	RCT, single-centre, parallel design
Participants	Inclusion/ Exclusion criteria: not stated.
Interventions	All protocols included an initial recombinant human FSH (Gonal-F) dose ranging from 150 to 300 IU daily, and the patients were grouped as follows: (A) rhFSH was continued in the full dose until follicles reached 13±14 mm, when the rhFSH dose was lowered to 75 IU and the patients began with 200 IU human chorionic gonatrophin (HCG) along with cetrorelix 0.25 mg (flexible); (B) same criteria in protocol (A) without using HCG, and; (C) rhFSH initiated after mid luteal pituitary desensitization with leuprolide
Outcomes	Number of mature oocytes retrieved Number of normally fertilized oocytes Number of cycles with high-quality embryos Number of embryo transfers Implantation rate Pregnancy rate Incidence of severe ovarian hyperstimulation syndrome (OHSS)
Notes	Number of participants at randomisation: 77 (cetrorelix: 49/ buserlin: 28) Number of participants at stimulation: 77 (cetrorelix: 49/ buserlin: 28) Number of participants at OPU: 77 (cetrorelix: 49/ buserlin: 28)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomised trial without any further details.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study

Serafini 2003 (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	The study appears to be free from other sources of bias. Study funding not reported

Tazegul 2008

Methods	RCT, single-centre
Participants	<p>96 poor responders who underwent ICSI-ET cycles</p> <p>Inclusion criteria: baseline follicle stimulating hormone (FSH) < 13 m IU/ml, estradiol level on the day of human chorionic gonadotropin (HCG) injection < 500 pg/ml and a poor response (failure in obtaining of at least three follicles > 16 mm in diameter and the number of mature oocytes retrieved less than four) after a previous ovarian stimulation cycle</p> <p>Exclusion criteria were: presence of a clinically significant systemic disease; diabetes mellitus; polycystic ovaries or any other endocrine disorder; submucosal polyp, myoma or uterine septum which were detected on hysteroscopy or hysterosalpingography. Intracytoplasmic sperm injection and assisted hatching were performed in all cycles</p> <p>Baseline characteristics: Age (years) 38.3 ± 4.23 vs 37.9 ± 74.87. Baseline FSH (IU/mL) 6.31 ± 2.19 vs 6.27 ± 2.82</p>
Interventions	<p>GnRH antagonist (n= 48): 300 IU r-FSH and hMG starting on the second day of menstruation for 6 days (adjusted) + 0.25 mg of cetrorelix (Cetrotide) or 0.25 mg ganirelix (Orgalutran) were administered subcutaneously per day when the leading follicle reached 14 mm in diameter until the hCG injection. (Flexible)</p> <p>GnRH agonist (n= 48): 1 mg/ day leuprolide acetate (Lucrin) started on the 21st day prior to menstruation for pituitary desensitization. When exogenous gonadotropins were started on day 2 of menstruation, the dose of leuprolide acetate was decreased to 0.5 mg/ day + 300 IU rFSH and hMG starting on the second day of menstruation for 6 days (adjusted)</p> <p>Oocyte maturation triggering: When the leading follicle reached 18 mm in diameter or at least two follicles were >17 mm in diameter, a total of 10,000 units of hCG were administered intramuscularly</p> <p>Oocyte retrieval: was performed 35-37 hrs later</p> <p>Embryos transfer: day 2-3</p> <p>luteal phase support: micronized vaginal progesterone, 600 mg/day, until the tenth week of gestation in cases where a pregnancy was achieved</p> <p>Follow up: clinical pregnancy was confirmed 28-35 days after embryo transfer by a gestational sac under ultrasound. Ongoing pregnancy was defined as fetal heart beat at 10-12 weeks of gestation. Early pregnancy loss was defined as the proportion of patients with initially positive HCG in whom pregnancy failed to develop before 12 weeks of gestation</p>

Tazegul 2008 (Continued)

Outcomes	Clinical and ongoing pregnancy per randomized patient, the duration of stimulation, consumption of gonadotrophins, cycle cancellation rate, the number of oocytes retrieved and embryos transferred The hormone levels throughout the cycle	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based program.
Allocation concealment (selection bias)	High risk	Not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not address by the study
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	Financial support was not reported, however the study appears to be free from other sources of bias

Tehraninejad 2010

Methods	RCT, single-centre trial
Participants	95 PCOs infertile women undergoing IVF/ICSI treatment Inclusion criteria: age < 35 years basal FSH < 10 IU/L and undergoing their first cycle of the ART Exclusion criteria: secondary infertility, previous IVF or ICSI, thyroid dysfunction, hyperprolactinemia, uterine abnormality and solitary ovary Baseline characteristics: Age (years) 28.99 ± 6.1 vs 30.43 ± 5/08. Duration of infertility (years) 7.82 ± 4.70 vs 8.6 ± 4.61 BMI (kg/m ²) 28.99 ± 6.12 vs 30.43 ± 5/08. Baseline FSH (IU/L) 5.4 ± 1.80 vs 5.3 ± 1.22
Interventions	GnRH antagonist (n= 45): OCP for 21 days in the previous cycles + 150-225 IU hMG (Merional) IM based on the patients' age and BMI + 0.25 GnRH antagonist (Cetrotide) when the leading follicle ≈ 14 mm (flexible multiple-dose protocol) GnRH agonist (n= 47): OCP (30 g ethinyl estradiol plus 0.3 mg levonorgestrol) for 21 days + 500 µg busarelin per day (Superfact) subcutaneously, commenced on day 19-20

	<p>of OCP cycle. Once the down-regulation is achieved, the dose of buserelin was reduced to 250 µg daily + 150-225 IU hMG (Merional) intramuscularly once daily depending on patients' age and body mass index (BMI) (GnRH agonist protocol)</p> <p>Oocyte maturation triggering: when at least two leading follicles were 18 mm in diameter, serum E2 levels were measured. If E2 level was measured to be less than 3000 pg/ml, patients in both groups would receive 10,000 IU hCG (Profasi) IM</p> <p>In the control group, if E2 level was > 3000 pg/ml, HMG administration was stopped while Superfact injection was continued. Daily measurement of E2 level was performed and HCG was administered when E2 level fell below 3000 pg/ml (Coasting). In the study group, if E2 > 3000 pg/ml, Superfact 500 mg SQ was administered for final oocyte maturation</p> <p>Oocyte retrieval: 34 - 36 hours later, followed by IVF/ICSI</p> <p>Maximum of embryo transferred: 3</p> <p>Luteal phase support: 800 mg vaginal micronized progesterone (Cyclogest) and 4 mg oral estradiol valerate daily started the evening after oocyte retrieval and continued until a negative pregnancy test or a 10-week gestation</p> <p>Follow up: the serum hCG level on day 16 after oocyte recovery was tested to determine chemical pregnancy, if any, vaginal ultra sonography would be carried out on day 35 of oocyte retrieval for documentation of fetal heart activity and confirming a clinical pregnancy</p>	
Outcomes	<p>The primary outcome measures: incidence of moderate and severe OHSS</p> <p>The secondary endpoints: fertilization and pregnancy rate</p> <p>Additional outcomes: number of oocytes retrieved, number of good quality embryos transferred, E2 level on the day of hCG administration, number of HMG ampoules used and the total days of treatment</p>	
Notes	The diagnosis of OHSS was based on the criteria by Golan et al	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomised schedules
Allocation concealment (selection bias)	Low risk	Sealed in envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Did not reported clearly
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes

Other bias	Unclear risk	Financial support was not reported, however the study appears to be free from other sources of bias
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Xavier 2005

Methods	RCT, single-centre, open-label design
Participants	131 infertile women undergoing IVF/ICSI Inclusion/ Exclusion criteria: patients were considered eligible if they were scheduled for controlled ovarian stimulation and IVF with or without ICSI. Women older than 40 years or with day 3 FSH =10 IU/L, or with more than three previous IVF/ICSI cycles were excluded from the study
Interventions	GnRH antagonist protocol (Fixed): rFSH treatment was begun on day 3 of the menstrual cycle. The starting dose for the first 5 days varied between 150 and 450IU, depending on age and previous experience and was administered daily by sc injection. Thereafter, the dose was adjusted on the basis of ultrasonographic and analytic findings. On day 6 of recombinant FSH (rFSH) treatment, cetorelix was started if the ovarian response was adequate (at least one follicle =13mm or serum estradiol levels =400pg/mL). If the ovarian response was not adequate, cetorelix administration was postponed until ultrasonographic or analytic criteria were achieved (Flexible). Two hundred fifty microgram was administered daily by sc injection. When at least three follicles =17mm were observed, recombinant FSH and cetorelix administration was interrupted and hCG (10.000IU IM) was administered for the timed oocyte retrieval 35h later. Vaginal micronized progesterone was started 24h after oocyte retrieval for luteal support in a standard dose of 600mg daily for 14 days. Serum hCG was to be measured approximately 2 weeks after embryo transfer. Any pregnancy was confirmed by vaginal ultrasound scan at 6 weeks' gestation. GnRH agonist protocol: on cycle days 21-23, 0.6mg of buserelin acetate was started, by daily sc injection until menses had begun and adequate suppression was achieved (serum estradiol level =50pg/mL), at which time treatment with rFSH was started. The starting dose for the first 5 days varied between 150 and 450 IU, depending on age and previous experience of the patient and was administered daily by sc injection. Thereafter, the dose was adjusted on the basis of ultrasonographic and analytic findings and the cycle management was the same in both groups
Outcomes	The main outcome measures for assessing efficacy and safety of both protocols were: the clinical pregnancy rate per cycle and per transfer (gestational sac visualized on ultrasound at 6 weeks gestation), number of oocytes collected, number of days of stimulation, number of days of analogue administration and the number of detected cases of moderate and severe ovarian hyperstimulation syndrome (OHS). Other variables assessed were the total amount of rFSH used, serum estradiol level on the day of hCG administration, number of follicles =15mm on the day of the oocyte retrieval, endometrial thickness on the day of the oocyte retrieval, fertilisation rate, quality of the embryos transferred and the number of cancelled cycles. The quality of embryos used for transfer were classified using the following grading system: (A) no fragmentation; (B) 1-20% fragmentation; (C) 21-50% fragmentation; (D) =51% fragmentation. The OHS classification utilised in this study was the one

Xavier 2005 (Continued)

	proposed by Golan et al	
Notes	Number of participants at randomisation: 131 (cetorelix: 66/ buserelin: 65) Number of participants at stimulation: 112 (cetorelix: 53/ buserelin: 59) Number of participants at OPU: 112 (cetorelix: 53/ buserelin: 59)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table, Randomisation:1:1 (Cetorelix: Buserelin) ratio
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcomes data, however LBR did not addressed by the study
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	Financial support was not reported, however the study appears to be free from other sources of bias

Ye 2009

Methods	RCT, single-centre
Participants	220 IVF/ICSI cycles were included, age 25 to 35 years old, BMI 18-25 kg/m ² ; the number of previous IVF cycles <3, and no previous poor response to ovarian stimulation (poor ovarian response was characterized by cancellation of the cycle due to either poor follicular development or ≤4 cumulus oocyte- complexes collected at oocyte retrieval) ; normal ovulatory cycles (25 to 35 days), both ovaries present and normal uterus; no hormone therapy within the past 3 months; and no current or past diseases affecting ovaries, gonadotrophin, sex steroid secretion, clearance or excretion. Baseline characteristics: Age (range) 30.3±2.8 (24-35) vs 30.2±2.8 (25-35), BMI (range) 20.7±1.9 (16.9-24.9) vs 21.0±1.8 (17.7-25), Basal FSH (IU/L) 6.2±1.6 vs 6.5±1.3
Interventions	Study group: E2 pre-treatment oral estradiol valerate 4 mg preceding the IVF cycle from day 21 until day 2 of next cycle + 225 IU of rFSH (Gonal-F, Serono) from day 3 + 0.25

	<p>GnRH antagonist (Cetrotide) was injected daily when the leading follicles reached 12-14 mm in diameter (flexible)</p> <p>Control group: troptorelin (Decapeptyl) 0.1 mg sc preceding the IVF cycle from day 21, when pituitary down-regulation was achieved, the troptorelin dose was reduced to 0.05 mg/d + 225 IU of r FSH (Gonal-F)</p> <p>Final oocyte maturation triggering: 10,000 IU hCG (Profasi) were given when at least three mature \geq 18 mm follicles were obtained</p> <p>Oocytes retrievals: 36 hrs later.</p> <p>Embryo transfer: 2 to 3 embryos were transferred at 72 hrs after IVF/ ICSI injection.</p> <p>Luteal phase support: I.M, progesterone 80 mg/day starting on the day of oocyte retrieval until the day of pregnancy test. If a pregnancy occurred, progesterone administration was extended up to 10 to 12 weeks of pregnancy</p>	
Outcomes	Number of oocytes collected, MII oocytes, fertilization, implantation, live birth and early pregnancy rate, and hormone profiles (LH, P, E2)	
Notes	The early pregnancy loss was defined as spontaneous abortion before 12 weeks	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include most expected outcomes
Other bias	Unclear risk	Financial support was not reported, however the study appears to be free from other sources of bias

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

Study	Reason for exclusion
Ashrafi 2004	No available data for inclusion
Bonduelle 2010	Retrospective analysis
Cattani 2000	No available data for inclusion
Causio 2004	Quasi-randomised study
Crosignani 2007	RCT in IUI cycles
D'Amato 2004	Quasi-randomised trials, were randomly assigned to all patients on the basis of the day of the week of their first appointment
Eijkemans 2006	Overlap with Heijnen 2007
Engmann 2008 b	RCT, patient randomised on the day of HCG to receive, evaluate the effect of using vaginal micronized E2 administration, in addition to P supplementation as luteal support, on clinical pregnancy rates in patients undergoing their first cycle of IVF/intracytoplasmic sperm injection (ICSI) treatment
Ficicioglu 2010	Retrospective study
Freitas 2004	No available data for inclusion
Ghosh 2003	Marked heterogeneity between the two study groups
Guivarc'h-Leveque 2009	RCT, quasi-randomised, as odd or even days of the consultation delivery of treatment
Kdous 2009	Retrospective study
Kim 2010	Retrospective study
Klerk 2007	Overlap with Heijnen 2007 ; Eijkemans 2006a ; Polinder 2007
Kyono 2004	Duplicate publication of data from another included study (Kyono et al 2004)
Lee 2008	Prospective observational/comparative study
Lin 1999	No available data for inclusion. Surrogate outcome. Failure to contact authors
Londra 2003	Not reported to be an RCT
Ludwig 2000	Duplicate publication of data from another included study (Albano et al 2000)
Marci 2002	Duplicate publication of data from another included study

(Continued)

Orvieto 2007	Prospective observational study
Orvieto 2008	Retrospective trial
Pabuccu 2005	No available data for inclusion.
Perino 2002	No available data for inclusion. Failure to contact authors
Pinto 2009	Prospective observational study
Polinder 2007	Overlap with Heijnen 2007
Prapas 2005	RCT, some women were used twice as donors
Shamma 2003	Donor oocyte cycles
Sonntag 2004	Duplicate publication of data from another included study (European and Middle East Orgalutran Study, 2001)
Vlaisavljevic 2003	Inadequate randomisation (quasi-randomised trial)
Willman 2005	No available data for inclusion
Zikopoulos 2005	IUI treatment cycles instead of IVF/ICSI

DATA AND ANALYSES

Comparison 1. GnRH antagonist versus long course GnRH agonist

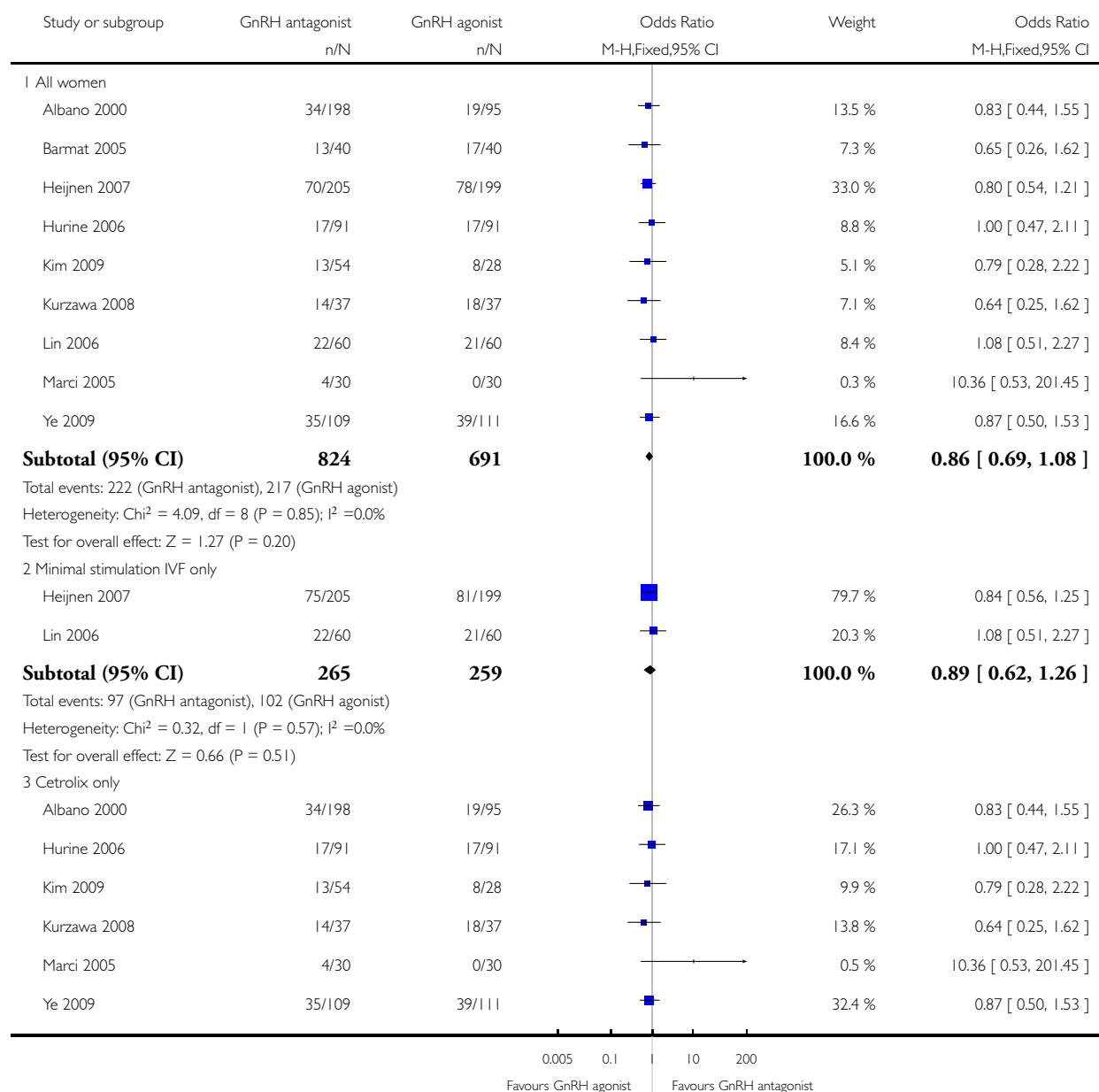
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per women randomised	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All women	9	1515	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.08]
1.2 Minimal stimulation IVF only	2	524	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.62, 1.26]
1.3 Cetrolx only	6	911	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.23]
1.4 Ganirelix only	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.26, 1.62]
2 Ongoing pregnancy rate per women randomised	28		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All women	28	5014	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.00]
2.2 Women with PCOS	7	727	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.67, 1.22]
2.3 Minimal stimulation IVF only	4	878	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.26]
2.4 Women receiving GnRH antagonist plus OCP	10	1250	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.09]
2.5 Flexible protocol only	15	1635	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.23]
2.6 Fixed protocol only	9	2392	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.06]
2.7 Cetrolx only	12	1536	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.19]
2.8 Ganirelix only	12	2722	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.06]
3 Clinical pregnancy rate per women randomised	41		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 All women	41	6571	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.94]
3.2 Women with PCOS	6	660	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.64, 1.19]
3.3 Poor responders	6	919	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.02]
3.4 Women receiving GnRH antagonist plus OCP	12	1236	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.66, 1.06]
4 Miscarriage rate per clinical pregnancy rate	27	1647	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.70, 1.31]
5 Ovarian hyperstimulation per woman randomised	29		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 All women	29	5417	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.05, -0.02]
5.2 Regular population	21	4634	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.03, -0.01]
5.3 Women with PCOS	8	783	Risk Difference (M-H, Fixed, 95% CI)	-0.10 [-0.14, -0.07]
6 Cycle cancellation	24		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cancelled or coasting due to high risk of OHSS	16	3512	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.33, 0.76]
6.2 Cancellation due to poor ovarian response	17	3200	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.56, 1.03]

Analysis 1.1. Comparison 1 GnRH antagonist versus long course GnRH agonist, Outcome 1 Live birth rate per women randomised.

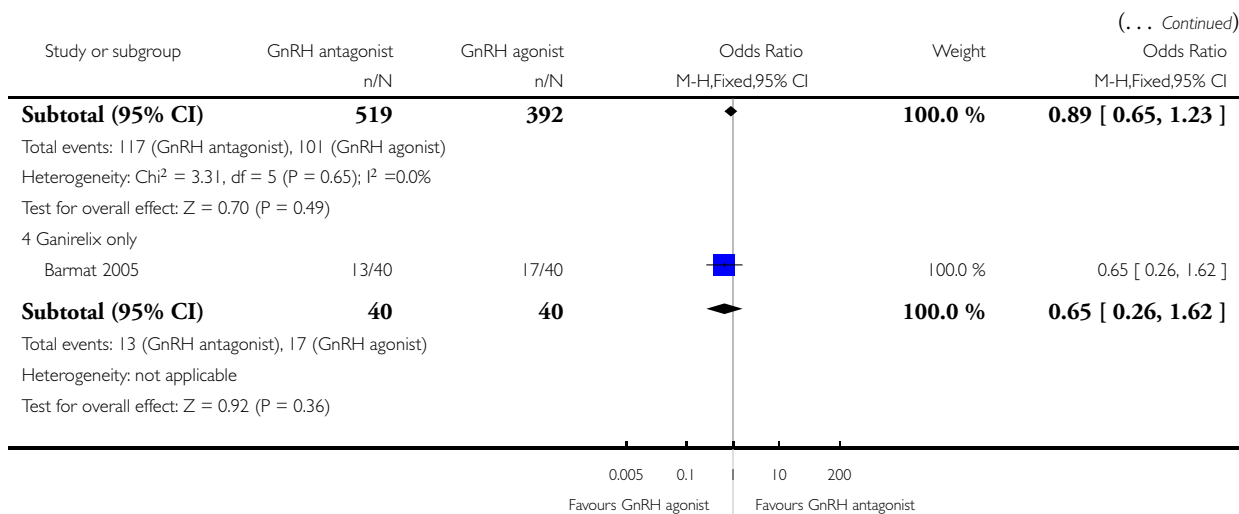
Review: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

Comparison: 1 GnRH antagonist versus long course GnRH agonist

Outcome: 1 Live birth rate per women randomised



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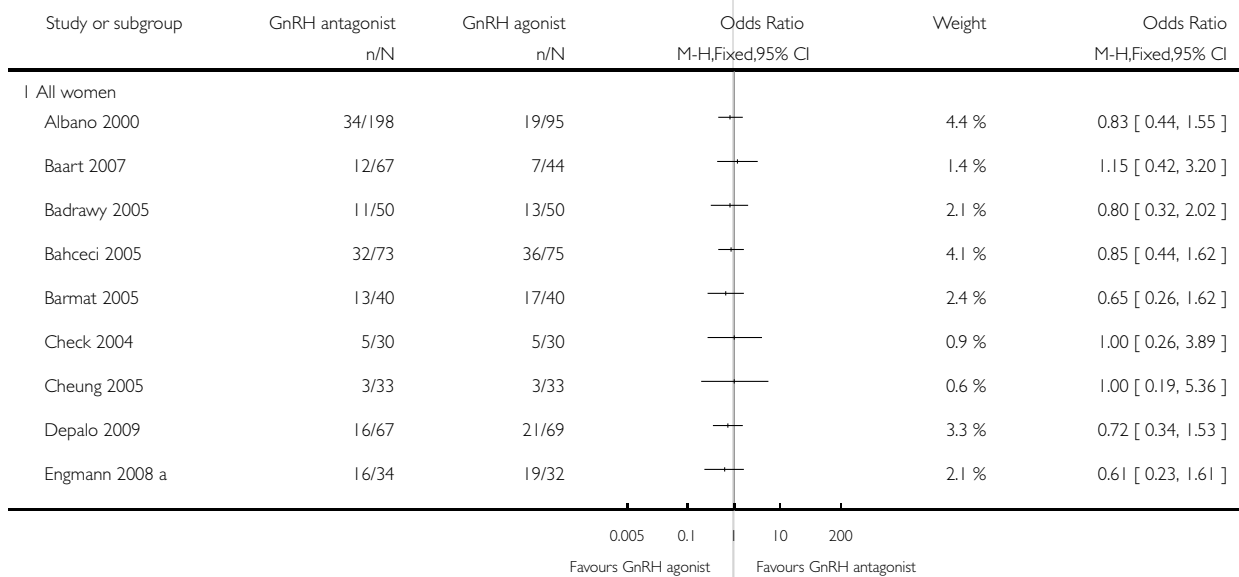


Analysis 1.2. Comparison 1 GnRH antagonist versus long course GnRH agonist, Outcome 2 Ongoing pregnancy rate per women randomised.

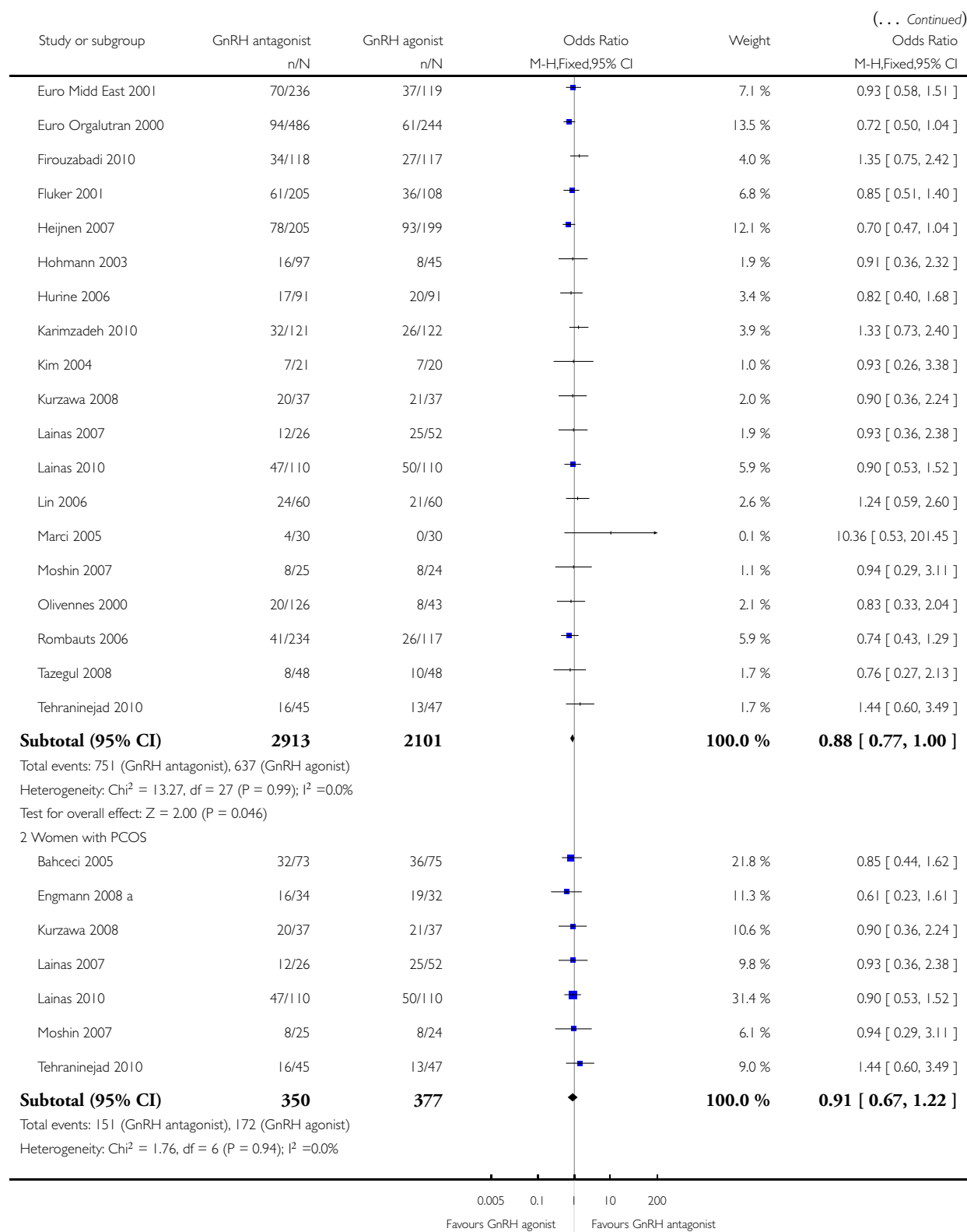
Review: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

Comparison: 1 GnRH antagonist versus long course GnRH agonist

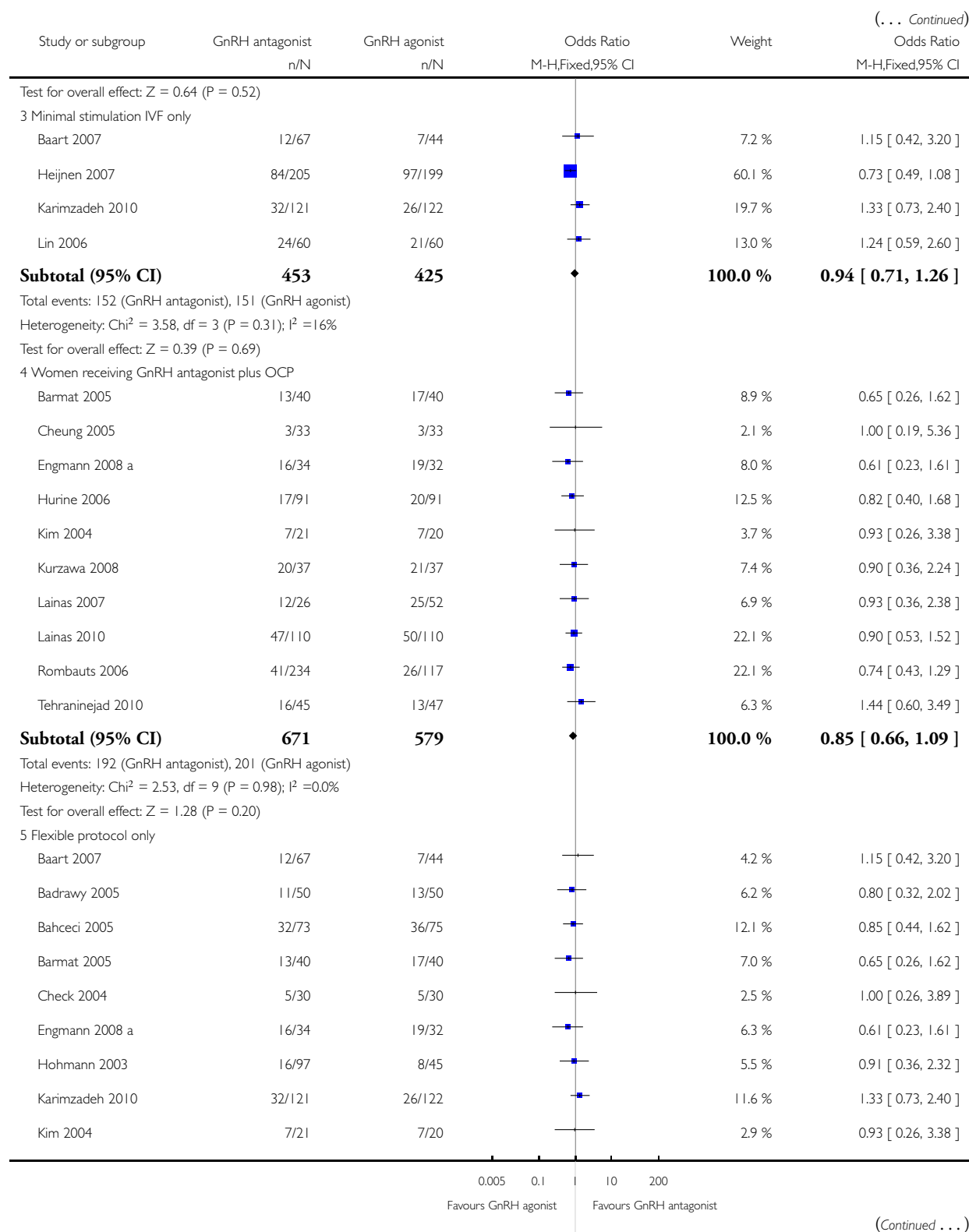
Outcome: 2 Ongoing pregnancy rate per women randomised

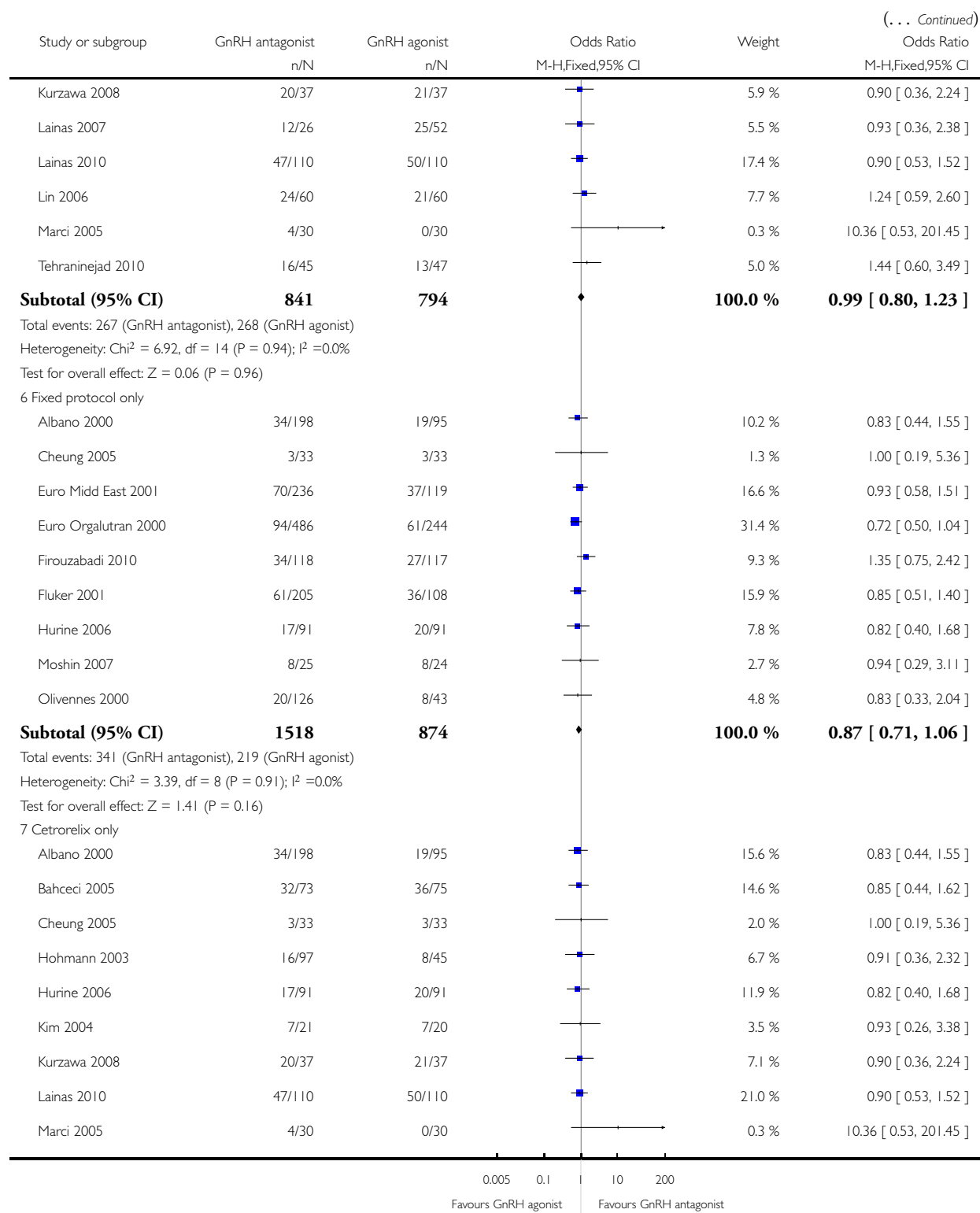


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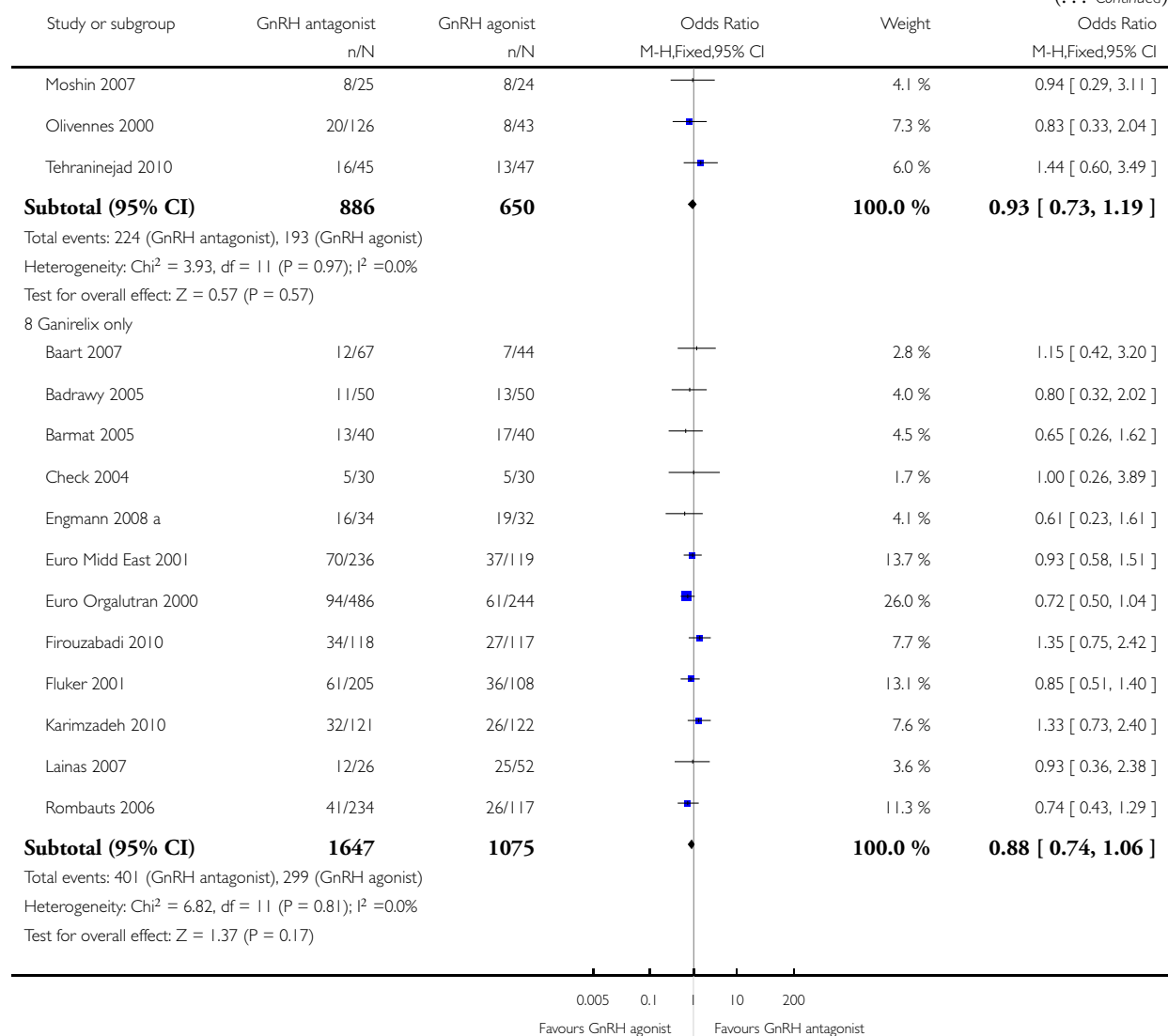
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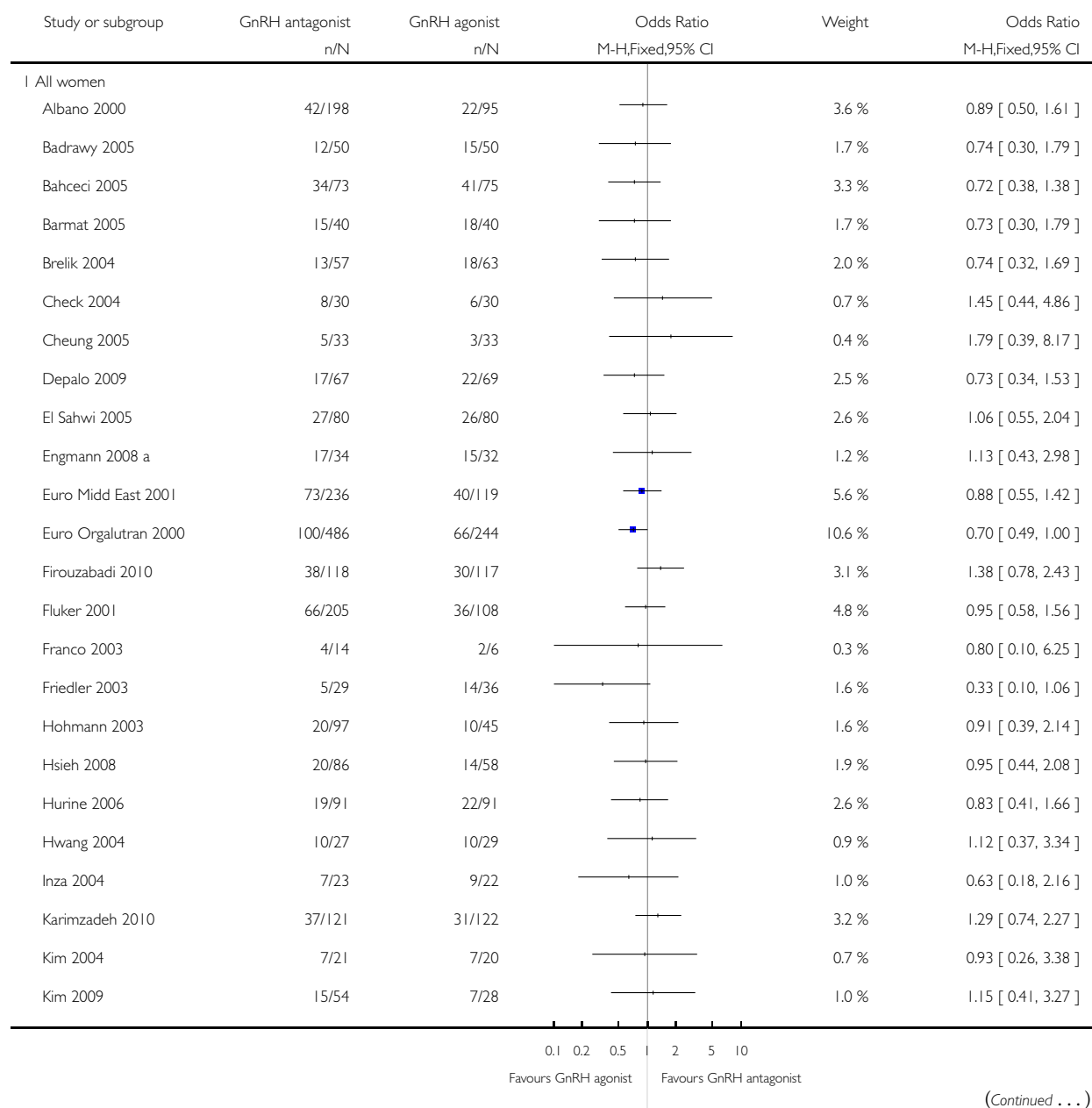


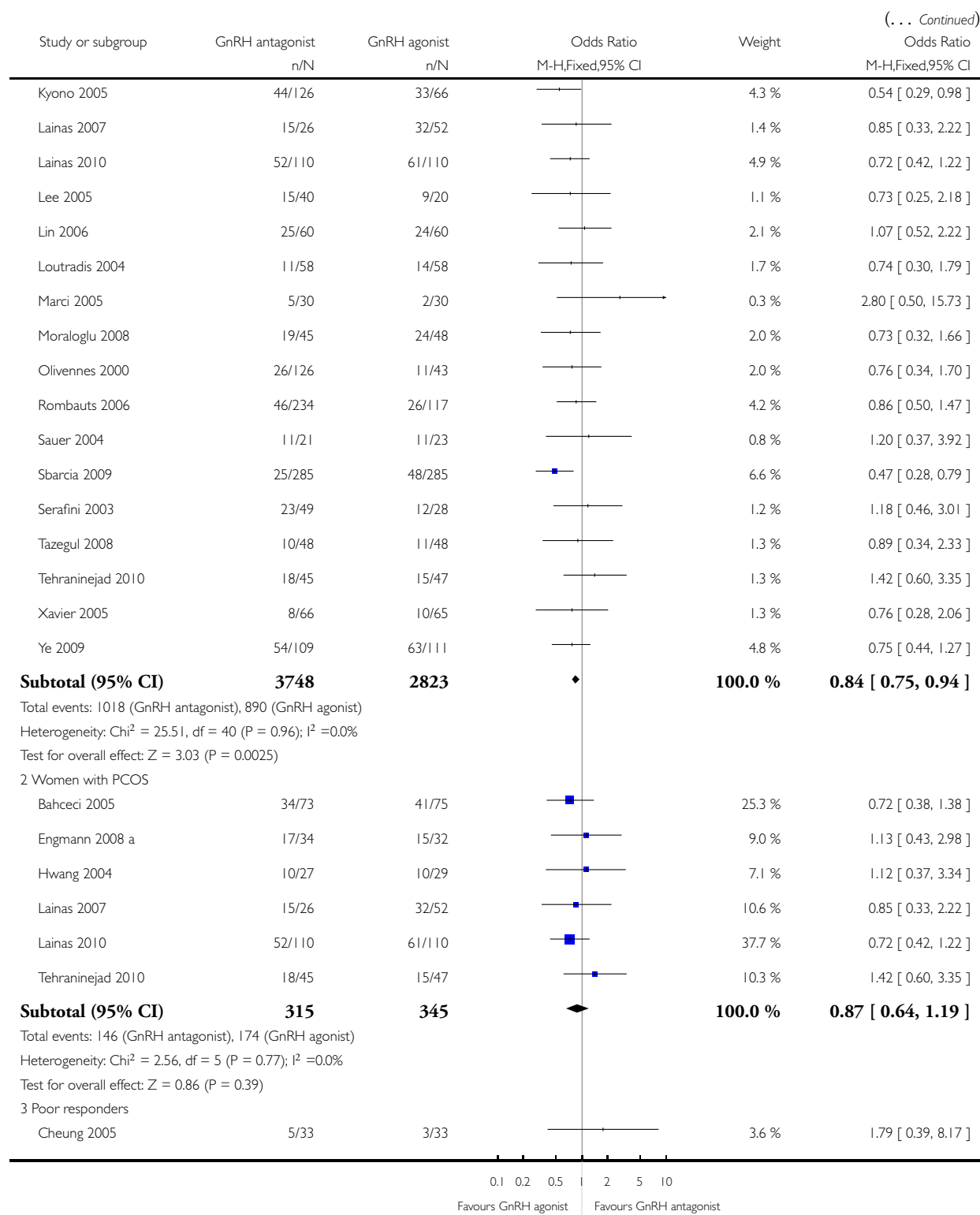
Analysis 1.3. Comparison 1 GnRH antagonist versus long course GnRH agonist, Outcome 3 Clinical pregnancy rate per women randomised.

Review: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

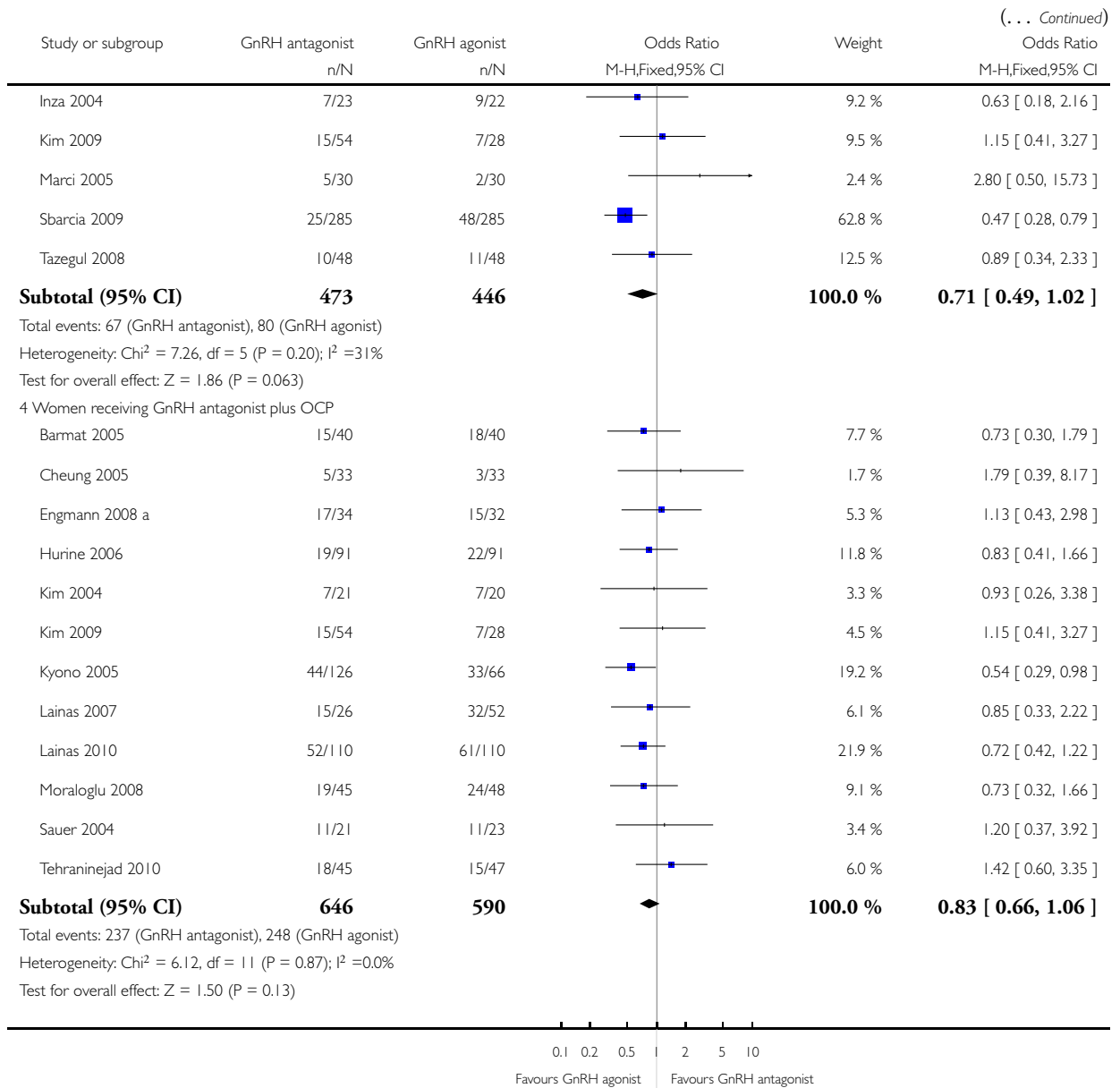
Comparison: 1 GnRH antagonist versus long course GnRH agonist

Outcome: 3 Clinical pregnancy rate per women randomised





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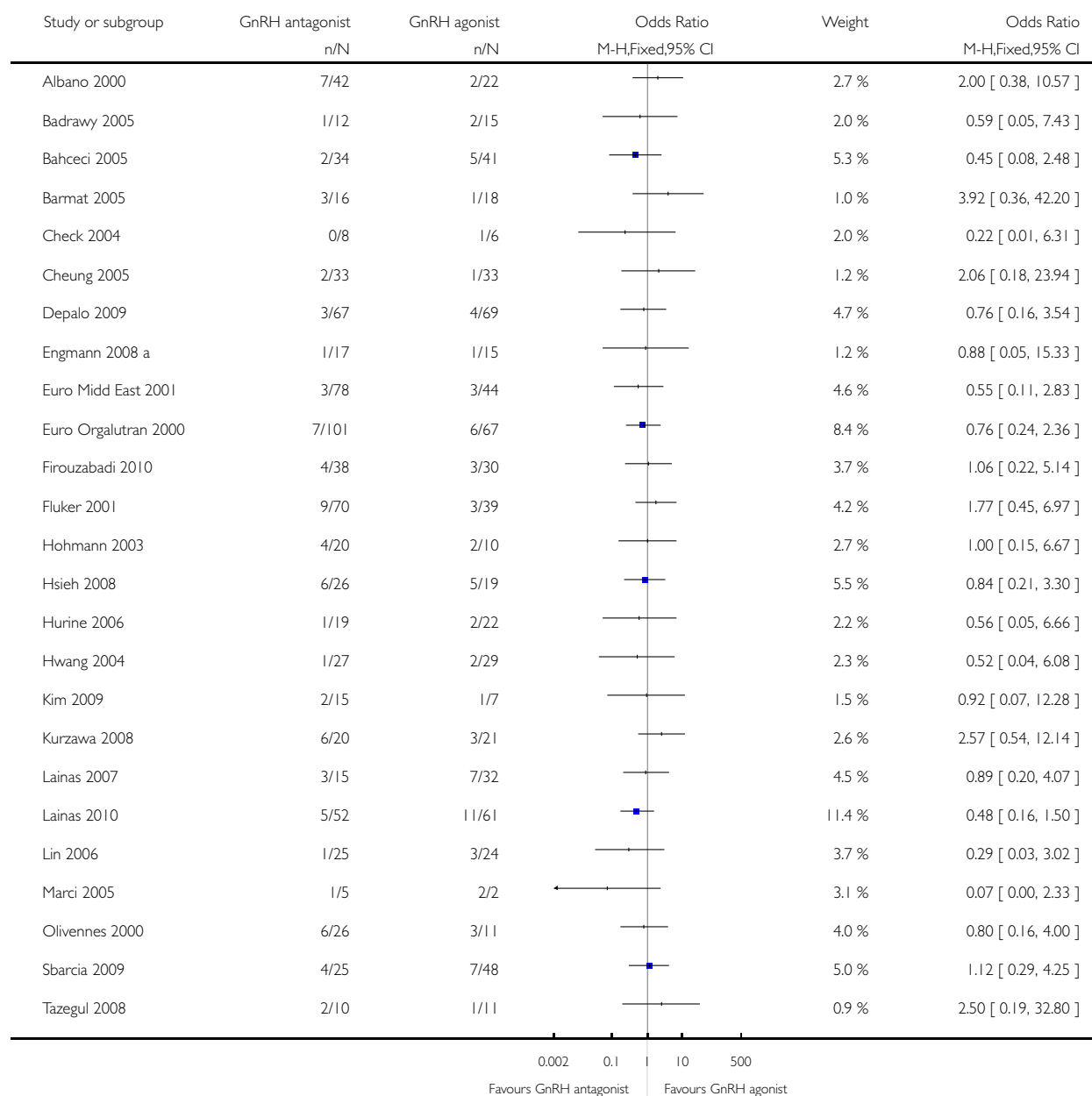


Analysis 1.4. Comparison 1 GnRH antagonist versus long course GnRH agonist, Outcome 4 Miscarriage rate per clinical pregnancy rate.

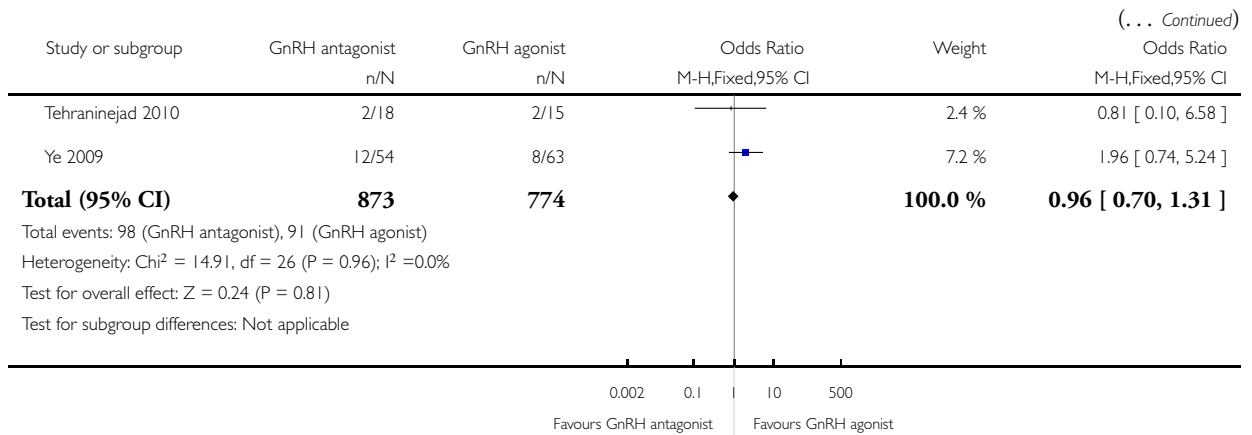
Review: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

Comparison: 1 GnRH antagonist versus long course GnRH agonist

Outcome: 4 Miscarriage rate per clinical pregnancy rate



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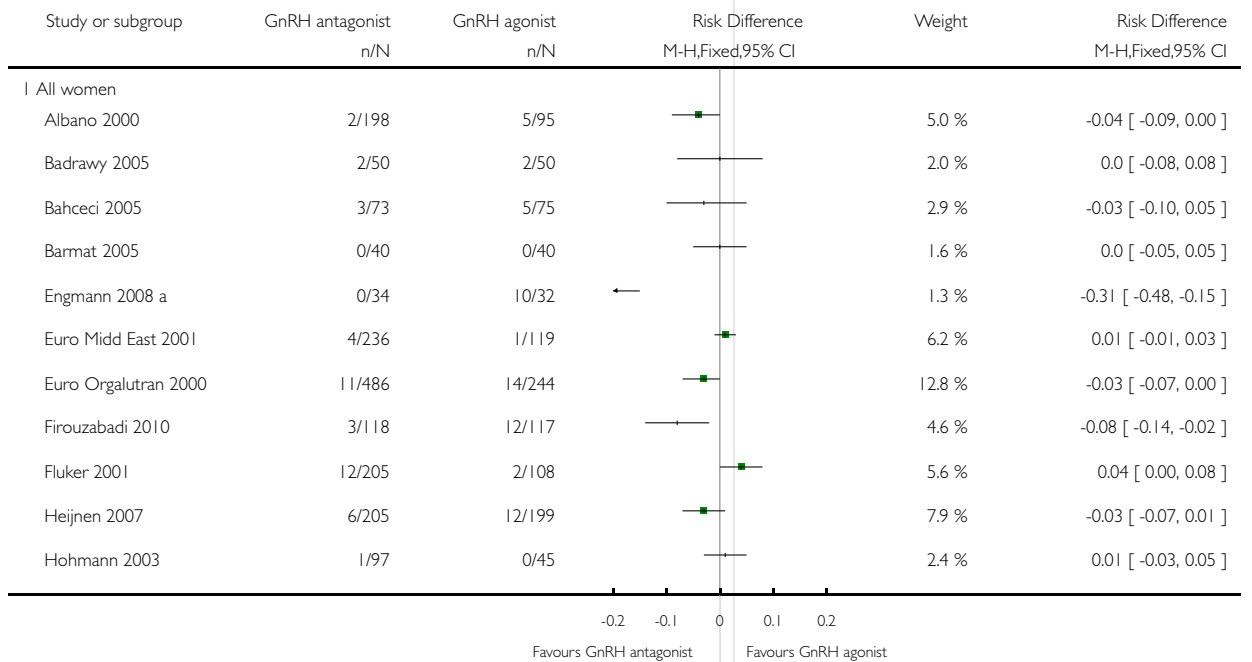


Analysis 1.5. Comparison 1 GnRH antagonist versus long course GnRH agonist, Outcome 5 Ovarian hyperstimulation per woman randomised.

Review: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

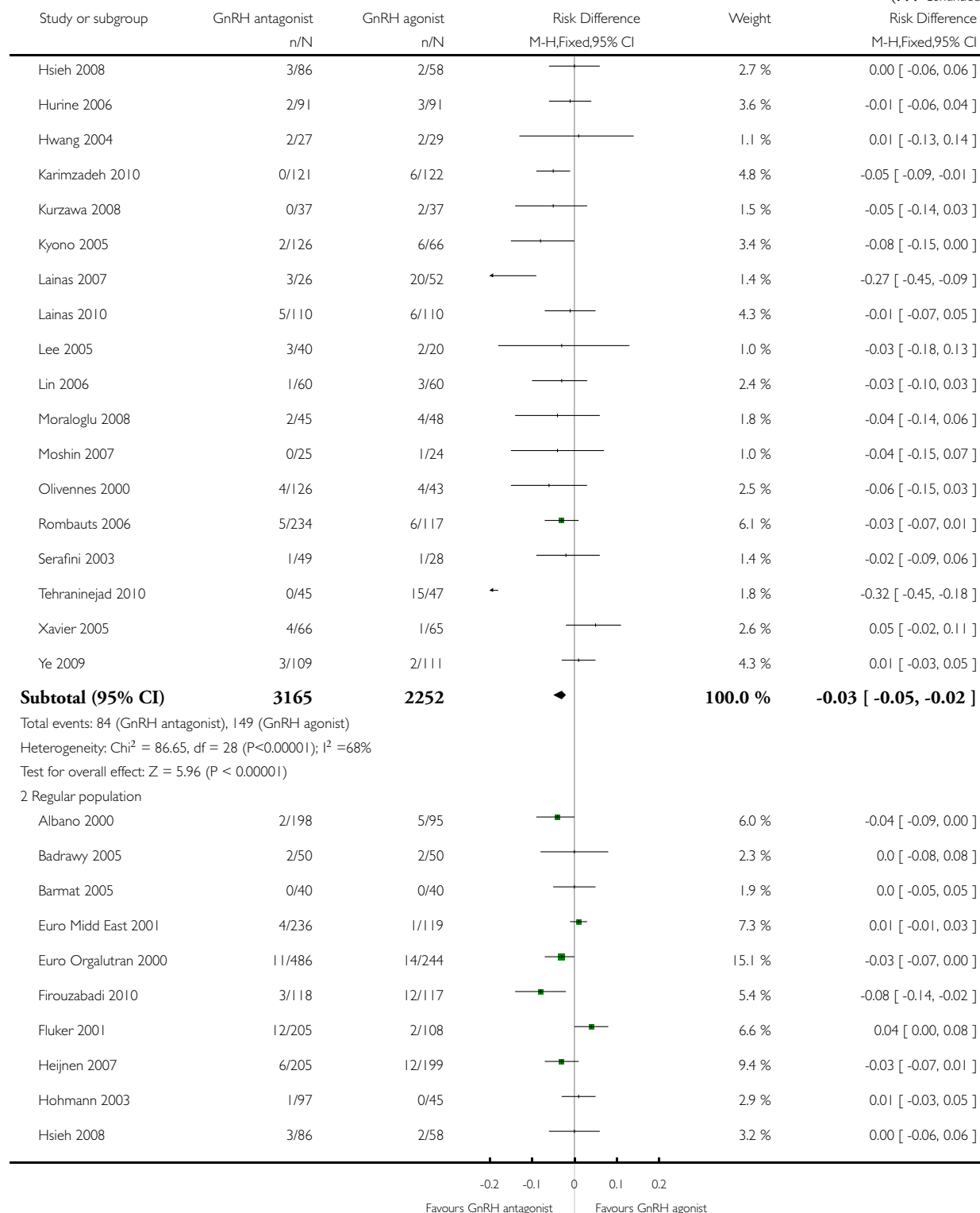
Comparison: 1 GnRH antagonist versus long course GnRH agonist

Outcome: 5 Ovarian hyperstimulation per woman randomised



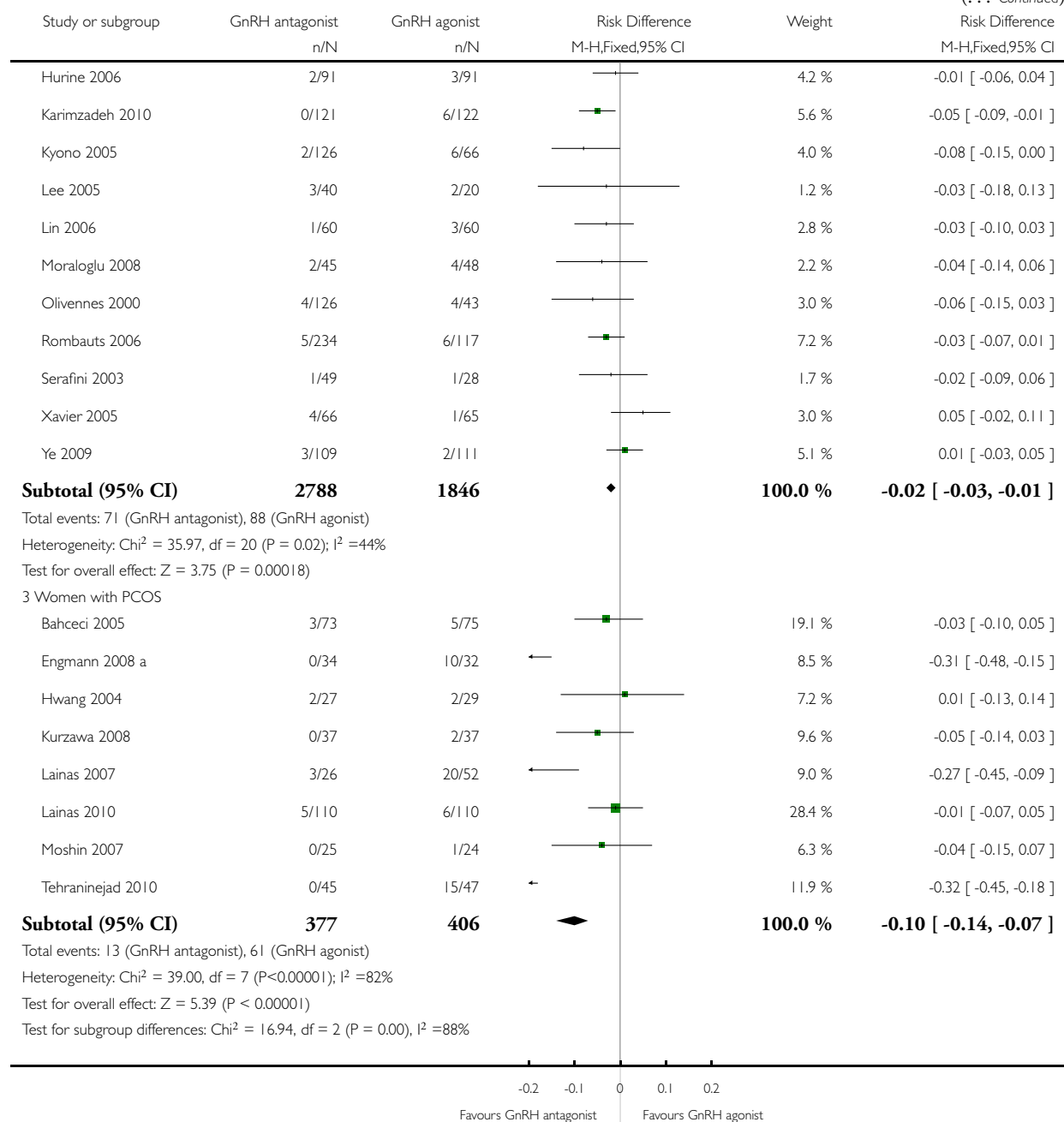
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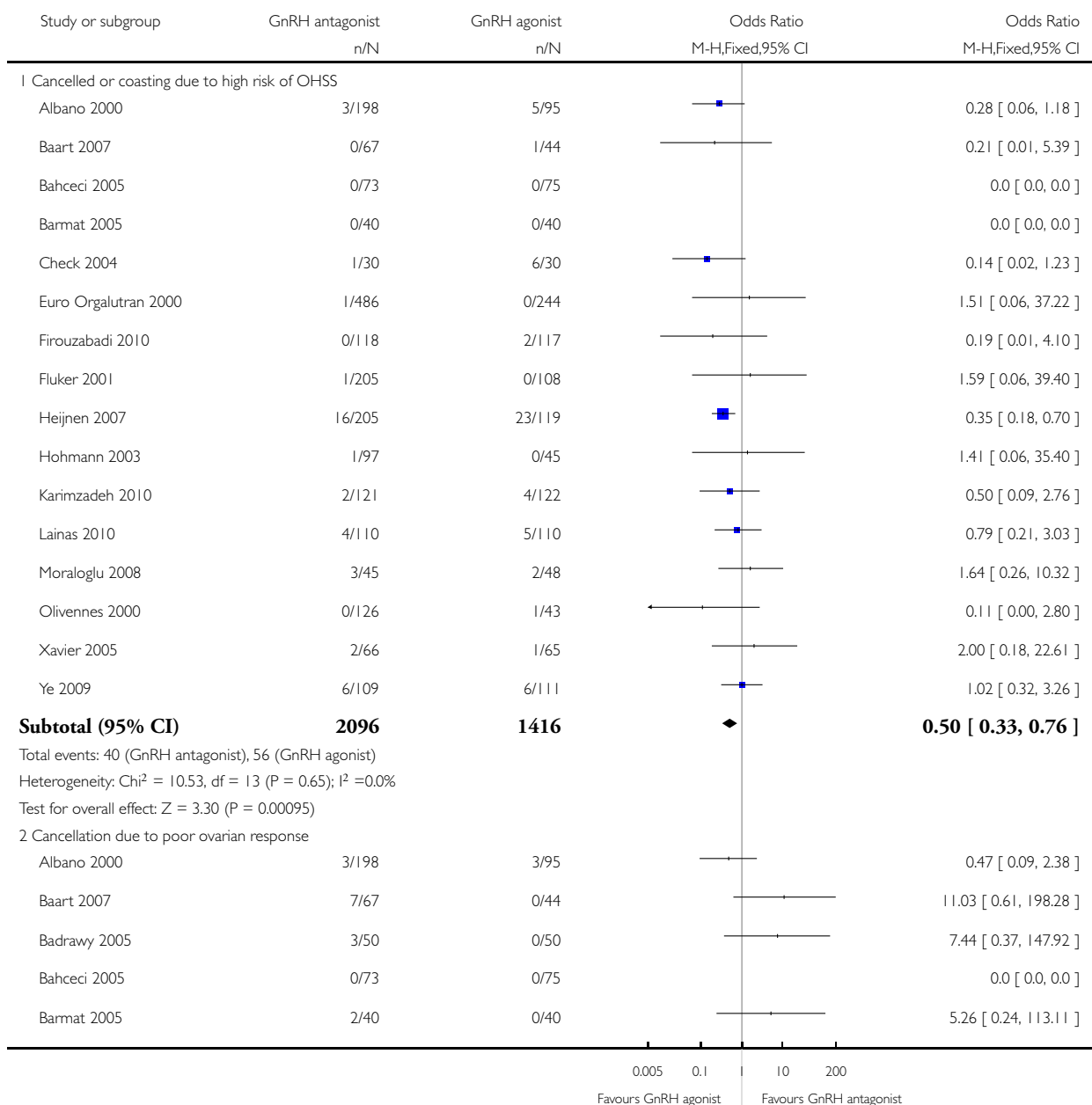


Analysis 1.6. Comparison 1 GnRH antagonist versus long course GnRH agonist, Outcome 6 Cycle cancellation.

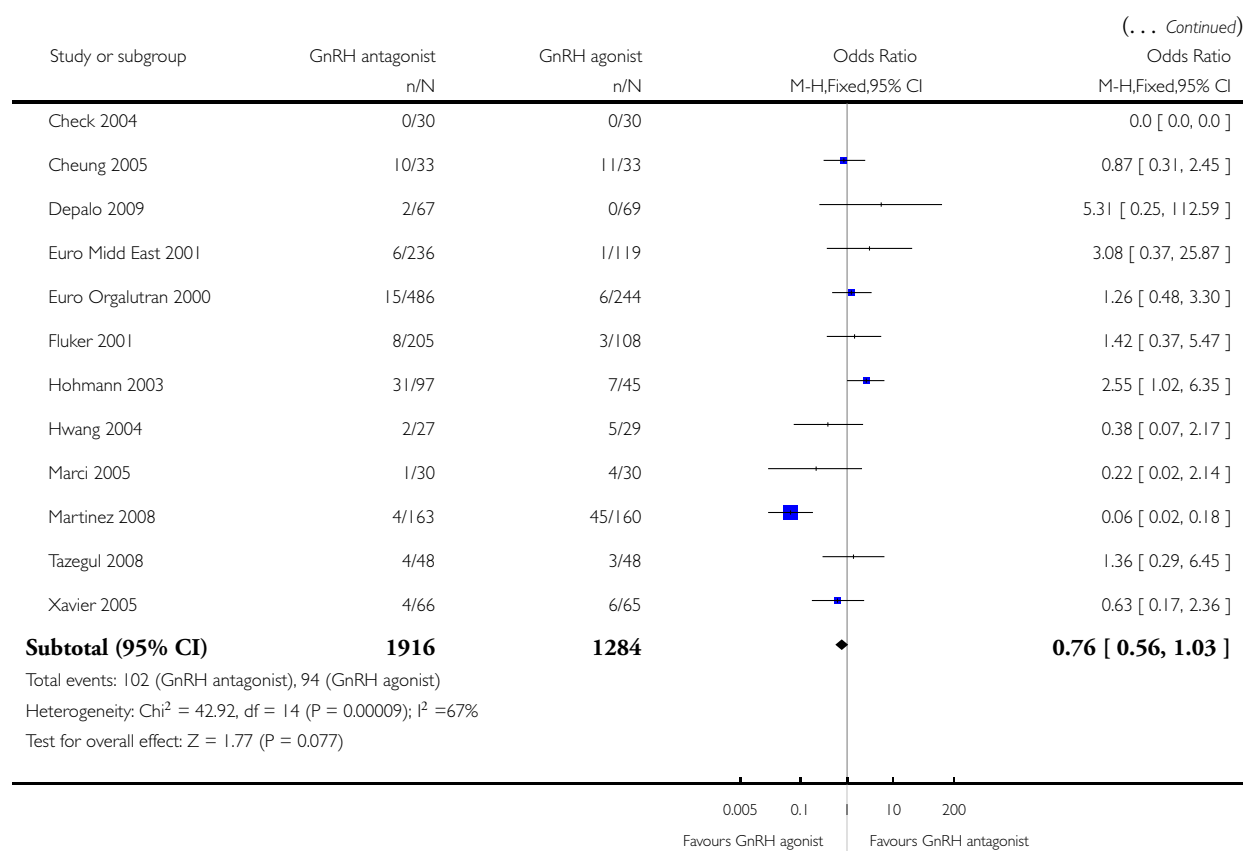
Review: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology

Comparison: 1 GnRH antagonist versus long course GnRH agonist

Outcome: 6 Cycle cancellation



(Continued . . .)



APPENDICES

Appendix I. Cochrane Central Register of Controlled Trials (CENTRAL)

<1st Quarter 2010>

- 1 Hormone Antagonists/ (211)
- 2 gonadotropin releasing hormone antagonist\$.tw. (45)
- 3 gonadotrophin releasing hormone antagonist\$.tw. (18)
- 4 GnRH antagonist\$.tw. (289)
- 5 Gn-RH antagonist\$.tw. (0)
- 6 (Cetrorelix or Cetrotide\$).tw. (101)
- 7 Ganirelix.tw. (61)
- 8 (Abarelix or Plenaxis).tw. (4)
- 9 Antagon.tw. (9)
- 10 or/1-9 (487)
- 11 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (1559)

- 12 gonadotropin releasing hormone agonist\$.tw. (277)
- 13 gonadotrophin releasing hormone agonist\$.tw. (128)
- 14 GnRH agonist\$.tw. (563)
- 15 Gn-RH agonist\$.tw. (4)
- 16 (buserelin or goserelin).tw. (551)
- 17 (leuprolide or nafarelin).tw. (428)
- 18 triptorelin.tw. (139)
- 19 (Lupron or Eligard).tw. (27)
- 20 (Suprefact or Suprecor).tw. (8)
- 21 Synarel.tw. (3)
- 22 Supprelin.tw. (0)
- 23 Zoladex.tw. (197)
- 24 deslorelin.tw. (8)
- 25 Suprelorin.tw. (0)
- 26 Ovuplant.tw. (0)
- 27 (decapeptyl or trelstar).tw. (50)
- 28 (profact or receptal).tw. (2)
- 29 suprecur.tw. (0)
- 30 tiloryth.tw. (0)
- 31 or/11-30 (2300)
- 32 10 and 31 (245)
- 33 limit 32 to yr="2006 - 2008" (80)
- 34 from 33 keep 1-80 (80)

Appendix 2. Ovid MEDLINE(R)

<1950 to January to April 2010>

- 1 Hormone Antagonists/ (3529)
- 2 gonadotropin releasing hormone antagonist\$.tw. (314)
- 3 gonadotrophin releasing hormone antagonist\$.tw. (83)
- 4 GnRH antagonist\$.tw. (1373)
- 5 Gn-RH antagonist\$.tw. (7)
- 6 (Cetrorelix or Cetrotide\$.tw. (319)
- 7 Ganirelix.tw. (98)
- 8 (Abarelix or Plenaxis).tw. (34)
- 9 Antagon.tw. (11)
- 10 or/1-9 (4789)
- 11 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (24648)
- 12 gonadotropin releasing hormone agonist\$.tw. (1297)
- 13 gonadotrophin releasing hormone agonist\$.tw. (373)
- 14 GnRH agonist\$.tw. (2551)
- 15 Gn-RH agonist\$.tw. (45)
- 16 (buserelin or goserelin).tw. (1698)
- 17 (leuprolide or nafarelin).tw. (1420)
- 18 triptorelin.tw. (387)
- 19 (Lupron or Eligard).tw. (130)
- 20 (Suprefact or Suprecor).tw. (21)
- 21 Synarel.tw. (11)
- 22 Supprelin.tw. (1)
- 23 Zoladex.tw. (352)

24 deslorelin.tw. (119)
 25 Suprelorin.tw. (1)
 26 Ovuplant.tw. (9)
 27 (decapeptyl or trelstar).tw. (194)
 28 (profact or receptal).tw. (20)
 29 suprecur.tw. (4)
 30 tiloryth.tw. (0)
 31 or/11-30 (25801)
 32 10 and 31 (1587)
 33 randomized controlled trial.pt. (262320)
 34 controlled clinical trial.pt. (78055)
 35 (randomized or randomised).ab. (206782)
 36 placebo.ab. (108612)
 37 drug therapy.fs. (1276917)
 38 randomly.ab. (126371)
 39 trial.ab. (180887)
 40 groups.ab. (877019)
 41 or/33-40 (2330804)
 42 (animals not (humans and animals)).sh. (3230706)
 43 41 not 42 (1974664)
 44 32 and 43 (541)
 45 limit 44 to yr="2006 - 2009" (182)
 46 from 45 keep 1-182 (182)

Appendix 3. EMBASE

<1980 to 2010>

1 Hormone Antagonist/ (534)
 2 Gonadorelin Antagonist/ (2570)
 3 gonadotropin releasing hormone antagonist\$.tw. (313)
 4 GnRh Antagonist\$.tw. (1396)
 5 Luteinizing Hormone Releasing Hormone Antagonist\$.tw. (68)
 6 Lhrh Antagonist\$.tw. (274)
 7 Cetorelix.tw. (376)
 8 cetorelix/ or ganirelix/ (1140)
 9 ganirelix.tw. (144)
 10 Cetrotide.tw. (311)
 11 Antagon.tw. (87)
 12 Orgalutr?n.tw. (191)
 13 or/1-12 (4011)
 14 Gonadorelin Agonist/ (7092)
 15 GnRH agonist\$.tw. (2541)
 16 gonadotropin releasing hormone agonist\$.tw. (1277)
 17 Lhrh Agonist\$.tw. (876)
 18 Luteinizing Hormone Releasing Hormone Agonist\$.tw. (396)
 19 TRIPTORELIN/ (2665)
 20 Triptorelin.tw. (429)
 21 (Arvekap or Decapeptyl or Detryptorelin or Trelstar).mp. or Tryptorelin.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1351)
 22 (Arvekap or Decapeptyl or Detryptorelin or Trelstar or Tryptorelin).tw. (1350)
 23 BUSERELIN/ (3311)

24 Buserelin.tw. (1147)
 25 (Bigonist or Busereline or Receptal or Superfact or Suprefact).tw. (954)
 26 or/14-25 (12427)
 27 13 and 26 (1478)
 28 Clinical Trial/ (529466)
 29 Randomized Controlled Trial/ (165330)
 30 exp randomization/ (26487)
 31 Single Blind Procedure/ (7943)
 32 Double Blind Procedure/ (71265)
 33 Crossover Procedure/ (20937)
 34 Placebo/ (122877)
 35 Randomized controlled trial\$.tw. (32123)
 36 Rct.tw. (2644)
 37 random allocation.tw. (633)
 38 randomly allocated.tw. (10096)
 39 allocated randomly.tw. (1344)
 40 (allocated adj2 random).tw. (559)
 41 Single blind\$.tw. (7397)
 42 Double blind\$.tw. (84141)
 43 ((treble or triple) adj blind\$.tw. (139)
 44 placebo\$.tw. (109040)
 45 prospective study/ (79804)
 46 or/28-45 (696200)
 47 case study/ (5906)
 48 case report.tw. (118159)
 49 abstract report/ or letter/ (489853)
 50 or/47-49 (611661)
 51 46 not 50 (671950)
 52 27 and 51 (525)
 53 limit 52 to yr="2007 - 2009" (124)
 54 from 53 keep 1-124 (124)

Appendix 4. PsycINFO

PsycINFO <1806 to February to April 2010>

1 Hormone Antagonists/ (0)
 2 gonadotropin releasing hormone antagonist\$.tw. (4)
 3 gonadotrophin releasing hormone antagonist\$.tw. (0)
 4 GnRH antagonist\$.tw. (9)
 5 Gn-RH antagonist\$.tw. (0)
 6 (Cetrorelix or Cetrotide\$.tw. (0)
 7 Ganirelix.tw. (0)
 8 (Abarelix or Plenaxis).tw. (0)
 9 Antagon.tw. (0)
 10 or/1-9 (10)
 11 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (0)
 12 gonadotropin releasing hormone agonist\$.tw. (34)
 13 gonadotrophin releasing hormone agonist\$.tw. (2)
 14 GnRH agonist\$.tw. (26)
 15 Gn-RH agonist\$.tw. (0)
 16 (buserelin or goserelin).tw. (13)

- 17 (leuprolide or nafarelin).tw. (38)
- 18 triptorelin.tw. (10)
- 19 (Lupron or Eligard).tw. (4)
- 20 (Suprefact or Suprecor).tw. (0)
- 21 Synarel.tw. (0)
- 22 Supprelin.tw. (0)
- 23 Zoladex.tw. (3)
- 24 deslorelin.tw. (1)
- 25 Suprelorin.tw. (0)
- 26 Ovuplant.tw. (0)
- 27 (decapeptyl or trelstar).tw. (2)
- 28 (profact or receptal).tw. (0)
- 29 suprecur.tw. (0)
- 30 tiloryth.tw. (0)
- 31 or/11-30 (96)
- 32 10 and 31 (1)
- 33 from 32 keep 1 (1)

WHAT'S NEW

Last assessed as up-to-date: 28 February 2010.

Date	Event	Description
7 July 2011	Amended	Minor amendments to new citation version published May 2011

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 4, 2001

Date	Event	Description
13 April 2011	New citation required and conclusions have changed	The conclusion has changed
13 April 2011	New search has been performed	<ul style="list-style-type: none"> • Authorship: new author added (Mohamed AFM Youssef) and order of authors changed • 27 new studies were added • New comparisons: cetrorelix versus ganirelix • New subgroups: poor responders; PCOS; GnRH antagonist plus OCP; flexible antagonist protocol; fixed antagonist protocol; mild IVF • A date limited search of Cochrane Menstrual Disorders and Subfertility Group Specialised Register, CENTRAL from April 2010 to April 2011 was run. 18

(Continued)

		studies have been entered into the Classification pending references section of this update. These studies will be appraised for inclusion or exclusion in the next update of this review, due April 2012.
13 June 2008	Amended	Converted to new review format.
19 May 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Hesham Al-Inany: took the lead in writing the protocol, review, and update performing initial searches of databases for trials, was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, and was responsible for statistical analysis and interpretation of the data.

Mohamed Abdel Fattah Mahmoud Youssef: performed updated searches of databases for new trials, was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, and was responsible for statistical analysis and interpretation of the data.

Mohamed Aboulghar: commented on drafts of the protocol and review.

Frank JM Broekmans: contributed to discussion and commented on review.

Monique D Sterrenburg: contributed to discussion and commented on review.

Janine G Smit: contributed to data analysis checks, and discussion and commented on review.

Ahmed Abou-Setta: was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, and contributed to discussion and interpretation of results.

DECLARATIONS OF INTEREST

Professor Dr Mohamed Aboulghar was an investigator in one of the included trials, the European Middle-East Orgalutran trial [Euro Midd East 2001](#)

SOURCES OF SUPPORT

Internal sources

- No source of support, Not specified.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Reproductive Techniques, Assisted; Gonadotropin-Releasing Hormone [agonists; *antagonists & inhibitors]; Ovarian Hyperstimulation Syndrome [prevention & control]; Ovulation Induction [methods]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans