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Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction (Review)

Siristatidis CS, Gibreel A, Basios G, Maheshwari A, Bhattacharya S

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[Intervention Review]

Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction

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ABSTRACT

Background

Gonadotrophin-releasing hormone agonists (GnRHa) are commonly used in assisted reproduction technology (ART) cycles to prevent a luteinising hormone surge during controlled ovarian hyperstimulation (COH) prior to planned oocyte retrieval, thus optimising the chances of live birth.

Objectives

To evaluate the effectiveness of the different GnRHa protocols as adjuncts to COH in women undergoing ART cycles.

Search methods

We searched the following databases from inception to April 2015: the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2015, Issue 3), MEDLINE, EMBASE, CINAHL, PsycINFO, and registries of ongoing trials. Reference lists of relevant articles were also searched.

Selection criteria

We included randomised controlled trials (RCTs) comparing any two protocols of GnRHa used in in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles in subfertile women.

Data collection and analysis

Two review authors independently selected studies, assessed trial eligibility and risk of bias, and extracted the data. The primary outcome measure was number of live births or ongoing pregnancies per woman/couple randomised. Secondary outcome measures were number of clinical pregnancies, number of oocytes retrieved, dose of gonadotrophins used, adverse effects (pregnancy losses, ovarian hyperstimulation, cycle cancellation, and premature luteinising hormone (LH) surges), and cost and acceptability of the regimens. We combined data to calculate odds ratios (OR) for dichotomous variables and mean differences (MD) for continuous variables, with 95% confidence intervals (CIs). We assessed statistical heterogeneity using the I^2 statistic. We assessed the overall quality of the evidence for the main comparisons using 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methods.

Main results

We included 37 RCTs (3872 women), one ongoing trial, and one trial awaiting classification. These trials made nine different comparisons between protocols. Twenty of the RCTs compared long protocols and short protocols. Only 19/37 RCTs reported live birth or ongoing pregnancy.

There was no conclusive evidence of a difference between a long protocol and a short protocol in live birth and ongoing pregnancy rates (OR 1.30, 95% CI 0.94 to 1.81; 12 RCTs, n = 976 women, I^2 = 15%, low quality evidence). Our findings suggest that in a population in which 14% of women achieve live birth or ongoing pregnancy using a short protocol, between 13% and 23% will achieve live birth or ongoing pregnancy using a long protocol. There was evidence of an increase in clinical pregnancy rates (OR 1.50, 95% CI 1.18 to 1.92; 20 RCTs, n = 1643 women, I^2 = 27%, moderate quality evidence) associated with the use of a long protocol.

There was no evidence of a difference between the groups in terms of live birth and ongoing pregnancy rates when the following GnRHa protocols were compared: long versus ultrashort protocol (OR 1.78, 95% CI 0.72 to 4.36; one RCT, n = 150 women, low quality evidence), long luteal versus long follicular phase protocol (OR 1.89, 95% CI 0.87 to 4.10; one RCT, n = 223 women, low quality evidence), when GnRHa was stopped versus when it was continued (OR 0.75, 95% CI 0.42 to 1.33; three RCTs, n = 290 women, I^2 = 0%, low quality evidence), when the dose of GnRHa was reduced versus when the same dose was continued (OR 1.02, 95% CI 0.68 to 1.52; four RCTs, n = 407 women, I^2 = 0%, low quality evidence), when GnRHa was discontinued versus continued after human chorionic gonadotrophin (HCG) administration in the long protocol (OR 0.89, 95% CI 0.49 to 1.64; one RCT, n = 181 women, low quality evidence), and when administration of GnRHa lasted for two versus three weeks before stimulation (OR 1.14, 95% CI 0.49 to 2.68; one RCT, n = 85 women, low quality evidence). Our primary outcomes were not reported for any other comparisons.

Regarding adverse events, there were insufficient data to enable us to reach any conclusions except about the cycle cancellation rate. There was no conclusive evidence of a difference in cycle cancellation rate (OR 0.95, 95% CI 0.59 to 1.55; 11 RCTs, n = 1026 women, I^2 = 42%, low quality evidence) when a long protocol was compared with a short protocol. This suggests that in a population in which 9% of women would have their cycles cancelled using a short protocol, between 5.5% and 14% will have cancelled cycles when using a long protocol.

The quality of the evidence ranged from moderate to low. The main limitations in the evidence were failure to report live birth or ongoing pregnancy, poor reporting of methods in the primary studies, and imprecise findings due to lack of data. Only 10 of the 37 included studies were conducted within the last 10 years.

Authors' conclusions

When long GnRHa protocols and short GnRHa protocols were compared, we found no conclusive evidence of a difference in live birth and ongoing pregnancy rates, but there was moderate quality evidence of higher clinical pregnancy rates in the long protocol group. None of the other analyses showed any evidence of a difference in birth or pregnancy outcomes between the protocols compared. There was insufficient evidence to make any conclusions regarding adverse effects.

PLAIN LANGUAGE SUMMARY

Gonadotrophin-releasing hormone agonists (GnRHa) used as an adjuvant to gonadotrophins in assisted reproduction treatments

Review question

Researchers from the Cochrane Collaboration reviewed the evidence about the most effective way of using gonadotrophin-releasing hormone agonists (GnRHa) as part of controlled ovarian stimulation in women undergoing assisted reproduction technology (ART).

Background

GnRHa are given along with hormone injections that stimulate the ovaries, in an attempt to prevent spontaneous release of eggs prior to their planned surgical retrieval. GnRHa have been proven to improve pregnancy rates; however, various regimens are described in the literature. We conducted this review to identify the most effective regimens.

Study characteristics

We found 37 randomised controlled trials (RCTs) of 3872 women comparing the use of GnRHa in various protocols. Twenty of these RCTs (1643 women) compared a long protocol with a short protocol. The evidence is current to April 2015.

Key results

In comparisons of long GnRHa protocols (where GnRHa is given for at least 14 days prior to the start of ovarian stimulation) versus short GnRHa protocols (when the GnRHa is given at the start of stimulation) there was no conclusive evidence of a difference in live birth and ongoing pregnancy rates. However there was moderate quality evidence of higher clinical pregnancy rates in the long protocol groups. Our findings suggest that in a population in which 14% of women achieve live birth or ongoing pregnancy using a short protocol, between 13% and 23% will achieve live birth or ongoing pregnancy using a long protocol.

None of the other analyses showed any evidence of a difference in birth or pregnancy outcomes between the protocols compared. There was insufficient evidence to make any conclusions regarding adverse effects. Further research is needed to determine which long protocol is most cost effective and acceptable to women.

Quality of the evidence

The quality of the evidence ranged from moderate to low. The main limitations in the evidence were failure to report live birth or ongoing pregnancy, poor reporting of methods in the primary studies, and imprecise findings due to lack of data. Only 10 of the 37 included studies were conducted within the last 10 years.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Long protocol compared with short protocol for pituitary suppression in assisted reproduction

Long protocol compared with short protocol for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long protocol
Comparison: short protocol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Short protocol	Long protocol				
Live birth or ongoing pregnancies per woman randomised	**138 per 1000**	**172 per 1000** (131 to 225)	**OR 1.3** (0.94 to 1.81)	976 (12 studies)	⊕⊕⊝⊝ Low[1,2]	No evidence of a difference between the groups
Clinical pregnancies per woman randomised	**137 per 1000**	**192 per 1000** (158 to 232)	**OR 1.5** (1.18 to 1.9)	1643 (20 studies)	⊕⊕⊕⊝ Moderate[1]	Benefit to long protocol group

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

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

[1]High risk of bias associated with poor reporting of methods in the primary studies.
[2]Imprecision: the confidence interval is compatible with benefit in one or both groups or with no effect.

Summary of findings 2. Long protocol compared with ultrashort protocol for pituitary suppression in assisted reproduction

Long protocol compared with ultrashort protocol for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long protocol

Comparison: ultrashort protocol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Ultrashort protocol	Long protocol				
Live birth and ongoing pregnancies per woman randomised	**122 per 1000**[1]	**198 per 1000** (91 to 376)	**OR 1.78** (0.72 to 4.36)	150 (1 study)	⊕⊕⊖⊖ Low[2,3]	No evidence of a difference between the groups
Clinical pregnancies per woman randomised	**161 per 1000**[4]	**230 per 1000** (133 to 370)	**OR 1.56** (0.8 to 3.06)	230 (2 studies)	⊕⊕⊖⊖ Low[2,3]	No evidence of a difference between the groups

*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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]High risk of bias associated with poor reporting of methods in the primary study or studies.
[3]Imprecision: the confidence interval is compatible with benefit in one or both groups or with no effect.
[4]The assumed risk in the control group was determined as the median value across included studies.

Summary of findings 3. Short compared with ultrashort protocol for pituitary suppression in assisted reproduction

Short protocol compared with ultrashort protocol for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: short protocol
Comparison: ultrashort protocol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Ultrashort protocol	**Short**				
Live birth and ongoing pregnancies per woman randomised	Not reported in the included study				-	-
Clinical pregnancies per woman randomised	**195 per 1000**[1]	**244 per 1000** **(102 to 480)**	**OR 1.33** **(0.47 to 3.81)**	82 (1 study)	⊕⊕⊝⊝ Very low[2,3]	No evidence of a difference between the groups

*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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]Applicability uncertain: the population is a selected group of participants (poor responders).
[3]Imprecision: single underpowered trial with a small number of events; the confidence interval is compatible with benefit in either group or with no effect.

Summary of findings 4. Long luteal phase protocol compared with long follicular phase protocol for pituitary suppression in assisted reproduction

Long luteal phase protocol compared with long follicular phase protocol for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long luteal phase protocol
Comparison: long follicular phase protocol

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Long follicular phase protocol	**Long luteal phase protocol**				
Live birth and ongoing pregnancies per woman randomised	**102 per 1000**[1]	**177 per 1000** (90 to 319)	**OR 1.89** (0.87 to 4.1)	223 (1 study)	⊕⊕⊝⊝ Low[2,3]	No evidence of a difference between the groups

Clinical pregnancies per woman randomised	**269 per 1000**[4]	**281 per 1000** (219 to 351)	**OR 1.06** (0.76 to 1.47)	750 (5 studies)	⊕⊕⊖⊖ Low[2,3]	No evidence of a difference between the groups

*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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]High risk of bias associated with poor reporting of methods in the primary study or studies.
[3]Imprecision: the confidence interval is compatible with benefit in either group or with no effect.
[4]The assumed risk in the control group was determined as the median value across included studies.

Summary of findings 5. Long protocol continued GnRH agonist compared with long protocol stop GnRH agonist for pituitary suppression in assisted reproduction

Long protocol continued GnRH agonist compared with long protocol stop GnRH agonist for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long protocol continued GnRH agonist
Comparison: long protocol stop GnRH agonist

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long protocol stop GnRH agonist	Long protocol continued GnRH agonist				
Live birth and ongoing pregnancies Number of live births or ongoing pregnancies per woman randomised	**276 per 1000**[1]	**222 per 1000** (138 to 336)	**OR 0.75** (0.42 to 1.33)	290 (3 studies)	⊕⊕⊖⊖ Low[2,3]	No evidence of a difference between the groups

Clinical pregnancies Number of clinical pregnancies per woman randomised	**235 per 1000**[1]	**207 per 1000** (135 to 302)	**OR 0.85** (0.51 to 1.41)	360 (4 studies)	⊕⊕⊖⊖ Low[2,3]	No evidence of a difference between the groups

*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; **GnRH**: gonadotrophin-releasing hormone; **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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]High risk of bias associated with poor reporting of methods in one or more of the primary studies.
[3]Imprecision: the confidence interval is compatible with benefit in either group or with no effect.

Summary of findings 6. Long protocol (continued same versus reduced dose GnRHa) for pituitary suppression in assisted reproduction

Long protocol (continued same versus reduced dose GnRHa) for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long protocol continued same

Comparison: long protocol reduced dose GnRHa

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Long protocol, reduced dose GnRHa	**Long protocol, continued same**				
Live birth and ongoing pregnancies per woman randomised	No studies reported this outcome				-	-
Clinical pregnancies per woman randomised	**377 per 1000**[1]	**382 per 1000** (292 to 479)	**OR 1.02** (0.68 to 1.52)	407 (4 studies)	⊕⊕⊖⊖ Low[2,3]	No evidence of a difference between the groups

*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; **GnRHa**: gonadotrophin-releasing hormone agonists; **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]The assumed risk in the control group was determined as the median value across included studies.
[2]High risk of bias associated with poor reporting of methods in one or more of the primary studies.
[3]Imprecision: the confidence interval is compatible with benefit in either group or with no effect.

Summary of findings 7. Long protocol (GnRHa until HCG) compared with long protocol (extend GnRHa 12 days after HCG) for pituitary suppression in assisted reproduction

Long protocol (GnRHa until HCG) compared with long protocol (extend GnRHa 12 days after HCG) for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long protocol (GnRHa until HCG)
Comparison: long protocol (extend GnRHa 12 days after HCG)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long protocol (extend GnRHa 12 days after HCG)	Long protocol (GnRHa until HCG)				
Live birth and ongoing pregnancies per woman randomised	**378 per 1000**[1]	**351 per 1000** (229 to 499)	**OR 0.89** (0.49 to 1.64)	181 (1 study)	⊕⊕⊖⊖ Low[2]	No evidence of a difference between the groups
Clinical pregnancies per woman randomised	**489 per 1000**[1]	**494 per 1000** (353 to 636)	**OR 1.02** (0.57 to 1.83)	181 (1 study)	⊕⊕⊖⊖ Low[2]	No evidence of a difference between the groups

*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; **GnRHa**: gonadotrophin-releasing hormone agonists; **HCG**: human chorionic gonadotrophin; **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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]The level of evidence was downgraded by two levels due to imprecision: only one underpowered trial with relatively small number of events and wide confidence interval compatible with benefit in either group or with no effect.

Summary of findings 8. Long protocol: administration of GnRHa for two versus three weeks before stimulation for pituitary suppression in assisted reproduction

long protocol: administration of GnRHa for two versus three weeks before stimulation for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: long protocol: administration of GnRHa for two weeks before stimulation
Comparison: long protocol: administration of GnRHa for three weeks before stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long protocol: administration of GnRHa for three weeks before stimulation	Long protocol: administration of GnRHa for two weeks before stimulation				
Live birth and ongoing pregnancies per woman randomised	**488 per 1000**[1]	**456 per 1000 (261 to 661)**	**OR 0.88 (0.37 to 2.05)**	85 (1 study)	⊕⊕⊖⊖ Low[2]	No evidence of a difference between the groups
Clinical pregnancies per woman randomised	**585 per 1000**[1]	**568 per 1000 (355 to 757)**	**OR 0.93 (0.39 to 2.21)**	85 (1 study)	⊕⊕⊖⊖ Low[2]	No evidence of a difference between the groups

*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; **GnRHa**: gonadotrophin-releasing hormone agonists; **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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]High risk of bias associated with poor reporting of methods in one or more of the primary studies.

Summary of findings 9. Short protocol compared with stop short protocol for pituitary suppression in assisted reproduction

Short protocol compared with stop short protocol for pituitary suppression in assisted reproduction

Population: women undergoing pituitary suppression in assisted reproduction
Intervention: short protocol
Comparison: stop short protocol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Stop short protocol	Short protocol				
Live birth and ongoing pregnancies per woman randomised	This outcome was not reported by the included trial				-	-
Clinical pregnancies per woman randomised	**226 per 1000[1]**	**147 per 1000** (81 to 255)	**OR 0.59** (0.3 to 1.17)	230 (1 study)	⊕⊕⊖⊖ Low [1,2]	No evidence of a difference between the groups

*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]The assumed risk in the control group was determined as a mean baseline risk from the study included in the comparison.
[2]High risk of bias associated with poor reporting of methods in one or more of the primary studies.

BACKGROUND

Description of the condition

Subfertility affects one in seven couples; a high proportion of them use assisted reproductive technology (ART) in an attempt to improve their chances of conception (Maheshwari 2008). In a natural cycle, only one oocyte is normally produced. Conversely, an ART cycle usually aims to produce more than one oocyte destined for fertilisation, to improve the chances of having a sufficient number of embryos to choose from. Concurrently, it is crucial to prevent an excessive response from the ovaries resulting in ovarian hyperstimulation. In order to produce more oocytes, the ovaries are stimulated with high doses of gonadotrophins. However, there is a risk of a premature surge of luteinising hormone (LH), which could disrupt both normal follicle and oocyte development, resulting in non-recovery of oocytes. The incorporation of gonadotrophin-releasing hormone agonists (GnRHa) in controlled ovarian hyperstimulation (COH) protocols has been used in ART to reversibly block pituitary function and prevent a premature LH surge. Use of GnRHa has resulted in significant improvements in treatment, including decreased cancellation of started treatment cycles prior to oocyte recovery and higher pregnancy rates (Fields 2013).

Description of the intervention

Different GnRHa drugs, routes of administration (nasal or systemic), and GnRHa protocols have been used in ART. There are three main protocols involving GnRHa administration, namely, the long, the short, and the ultrashort protocol.

- Long protocol: GnRHa is administered at least two weeks before starting stimulation (to achieve suppression of the ovarian activity) and continued up until human chorionic gonadotrophin (HCG) is given, starting from either the second day of the menstrual cycle (long follicular protocol) or the mid-luteal phase (21st day) of the previous cycle (long luteal protocol).
- Short protocol: GnRHa is administered from day one or two of the cycle (day one being the start of the menstrual bleed) and continued with stimulation until the day of HCG administration.
- Ultrashort protocol: GnRHa is given for three days, from day two of the cycle (hence, using only the flare-up effect).

How the intervention might work

Administration of multiple doses of GnRHa causes a reversible blockade of pituitary function after an initial stimulatory phase, the so-called flare effect. GnRHa suppresses GnRH receptors and causes inhibition of postreceptor events (Daya 2000). The resulting reduction in bioactive LH levels in the serum (Regan 1990) allows multiple follicular development to continue (until ready for oocyte recovery) avoiding the risk of a LH surge and hence premature ovulation (Barlow 1998).

GnRHa are the most commonly used adjuvants for controlled ovarian stimulation (www.ivf-worldwide.com/survey/survey). Traditionally, the long protocol involves GnRHa use during the entire stimulation phase until HCG administration. Reports showed that low endogenous LH concentrations persist until 10 to 14 days after discontinuation of the GnRHa (Donderwinkel 1993; Sungurtekin 1995). Earlier studies have argued that continuation of GnRHa during the stimulation phase can also lead to profound suppression of mid-follicular LH, which might be associated with early pregnancy loss (Westergaard 2000). Therefore, GnRHa could be stopped earlier in the long protocol stimulation cycle (Simons 2005), allowing the pituitary to recover in time for the luteal phase without risking a premature LH surge. This could reduce both cost and inconvenience as fewer injections would be needed.

Why it is important to do this review

The original Cochrane review on the topic, published in 1998 and updated in 2009, showed superiority of the long protocols compared with the short or ultrashort protocols. Of note, long protocols are traditionally used in ART, whereas most of the newer alternatives (e.g., antagonists or mild protocols) have been compared with them (Mancini 2011; Mohsen 2013). The second update of this review aimed to examine whether evidence in the last three years on the relative effectiveness of the different GnRHa protocols used as adjuncts to hormonal ovarian stimulation for ART supports the conclusions of the first update.

OBJECTIVES

To evaluate the effectiveness of the different GnRHa protocols as adjuncts to COH in women undergoing ART cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) comparing various gonadotrophin-releasing hormone agonist protocols in assisted reproductive technology (ART). We included in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment cycles. We excluded trials if we found allocation to be non-random as they are associated with a high risk of bias. We also excluded cross-over trials as the design is not suitable for this review. We excluded quasi-randomised trials even if they had been included in the original review.

Types of participants

Women/couples with all types of infertility were eligible for inclusion, undergoing ART and using GnRHa for pituitary down-regulation.

Types of interventions

Inclusion criteria

Studies comparing any two protocols using gonadotrophin-releasing hormone agonists (GnRHa) for pituitary suppression in an ART programme. We included ultrashort, short, and long (follicular or luteal with or without discontinuation during the stimulation phase) protocols.

The definitions used in this review for the various protocols were as follows.

- Long protocol: GnRHa commenced at least two weeks before starting stimulation and continued up until human chorionic gonadotrophin (HCG) was given.

- Short protocol: GnRHa commenced at the same time as starting stimulation and continued up until the day of HCG administration.
- Ultrashort protocol: stimulation was commenced one to two days after starting GnRHa (and given only for three days).

Exclusion criteria

We excluded women receiving donor oocytes.

We also excluded the following study comparisons.

1. GnRHa versus GnRH-antagonist protocols.
2. Different routes of administration of GnRHa.
3. GnRHa versus placebo protocols (Hughes 1992).
4. Depot versus daily administration of GnRHa, as this is the topic of another Cochrane review (Albuquerque 2013).
5. Addition of any drug in GnRHa protocols.

Types of outcome measures

We measured the following primary and secondary outcome measures.

Primary outcomes

1. Number of live births or ongoing pregnancies per woman/couple randomised.

We defined live birth as the delivery of a live foetus after 20 completed weeks of gestational age. We defined ongoing pregnancy as evidence of a gestational sac with foetal heart motion at 12 weeks or later, confirmed with an ultrasound. We decided to combine the two outcomes, as ongoing pregnancy comprises a more meaningful clinical measure compared with any other and in order to give more power to the results of the current update.

When there were multiple live births (e.g., twins or triplets), we counted these as one live birth event.

Secondary outcomes

1. Number of clinical pregnancies per woman/couple randomised, defined as evidence of a gestational sac with foetal heart motion at six weeks or later, confirmed with an ultrasound. When there were multiple gestational sacs in one woman, we counted these as one clinical pregnancy (Griffin 2002).
2. Number of oocytes retrieved per woman randomised.
3. Amount of gonadotrophins administered per woman randomised.

Adverse outcomes

1. Number of pregnancy losses, defined as the sum of the number of miscarriages (pregnancy loss before 20 completed weeks of gestation) and the number of stillbirths (pregnancy loss after 20 completed weeks of gestation) (Griffin 2002).
2. Number of ovarian hyperstimulation syndrome (OHSS) events per woman randomised.
3. Cycle cancellation (defined as cancelled cycle before oocyte retrieval).
4. Number of premature luteinising hormone (LH) surges.

Other outcomes

1. Cost of treatment.
2. Acceptability of the regimen.

Search methods for identification of studies

We analysed all published and unpublished RCTs comparing the various regiments for pituitary down-regulation using GnRHa in ART without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

We searched the following databases on 23 April 2015, using the search strategy developed by the Menstrual Disorders and Subfertility Group:

- the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 3, 2015);
- MEDLINE;
- EMBASE;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature); and
- PsycINFO.

The searches were conducted using the search strategies listed in the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5).

Searching other resources

We searched the citation lists of relevant publications, review articles, abstracts of scientific meetings, and included studies. In liaison with the Trials Search Co-ordinator, we included in the review published articles and conference abstracts that are not covered in the Menstrual Disorders and Subfertility Group Specialised Register. In addition, OpenGrey, a system for grey literature produced in Europe, such as research reports, doctoral dissertations, and conference papers (www.opengrey.eu/), was searched.

We searched the following trials registries for published, ongoing, or registered trials:

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register, a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch/Default.aspx).

Data collection and analysis

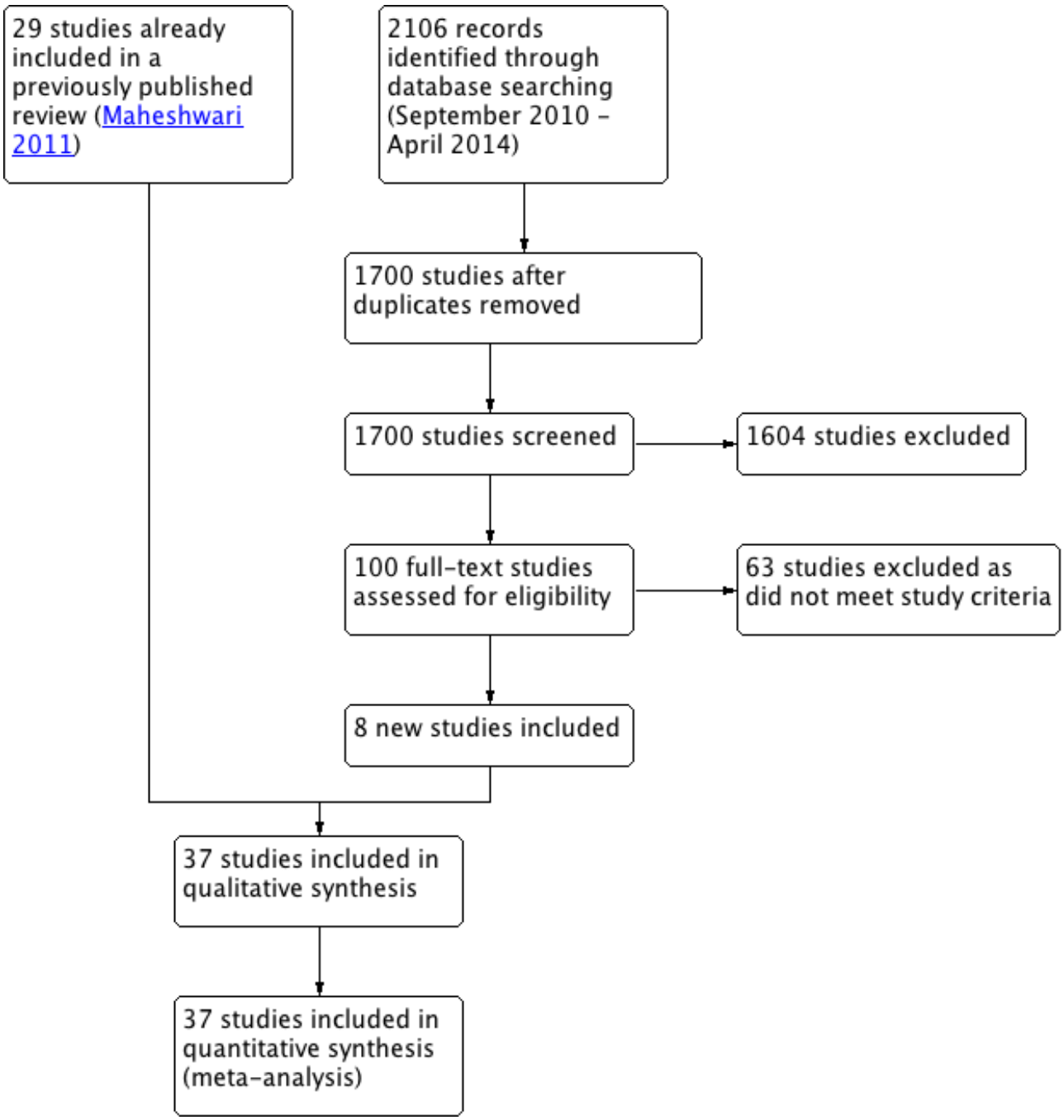
Selection of studies

Four review authors (AM, CS, AG, and GB), in pairs, independently selected the trials for inclusion using forms designed according to Cochrane guidelines. We sought, via e-mail, additional information on trial methodology and missing data from the authors of trials that appeared to meet the eligibility criteria but had unclear

methodology or data that were in an unsuitable form for meta-analysis. Discussion with SB resolved differences of opinion.

We documented the selection process with a 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) flow chart (Figure 1).

Figure 1. Study flow diagram.



We constructed 'Characteristics of included studies' tables for those trials considered suitable for inclusion (Characteristics of included studies). The 'Characteristics of excluded studies' tables list the excluded studies with reasons for exclusion (Characteristics of excluded studies).

Data extraction and management

Two review authors (AG and GB) independently extracted data from eligible studies using a data extraction form, which we had designed and pilot tested. A third review author (CS) resolved disagreements. Data extracted included study characteristics and outcome data. Where studies had multiple publications, we collated the multiple reports of the same study, so that each study - rather than each report - was the unit of interest in the review,

and such studies have a single study identification with multiple references. As required, we corresponded with study investigators for further data on methods, results, or both, via e-mail.

The data extraction forms included 'Risk of bias' criteria and methodological details, which we have presented in the 'Characteristics of included studies' tables. We managed the data using Review Manager 5.3 software (RevMan 2014).

Appendix 6 shows the information extracted from the studies selected for the review.

Assessment of risk of bias in included studies

Two review authors (AG and GB) independently assessed the included studies for risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011) to assess selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. A third review author (CS) resolved disagreements. We described all judgements fully and presented them in the 'Characteristics of included studies' tables, including commentary about each of the domains. This led to an overall assessment of the risk of bias of included studies (Figure 2 and Figure 3).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

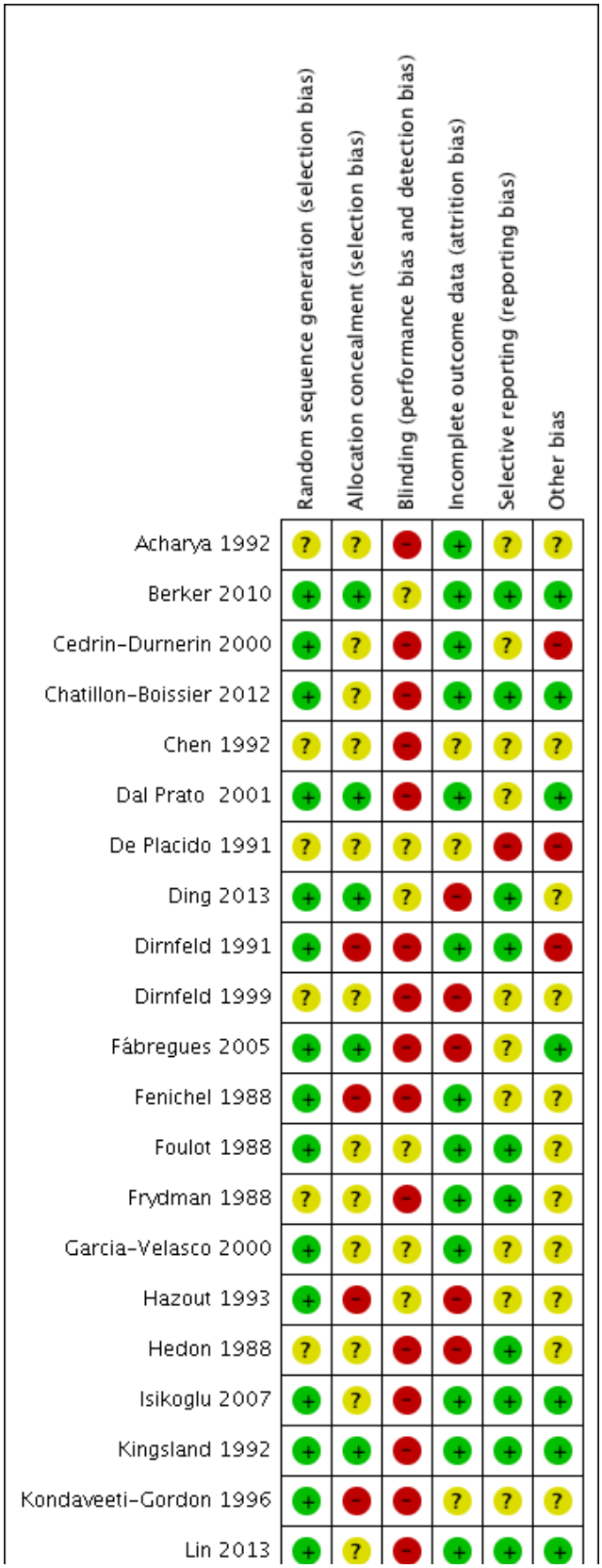


Figure 2. (Continued)

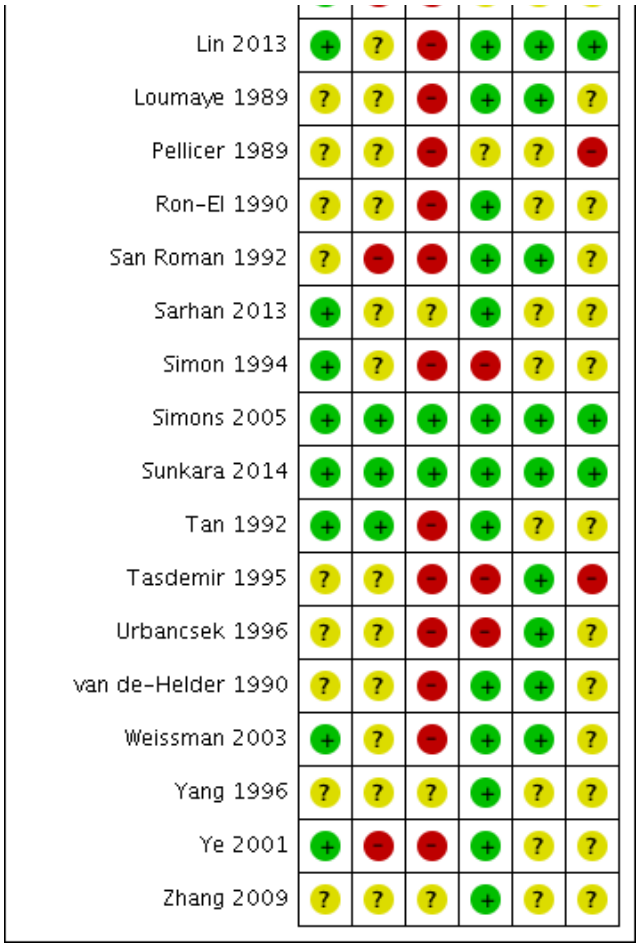
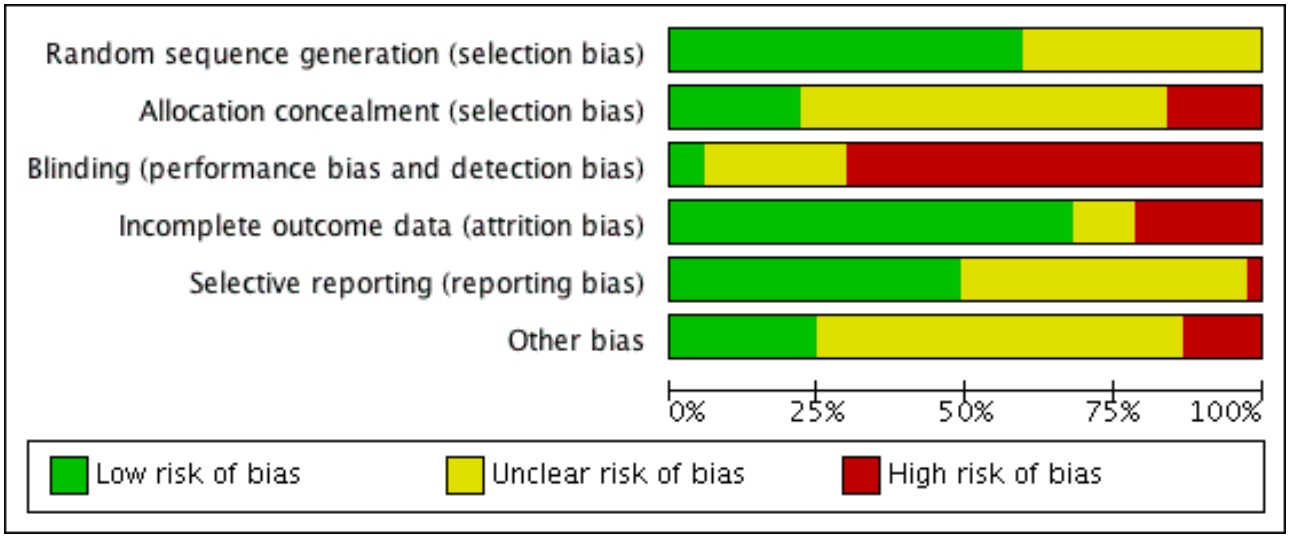


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



We searched for within-trial selective reporting, such as trials failing to report obvious outcomes or reporting them in insufficient detail to allow inclusion. We sought published protocols and compared the outcomes between the protocol and the final published study.

Measures of treatment effect

For dichotomous data (e.g., live birth and ongoing pregnancy rates), we used the numbers of events in the control and intervention groups of each study to calculate Mantel–Haenszel odds ratios (ORs). For continuous data (e.g., number of oocytes retrieved), we calculated the mean difference (MD) between treatment groups. We presented 95% confidence intervals for all outcomes. Where data to calculate ORs or MDs were not available, our intention was to utilise the most detailed numerical data available that might facilitate similar analyses of included studies (e.g., test statistics, P values). We compared the magnitude and direction of effect reported by studies with how they are presented in the review, taking account of legitimate differences.

Unit of analysis issues

The primary analysis was per woman randomised; we included per-pregnancy data for some outcomes (e.g., miscarriage). We counted multiple live births (e.g., twins or triplets) as one live birth event.

Dealing with missing data

In the case of missing data in the included studies, we contacted the original investigators by e-mail or post to request relevant missing information. (We sent a reminder if we had received no reply during the first 20 days.) We reported the data according to intention-to-treat principles wherever possible. We assumed that live births had not occurred in participants without a reported outcome. For other outcomes, we analysed only the available data.

If studies reported sufficient detail to calculate MDs but provided no information on the associated standard deviation (SD), we assumed the outcome to have a SD equal to the highest SD from other studies within the same analysis.

Assessment of heterogeneity

Before any meta-analysis was done, we judged whether there was sufficient similarity between the eligible studies in their design and clinical characteristics to ensure that pooling was valid. We assessed statistical heterogeneity in the results of trials by using the X^2 test. A low P value (or a large X^2 statistic relative to its degree of freedom) potentially provides evidence of heterogeneity of intervention effects and shows that results are not influenced by chance alone (Higgins 2011). We used the I^2 statistic to assess the impact of the heterogeneity on the meta-analysis and interpreted an I^2 statistic > 50% as marked heterogeneity (Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. In the presence of 10 or more studies in an analysis, we used a funnel plot to explore the possibility of small study effects. This was to guide whether the difference was due to publication or reporting bias. We were aware that there are other sources of asymmetry in funnel plots (Stuck 1998).

Data synthesis

The various comparison groups were as follows:

1. any long protocol versus any short protocol;
2. any long protocol versus ultrashort protocol;
3. any short protocol versus ultrashort protocol;
4. long luteal protocol versus long follicular phase protocol;
5. long protocol: continuation versus discontinuation of the GnRHa at start of stimulation;
6. long protocol: continuation of same-dose GnRHa versus reduced-dose GnRHa until HCG administration;
7. long protocol: discontinuing versus continuing GnRHa after HCG administration;
8. long protocol: administration of GnRHa for two versus three weeks before stimulation; and
9. short protocol: continuation of GnRHa versus stopping GnRHa.

We performed analysis using RevMan 5.3 software (RevMan 2014). For binary (or dichotomous) outcomes, we expressed the results for each study as odds ratios (OR) with 95% confidence intervals (CI) and combined them for meta-analysis, where appropriate. For continuous outcome data, we expressed the results from each study as a difference in means with 95% CI and combined for meta-analysis using the mean difference (MD).

An increase in the odds of a particular outcome, which may be beneficial (e.g., live birth) or detrimental (e.g., adverse effects), are displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

Where data were available, we planned to conduct subgroup analyses to determine the separate evidence within the following subgroups: normal or poor responders, number of embryos transferred, previous failed cycles, maternal age, and duration of treatment. In cases of substantial heterogeneity, our aim was to explore possible explanations in sensitivity analyses. We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect. We used a fixed-effect model.

Sensitivity analysis

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

1. if we had restricted eligibility to studies without high risk of bias (e.g., clear description of sequence generation and allocation concealment methods);
2. if we had adopted a random-effects model;
3. if we had implemented alternative imputation strategies; or
4. if the summary effect measure we had used was relative risk rather than odds ratio.

We did so by excluding studies with unclear randomisation and studies with incomplete data. There were not enough studies to support meta-regression or other formal considerations of prognostic factors.

Overall quality of the body of evidence: 'Summary of findings' tables

We prepared 'Summary of findings' tables using GRADEprofiler (GRADEpro). These tables evaluate the overall quality of the body of evidence for the main review outcomes (live birth and clinical pregnancy) using GRADE criteria (study limitations (i.e., risk of bias), consistency of effect, imprecision, indirectness, and publication bias). We justify our judgements about evidence quality (high, moderate, or low) and have documented and incorporated these into the reporting of results for each outcome.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies, and the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) flowchart (Figure 1).

Results of the search

After searching the electronic databases, we found a total of 2503 studies: 641 in the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, 722 in the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, 485 in MEDLINE, 369 in EMBASE, 266 in CINAHL (Cumulative Index to Nursing and Allied Health Literature), and 20 studies in PsycINFO. After removing the duplicates and searching other resources, there were approximately 1700 studies left. Of these, 100 seemed eligible for inclusion, and after reading the full text articles, we were able to include 37 studies in the review (eight more than was in the last update). Of note, we considered one study as two different comparisons (De Placido 1991), which were present in the study. One study is ongoing (NCT01006954).

We sent two e-mails to trial authors (with a reminder); we received responses from nine out of 15 study authors (Chatillon-Boissier 2012; Corson 1992; Isikoglu 2007; Lin 2013; NCT00436319; Sarhan 2013; Sunkara 2014; Tanaka 2014; Tarin 1990).

Included studies

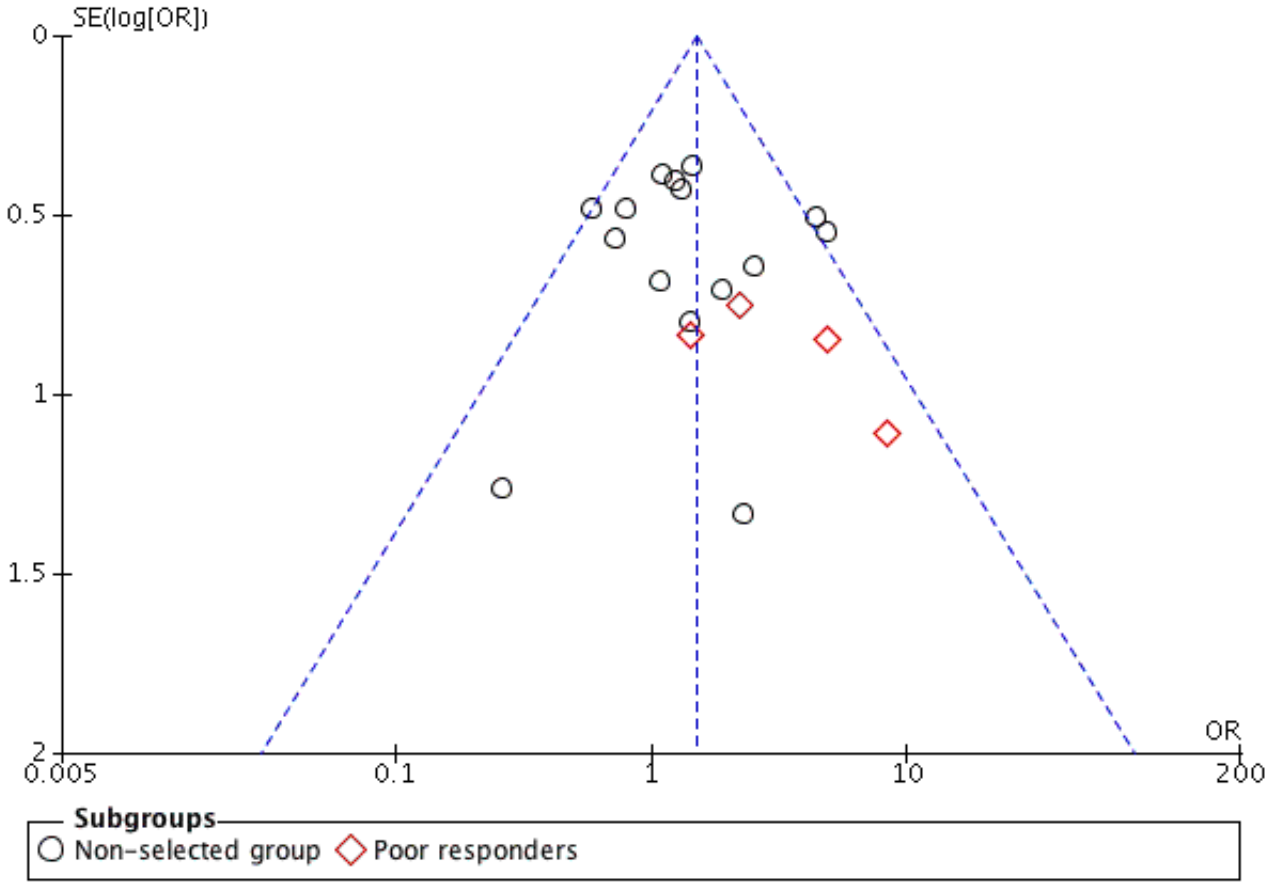
Design

We included 37 studies (3872 women). All were parallel group randomised controlled trials (RCTs). There were nine different comparison groups.

1. Long versus short protocol

Twenty studies featured this comparison. An a priori power calculation was a feature in one study (Sunkara 2014). Weissman 2003 did a power calculation for pregnancy as the outcome but decided to proceed with number of oocytes as the primary outcome measure because of the large sample size required for determining a significant difference in the pregnancy rate. Only nine studies out of 20 reported adequate randomisation (Chatillon-Boissier 2012 ; Dirnfeld 1991 ; Fenichel 1988 ; Foulot 1988 ; Hazout 1993 ; Sunkara 2014 ; Tan 1992; Weissman 2003; Ye 2001). Three studies, Chatillon-Boissier 2012; Sunkara 2014; Tan 1992, reported concealed allocation. The funnel plot did not suggest any publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 1 Long versus short protocol, outcome: 1.2 Clinical pregnancies.



2. Long versus ultrashort protocol

Two studies featured this comparison. Of the two (Chen 1992; Kingsland 1992), the former reported adequate randomisation and concealed allocation. An a priori power calculation was not a feature of any study.

3. Short versus ultrashort protocol

One study featured this comparison (Berker 2010): the paper described an a priori power calculation, randomisation, and allocation concealment.

4. Long protocol: luteal versus follicular start of gonadotrophin-releasing hormone agonists (GnRHa)

Five studies featured this comparison. Of them, only Kondaveeti-Gordon 1996 had an a priori power calculation. Kondaveeti-Gordon 1996; Urbancsek 1996; and Sarhan 2013 reported clear randomisation and concealment. Although blinding until objective outcome assessment was planned for one study (Kondaveeti-Gordon 1996), it was revealed after the study was started. Urbancsek 1996 reported more than one cycle per participant.

5. Long protocol: continuation of GnRHa versus stopping GnRHa at start of stimulation

Three studies featured this comparison (Dirnfeld 1999; Garcia-Velasco 2000; Simons 2005). Of them, only one was double blinded (Simons 2005). All of the three studies reported adequate randomisation and concealment.

6. Long protocol: continuation of same-dose GnRHa versus reduced-dose GnRHa until HCG administration

Four studies featured this comparison. All of them reported adequate randomisation, while three reported concealed allocation (Dal Prato 2001; Ding 2013; Fábregues 2005).

7. Long protocol: discontinuing versus continuing GnRHa after HCG administration

One study featured this comparison (Isikoglu 2007). The study reported adequate randomisation (computer-generated list), blinding, and concealment, but there was no power calculation.

8. Long protocol: administration of GnRHa for two versus three weeks before stimulation

One study featured this comparison (Lin 2013). The study reported adequate randomisation (computer-generated random numbers two weeks after GnRHa administration), but there was no concealment or blinding.

9. Short protocol: continuation versus stopping GnRHa

One study featured this comparison (Cedrin-Durnerin 2000). The study reported adequate randomisation, but there was no concealment or blinding.

Participants

1. Long versus short protocol

Inclusion criteria for included studies varied widely. Some studies included women with all causes of infertility, Acharya 1992; Tan 1992; Tasdemir 1995, while others restricted inclusion to women with only tubal factor infertility, Fenichel 1988; Frydman 1988; Loumaye 1989; van de-Helder 1990; Zhang 2009, or tubal and unexplained infertility (Hazout 1993; Hedon 1988). Some studies excluded women with polycystic ovary syndrome (PCOS) (Foulot 1988; Yang 1996).

The age of the women included was variable in the different studies. Some included only women under 38 years (Fenichel 1988; Hazout 1993; Zhang 2009); others included women up until the age of 40 years (Chatillon-Boissier 2012; Loumaye 1989; Sunkara 2014; van de-Helder 1990).

Some studies included women undergoing only the first in vitro fertilisation (IVF) cycle, San Roman 1992; Tasdemir 1995, while others included all IVF cycles (Hazout 1993). Some included only previous low or poor responders, Chatillon-Boissier 2012; Dirnfeld 1991; Sunkara 2014; Weissman 2003, whereas others excluded previous poor responders (Frydman 1988; van de-Helder 1990).

2. Long versus ultrashort protocol

Couples with all causes of infertility were included in both studies. Kingsland 1992 only included women with the first cycle.

3. Short versus ultrashort protocol

A total of 82 poor responder participants who underwent intracytoplasmic sperm injection (ICSI) were included in this comparison. Criteria included at least one of the following: day 3 serum follicle-stimulating hormone (FSH) level > 10 mIU/mL, < 6 total antral follicles, prior cycle cancellation, prior poor response to controlled ovarian hyperstimulation (COH) (either peak E2 < 500 pg/mL, < 6 oocytes retrieved, or both), and aged > 41 (Berker 2010).

4. Long protocol: luteal versus follicular start of GnRHa

Ron-El 1990 included consecutive women whereas Pellicer 1989 included women with normal ovarian function; Urbancsek 1996 included women with tubal and unexplained infertility, and Sarhan 2013 included women with all types of infertility.

5. Long protocol: continuation of GnRHa versus stopping GnRHa at start of stimulation

Dirnfeld 1999 excluded women with irregular cycles, and Simons 2005 excluded women with PCOS or poor ovarian reserve. Simons 2005 included only women under 39 years of age whereas Dirnfeld 1999 included women up to the age of 42 years. Garcia-Velasco 2000 had no exclusion criteria for age.

Dirnfeld 1999 included only women with a previous poor response or high FSH; some studies included only previous low responders (Garcia-Velasco 2000; Simons 2005).

6. Long protocol: continuation of same-dose GnRHa versus reduced-dose GnRHa until HCG administration

Inclusion criteria for the included studies varied widely. One, Simon 1994, restricted inclusion to only tubal factor infertility while another included tubal and unexplained infertility (Dal Prato 2001). Dal Prato 2001 excluded women with a risk of hyperstimulation or with poor ovarian reserve while Ding 2013 included women with high response to gonadotrophin stimulation, that is, "women with eight or more subcapsular follicles of 2 to 8 mm in diameter in one plane in either ovary". The age of the women included was variable in the different studies: under 35 (Ding 2013), 38 (Dal Prato 2001), and under 39 years (Simon 1994). Fábregues 2005 and Ding 2013 included women undergoing their first IVF cycle.

7. Long protocol: discontinuing versus continuing GnRHa after HCG administration

One hundred eighty-one women undergoing 181 consecutive ICSI cycles were included, with a mean age of 30 years.

8. Long protocol: administration of GnRHa for two versus three weeks before stimulation

One hundred participants undergoing IVF/ICSI cycle were included, with a mean age of 29 years. Inclusion criteria: (a) subfertile participants undergoing first IVF/(ICSI) with tubal factor, male factor, or unexplained factor; (b) undertaking a luteal long protocol; (c) basal FSH levels 10 IU/L; and (d) aged 35 years. Exclusion criteria: (a) endometriosis, (b) adenomyosis, and (c) polycystic ovarian syndrome.

9. Short protocol: continuation versus stopping GnRHa

Cedrin-Durnerin 2000 excluded women older than 43 years and those with anovulation.

Interventions

1. Long versus short protocol

Twenty trials compared a long protocol with a short protocol. In six studies, Acharya 1992; Foulot 1988; Frydman 1988; Hazout 1993; Hedon 1988; Tan 1992, GnRHa was commenced in the follicular phase whereas it was commenced in the luteal phase in the rest of the studies (Chatillon-Boissier 2012; De Placido 1991; Fenichel 1988; Loumaye 1989; San Roman 1992; Sunkara 2014; Tasdemir 1995; van de-Helder 1990; Weissman 2003; Ye 2001; Zhang 2009). In two studies, Dirnfeld 1991; Yang 1996, it was not clear whether a follicular or luteal start was used.

There was a wide variation in the dose, type, and route of GnRHa used for down-regulation in long protocols. Buserelin was used either by nasal spray or subcutaneous injections: 1000 µg twice a day (Dirnfeld 1991); 200 µg five times a day (Acharya 1992); 900 µg/day (Loumaye 1989; Tasdemir 1995; Ye 2001); 300 µg twice a day (De Placido 1991; Frydman 1988; Hedon 1988); 200 µg three times daily (van de-Helder 1990); 0.3 ml daily (Foulot 1988); 200 µg daily (Tan 1992); and 100 µg/day (Weissman 2003). Decapeptyl was used either as a short-acting (100 µg/day) (Cedrin-Durnerin 2000; Chatillon-Boissier 2012) or long-acting single intramuscular injection (3.75 mg) (Fenichel 1988) or 1.88 mg of intramuscular Diphereline® (Zhang 2009). Other studies used leuprolide acetate (1 mg/day) (San Roman 1992; Yang 1996). Hazout 1993 repeated the decapeptyl injection twice, which may explain a much higher requirement of gonadotrophins. One study, Sunkara 2014, used nafarelin nasal spray 400 mg twice daily.

In studies comparing a long protocol versus a short protocol, GnRHa was continued at the same dose until HCG administration except in five studies that reduced the dose at confirmation of down-regulation: reduced from 1000 µg to 600 µg (Dirnfeld 1991), reduced from 1 mg to 0.5 mg/day (San Roman 1992), while Weissman 2003

and Chatillon-Boissier 2012 halved the agonist dose, and Sunkara 2014 continued with a reduced dose of nafarelin 200 mg twice daily until the administration of HCG injection.

Similarly, the dose of GnRHa for short protocols varied. Weissman 2003 applied a modified short protocol using the flare effect initially (500 µg/day for the initial four days followed by 100 µg until the day of HCG). Yang 1996 used another modification of the short protocol where GnRHa was stopped after seven days.

Dose, regimen, and drugs used for stimulation also varied in all studies as did the inclusion criteria of the population studied (please see the 'Characteristics of included studies' tables).

2. Long versus ultrashort protocol

Of the two studies included in this comparison, Kingsland 1992 used 200 µg daily of buserelin whereas Chen 1992 used 1 mg daily of subcutaneous decapeptyl for the long protocol. Both studies discontinued GnRHa after confirmation of down-regulation.

The dose of GnRHa for the ultrashort protocol was different as well. Chen 1992 used leuprolide acetate 1 mg daily whereas Kingsland 1992 used 500 µg/day of buserelin on days two, three, and four of the cycle.

Chen 1992 used follicle-stimulating hormone (FSH) + human menopausal gonadotrophin (HMG) for stimulation whereas Kingsland 1992 used HMG alone

3. Short versus ultrashort protocol

Participants were randomised into two groups.

1. The participants in the ultrashort gonadotrophin-releasing hormone (GnRH) agonist/GnRH antagonist group (n = 41) were administered leuprolide acetate at 40 microg subcutaneously/twice daily, started on day two of menses and continued for three consecutive days, followed by gonadotrophins, and GnRH antagonist cetrorelix at 0.25 mg/day when the leading follicle was more than 14 mm, which was continued up to HCG injection.
2. The participants in the microdose group (n = 41) started to use leuprolide acetate at 40 microg subcutaneously/twice daily on day two of menses, and two days after initiation of GnRHa, gonadotropin stimulation was initiated and continued until HCG day.

The starting dose of recombinant FSH depended on age, body mass index (BMI), and ovarian response to the previous cycle and increased to a maximum of 450 IU/day depending on the ovarian response; it was then individualised after day five (Berker 2010).

4. Long protocol: luteal versus follicular start of GnRHa

Three studies out of five included in this comparison used the same dose of GnRHa for down-regulation (1200 µg/day), Kondaveeti-Gordon 1996; Urbancsek 1996, and 0.1 mg of triptorelin subcutaneously daily (Sarhan 2013). Ron-El 1990 used a long-acting preparation (3.2 mg decapeptyl) whereas Pellicer 1989 used 600 µg/day buserelin in two divided doses. In Pellicer 1989, the day for luteal start varied, ranging from four to 10 days after ovulation compared with the day 21 to 22 start in the other included studies. This might have had some impact on the outcomes of the luteal phase results. Urbancsek 1996 considered more than one cycle per woman whereas the remaining four studies evaluated only the first cycle. All studies except Pellicer 1989 and Sarhan 2013 used HMG for ovarian stimulation; the former used HMG + FSH, and the latter administered either HMG or FSH.

5. Long protocol: continuation of GnRHa versus stopping GnRHa at start of stimulation

Of the three studies included in this comparison, one used buserelin (1000 µg/day) (Dirnfeld 1999), one used leuprolide acetate (1 mg/day) (Garcia-Velasco 2000), and the third used triptorelin (0.1 mg/day) (Simons 2005) for down-regulation. All of the studies stopped GnRHa at confirmation of down-regulation in the test arm.

Apart from one study (Garcia-Velasco 2000), which used FSH + HMG, all used HMG alone for stimulation.

6. Long protocol: continuation of same-dose GnRHa versus reduced-dose GnRHa until HCG administration

For the four studies in this comparison, there was a variation in the type and dose of GnRHa and the reduction in dose after down-regulation was confirmed: luteinising hormone-releasing hormone agonist (LHRHa) commenced at 0.5 mg/day and reduced to 0.1 mg/day (Simon 1994); triptorelin acetate commenced at 0.1 mg/day and reduced to 0.05 mg/day (Fábregues 2005); GnRHa commenced at 100 µg/day and reduced to 50 µg/day (Dal Prato 2001); and triptorelin was initiated during the luteal phase, 0.1 mg/day for 10 days followed by 0.05 mg/day until the concentration of serum oestradiol was </= 40 pg/ml, then the stimulation of the ovaries started and when the diameter of one or more follicles was 14 mm, triptorelin (0.05 mg/day) was withdrawn for two (15/47) or three (32/47) days (Ding 2013).

The stimulation drug varied amongst the studies. Simon 1994 used HMG, Fábregues 2005 and Ding 2013 used recombinant FSH, while Dal Prato 2001 used metrodin.

7. Long protocol: discontinuing versus continuing GnRHa after HCG administration

GnRHa was administered from the 21st day of the preceding cycle. Participants were divided into two groups: (1) (n = 90 participants) participants were continuously administered GnRHa for 12 days after embryo transfer; (2) (n = 91 participants) GnRHa was stopped on the day of HCG administration.

8. Long protocol: administration of GnRHa for two versus three weeks before stimulation

In both groups, a single dose of long-acting GnRHa (Diphereline®, 1.25 mg) was administered in the mid-luteal phase. Participants were divided into two groups according to the initiation of gonadotrophins (14 or 21 days after GnRHa administration). Either recombinant follicle-stimulating hormone (rFSH) or HMG was used for ovarian stimulation.

9. Short protocol: continuation versus stopping GnRHa

There was only one study in this comparison. A short protocol was compared with stopping GnRHa halfway through stimulation rather than continuing until the day of HCG.

Outcomes

Nineteen studies reported either live birth rate or ongoing pregnancy rate (Acharya 1992; Chatillon-Boissier 2012; Ding 2013;

Dirnfeld 1991; Dirnfeld 1999; Foulot 1988; Frydman 1988; Isikoglu 2007; Kingsland 1992; Lin 2013; Loumaye 1989; San Roman 1992; Simons 2005; Sunkara 2014; Urbancsek 1996; van de-Helder 1990; Yang 1996; Ye 2001; Zhang 2009). With regard to adverse outcomes, 22 studies reported cycle cancellation rate (Acharya 1992; Berker 2010; Cedrin-Durnerin 2000; Chatillon-Boissier 2012; Dal Prato 2001; Ding 2013; Dirnfeld 1991; Dirnfeld 1999; Foulot 1988; Frydman 1988; Garcia-Velasco 2000; Hazout 1993; Isikoglu 2007; Kingsland 1992; Kondaveeti-Gordon 1996; San Roman 1992; Sarhan 2013; Simons 2005; Sunkara 2014; van de-Helder 1990; Weissman 2003; Zhang 2009), while two trials reported ovarian hyperstimulation syndrome (OHSS), Ding 2013; Lin 2013, and one study reported miscarriage rate (Lin 2013).

1. Long versus short protocol

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in 12 studies (Acharya 1992; Chatillon-Boissier 2012; Dirnfeld 1991; Foulot 1988; Frydman 1988; Loumaye 1989; San Roman 1992; Sunkara 2014; van de-Helder 1990; Yang 1996; Ye 2001; Zhang 2009), clinical pregnancies in 19 studies (Acharya 1992; Chatillon-Boissier 2012; De Placido 1991; Dirnfeld 1991; Fenichel 1988; Foulot 1988; Frydman 1988; Hazout 1993; Hedon 1988; Loumaye 1989; San Roman 1992; Sunkara 2014; Tan 1992; Tasdemir 1995; van de-Helder 1990; Weissman 2003; Yang 1996; Ye 2001; Zhang 2009), number of oocytes in 10 studies (Chatillon-Boissier 2012; Dirnfeld 1991; Hazout 1993; Loumaye 1989; San Roman 1992; Sunkara 2014; Weissman 2003; Yang 1996; Ye 2001; Zhang 2009), dose of gonadotrophins in eight studies (Chatillon-Boissier 2012; Dirnfeld 1991; Hazout 1993; Sunkara 2014; Weissman 2003; Yang 1996; Ye 2001; Zhang 2009), cycle cancellation in 11 studies (Acharya 1992; Chatillon-Boissier 2012; Dirnfeld 1991; Foulot 1988; Frydman 1988; Hazout 1993; San Roman 1992; Sunkara 2014; van de-Helder 1990; Weissman 2003; Zhang 2009), and other outcomes in none of the included studies.

2. Long versus ultrashort protocol

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in one study (Kingsland 1992), clinical pregnancies in two studies (Chen 1992; Kingsland 1992), number of oocytes in two studies (Chen 1992; Kingsland 1992), dose of gonadotrophins in one study (Chen 1992), cycle cancellation in one study (Kingsland 1992), and other outcomes in none of the included studies.

3. Short versus ultrashort protocol

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in none of the included studies, clinical pregnancies in one study (Berker 2010), number of oocytes in one study (Berker 2010), dose of gonadotrophins in one study (Berker 2010), cycle cancellation in one study (Berker 2010), and other outcomes in none of the included studies.

4. Long protocol: luteal versus follicular start of GnRHa

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in one study (Urbancsek 1996), clinical pregnancies in five studies (Kondaveeti-Gordon 1996; Pellicer 1989; Ron-El 1990; Sarhan 2013; Urbancsek 1996), number of oocytes in four studies (Kondaveeti-Gordon 1996; Pellicer 1989; Ron-El 1990; Sarhan 2013), dose of gonadotrophins in four studies (Kondaveeti-Gordon 1996; Pellicer 1989; Ron-El 1990; Sarhan 2013), cycle cancellation in two studies (Kondaveeti-Gordon 1996; Sarhan 2013), and other outcomes in none of the included studies.

5. Long protocol: continuation of GnRHa versus stopping GnRHa at start of stimulation

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in three studies (Ding 2013; Dirnfeld 1999; Simons 2005), clinical pregnancies in four studies (Ding 2013; Dirnfeld 1999; Garcia-Velasco 2000; Simons 2005), number of oocytes in four studies (Ding 2013; Dirnfeld 1999; Garcia-Velasco 2000; Simons 2005), dose of gonadotrophins in four studies (Ding 2013; Dirnfeld 1999; Garcia-Velasco 2000; Simons 2005), cycle cancellation in three studies (Dirnfeld 1999; Garcia-Velasco 2000; Simons 2005), and other outcomes (OHSS) in one study (Ding 2013).

6. Long protocol: continuation of same-dose GnRHa versus reduced-dose GnRHa until HCG administration

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in none of the included studies, clinical pregnancies in four studies (Dal Prato 2001; Ding 2013; Fábregues 2005; Simon 1994), number of oocytes in three studies (Ding 2013; Fábregues 2005; Simon 1994) dose of gonadotrophins in two studies (Dal Prato 2001; Ding 2013), cycle cancellation in two studies (Dal Prato 2001; Ding 2013), and other outcomes in none of the included studies.

7. Long protocol: discontinuing versus continuing GnRHa after HCG administration

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in one study (Isikoglu 2007), clinical pregnancies in one study (Isikoglu 2007), number of oocytes in one study (Isikoglu 2007), dose of gonadotrophins in one study (Isikoglu 2007), cycle cancellation in one study (Isikoglu 2007), and other outcomes in none of the included studies.

8. Long protocol: administration of GnRHa for two versus three weeks before stimulation

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies in one study (Lin 2013), clinical pregnancies in one study (Lin 2013), number of oocytes in one study (Lin 2013) and dose of gonadotrophins in one study (Lin 2013). None of the included studies reported cycle cancellation or other outcomes of interest.

9. Short protocol: continuation versus stopping GnRHa

The outcomes reported in this comparison group were as follows: live birth/ongoing pregnancies rate in none of the included studies, clinical pregnancies in one study (Cedrin-Durnerin 2000), number of oocytes in none of the included studies, dose of gonadotrophins in one study (Cedrin-Durnerin 2000), cycle cancellation in one study (Cedrin-Durnerin 2000), and other outcomes in none of the included studies.

For the characteristics of included studies, see the 'Characteristics of included studies' tables.

Excluded studies

A list of the 63 excluded studies is provided in a table, along with the reasons for exclusion (please see the 'Characteristics of excluded studies' tables).

Risk of bias in included studies

A complete overview of our classification of risk of bias domains can be found in the 'Characteristics of included studies' tables. The following is a summary of methods, participants, and interventions in the included studies for the various comparisons. See Figure 2 and Figure 3.

Allocation

Random sequence generation

Adequate sequence generation was present in 22 out of 37 included studies, which we considered as at low risk of selection bias. For the remaining 15 studies, there was no clear mention of the method of randomisation (Acharya 1992; Chen 1992; De Placido 1991; Dirnfeld 1999; Frydman 1988; Hedon 1988; Loumaye 1989; Pellicer 1989; Ron-El 1990; San Roman 1992; Tasdemir 1995; Urbancsek 1996; van de-Helder 1990; Yang 1996; Zhang 2009), so we judged them to be at unclear risk of bias. We rated 22 studies as low risk of this bias, no studies as high risk, and 16 studies as at unclear risk.

Allocation concealment

Eight studies used adequate methods for concealment of the random sequence, using sealed envelopes, and we judged these to be at low risk of selection bias (Berker 2010; Dal Prato 2001; Ding 2013; Fábregues 2005; Kingsland 1992; Simons 2005; Sunkara 2014; Tan 1992). Twenty-three studies did not report an attempt to conceal the allocation; we judged these to be at unclear risk of bias. We rated six studies as high risk as the authors reported no concealment of allocation (Dirnfeld 1991; Fenichel 1988; Hazout 1993; Kondaveeti-Gordon 1996; San Roman 1992; Ye 2001) (Figure 2; Figure 3).

Blinding

Although our outcomes of interest were objective, we believe that blinding of clinicians and participants is important in order to avoid performance and detection biases. Blinding the clinician or participants was not a feature in 26 studies included in the review. We judged only two studies as low risk (Simons 2005; Sunkara 2014). We rated nine studies as "unclear" concerning risk of bias, as there were no data regarding blinding (Berker 2010; Dal Prato 2001; De Placido 1991; Ding 2013; Foulot 1988; Garcia-Velasco 2000; Sarhan 2013; Yang 1996; Zhang 2009).

We rated two studies as at low risk of bias, 26 studies as at high risk, and nine studies as at unclear risk regarding blinding.

Incomplete outcome data

We rated eight out of 37 studies as at high risk of attrition bias (Ding 2013; Dirnfeld 1999; Fábregues 2005; Hazout 1993; Hedon 1988; Simon 1994; Tasdemir 1995; Urbancsek 1996), four out of 37 studies as at unclear risk of attrition bias (Chen 1992; De Placido 1991; Kondaveeti-Gordon 1996; Pellicer 1989), and the rest of them as at low risk of attrition bias (Acharya 1992; Berker 2010; Cedrin-Durnerin 2000; Chatillon-Boissier 2012; Dal Prato 2001; Dirnfeld 1991; Fenichel 1988; Foulot 1988; Frydman 1988; Garcia-Velasco 2000; Isikoglu 2007; Kingsland 1992; Lin 2013; Loumaye 1989; San Roman 1992; Sarhan 2013; Simons 2005; Sunkara 2014; Tan 1992; van de-Helder 1990; Weissman 2003; Yang 1996; Ye 2001; Zhang 2009).

We rated 25 studies as at low risk of attrition bias, five studies as at unclear risk, and eight studies as at high risk.

Selective reporting

Eighteen studies reported at least one of the two primary outcomes: live birth or ongoing pregnancy rate. We judged these to be at low risk of reporting bias (Berker 2010; Chatillon-Boissier 2012; Ding 2013; Dirnfeld 1991; Foulot 1988; Frydman 1988; Hedon 1988; Isikoglu 2007; Kingsland 1992; Lin 2013; Loumaye 1989; San Roman 1992; Simons 2005; Sunkara 2014; Tasdemir 1995; Urbancsek 1996; van de-Helder 1990; Weissman 2003). Eighteen trials failed to report either of the two primary outcomes for this review, so we judged these to be at unclear risk of reporting bias. We judged one trial to be at high risk because it reported only clinical pregnancy, without reporting any other outcomes (De Placido 1991).

We rated 18 studies as at low risk of bias, one study as at high risk, and 18 studies as at unclear risk regarding selective reporting.

Other potential sources of bias

In the majority of included studies (23 studies), there was insufficient information to assess whether an important risk of bias existed. We judged five trials as high risk for different reasons (Cedrin-Durnerin 2000; De Placido 1991; Dirnfeld 1991; Pellicer 1989; Tasdemir 1995). In one trial, the median number of embryos transferred was significantly different between the intervention and the control group. Besides, there was no mention of the exact number of participants in each group (Tasdemir 1995). In one study, the intervention and the control group commenced GnRHa on different days (Pellicer 1989). In one study, the long GnRH protocol was commenced in either the luteal or follicular phase (Dirnfeld 1991). In two trials, data regarding the number of participants and other inclusion criteria were lacking (De Placido 1991). One trial excluded an important group of IVF participants (participants with chronic anovulation) from participation and used two variants of short protocol (Cedrin-Durnerin 2000). We judged the rest of the trials (nine trials) as at low risk for other potential sources of bias.

We rated nine studies as at low risk of bias, five studies as at high risk, and 23 studies as at unclear risk in this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Long protocol compared with short protocol for pituitary suppression in assisted reproduction; **Summary of findings 2** Long protocol compared with ultrashort protocol for pituitary suppression in assisted reproduction; **Summary of findings 3** Short compared with ultrashort protocol for pituitary suppression in assisted reproduction; **Summary of findings 4** Long luteal phase protocol compared with long follicular phase protocol for pituitary suppression in assisted reproduction; **Summary of findings 5** Long protocol continued GnRH agonist compared with long protocol stop GnRH agonist for pituitary suppression in assisted reproduction; **Summary of findings 6** Long protocol (continued same versus reduced dose GnRHa) for pituitary suppression in assisted reproduction; **Summary of findings 7** Long protocol (GnRHa until HCG) compared with long protocol (extend GnRHa 12 days after HCG) for pituitary suppression in assisted reproduction; **Summary of findings 8** Long protocol: administration of GnRHa for two versus three weeks before stimulation for pituitary suppression

in assisted reproduction; **Summary of findings 9** Short protocol compared with stop short protocol for pituitary suppression in assisted reproduction

1. Long versus short protocol

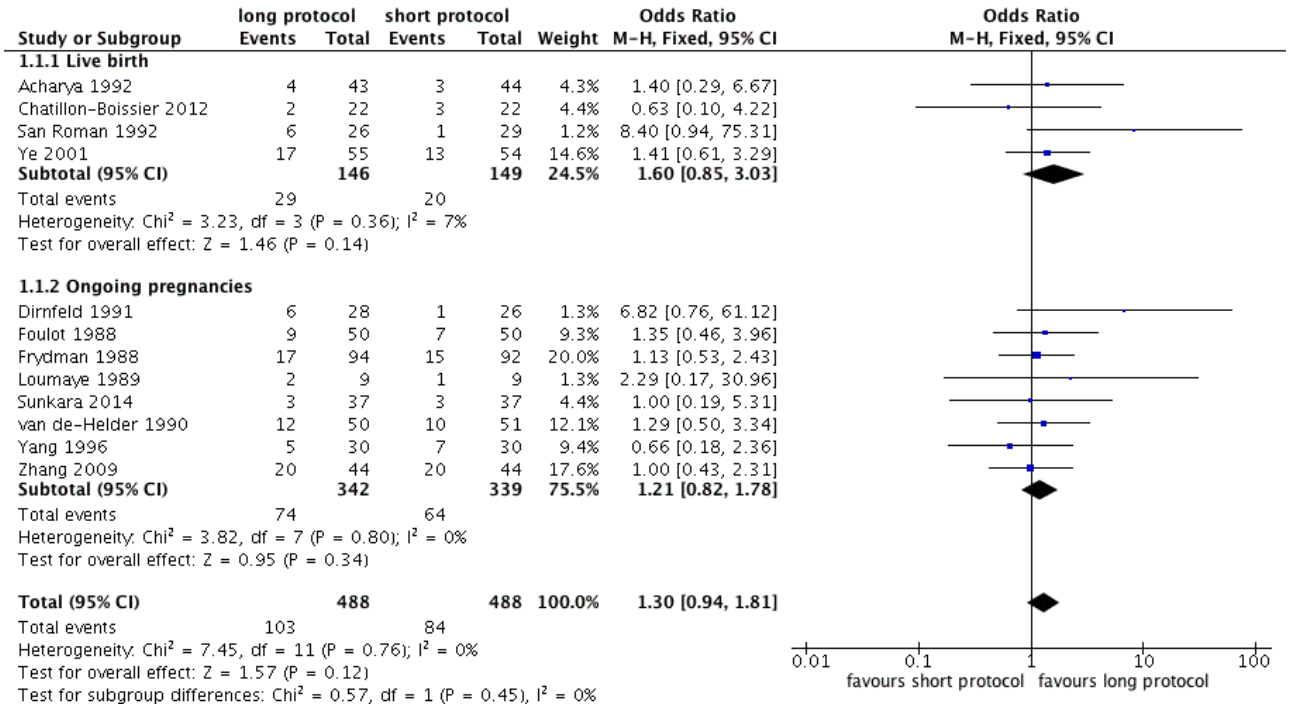
We included 20 studies in this comparison (Summary of findings for the main comparison).

Primary outcome measure

1.1 Live birth and ongoing pregnancy rates

There was no evidence of a difference in live birth and ongoing pregnancy rates between the two protocols (odds ratio (OR) 1.30, 95% confidence interval (CI) 0.94 to 1.81; 12 RCTs, n = 976 women, I^2 = 15%, low quality evidence) (Analysis 1.1; Figure 5; Summary of findings for the main comparison). Analyses 1.1.1 and 1.1.2 present separately the differences in live and ongoing pregnancy rates. A sensitivity analysis including only studies with adequate randomisation and complete outcome data reporting included five studies (Chatillon-Boissier 2012; Dirnfeld 1991; Foulot 1988; Sunkara 2014; Ye 2001): there was no evidence of a difference in live birth and ongoing pregnancy rates between the two protocols (OR 1.45, 95% CI 0.83 to 2.52; five RCTs, n = 481 women, I^2 = 0%, moderate quality evidence).

Figure 5. Forest plot of comparison: 1 Long versus short protocol, outcome: 1.1 Live birth/ongoing pregnancies.

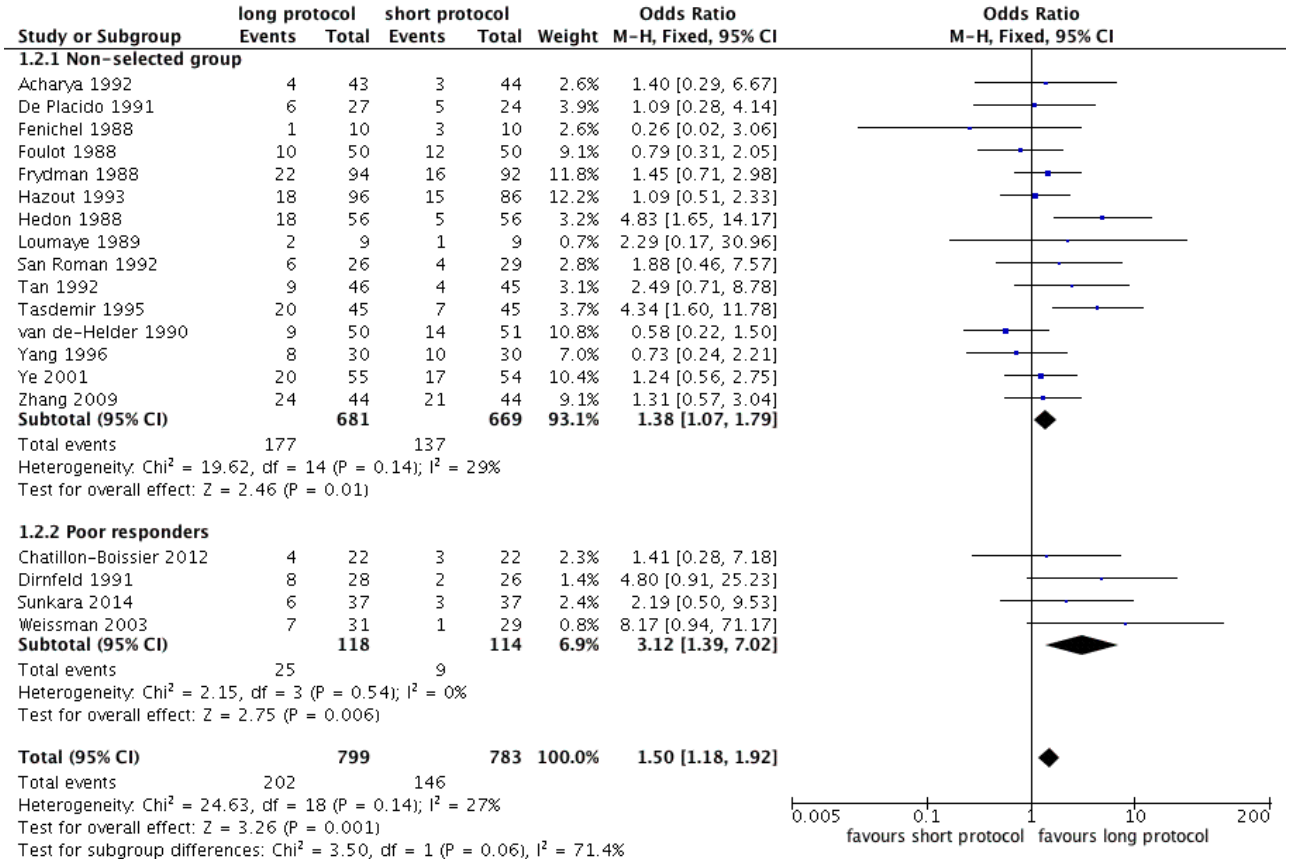


Secondary outcomes

1.2 Clinical pregnancy rate

There was evidence of an increase in clinical pregnancy rate (OR 1.50, 95% CI 1.18 to 1.92; 20 RCTs, n = 1643 women, I^2 = 27%, moderate quality evidence) in the long protocol group when compared with the short protocol group (Analysis 1.2; Figure 6). The subgroup of studies including poor responders only also showed a difference in clinical pregnancy rates (OR 3.12, 95% CI 1.39 to 7.02; four RCTs, n = 232 women, I^2 = 0%, moderate quality evidence), favouring the long protocol (Analysis 1.2; Figure 6).

Figure 6. Forest plot of comparison: 1 Long versus short protocol, outcome: 1.2 Clinical pregnancies.



1.3 Number of oocytes

Due to the high heterogeneity of the pooled analysis (10 RCTs, n = 789 women, I^2 = 91%), we did not pool data. The heterogeneity was among the six studies of unselected women. Of these studies, two showed a significant difference in favour of the long protocol. Subgroup analysis of the four studies including poor responders showed evidence of an increase in the number of oocytes in the long protocol compared with the short protocol (mean difference (MD) 1.40, 95% CI 0.75 to 2.06; four RCTs, n = 227 women, I^2 = 0%, low quality evidence) (Analysis 1.3).

1.4 Number of ampoules of gonadotrophins

Due to the high heterogeneity of the pooled analysis (eight RCTs, n = 666 women, I^2 = 94%), we did not pool data. The heterogeneity was among the four studies of unselected women. All of these studies showed a significant difference in favour of the long protocol. Subgroup analysis of the studies including poor responders showed evidence of a substantial increase in the requirement of gonadotrophins in a long protocol compared with a short protocol (MD 7.07, 95% CI 3.06 to 11.08; four RCTs, n = 227 women, I^2 = 0%, low quality evidence) (Analysis 1.4).

1.5 Cycle cancellation rate

There was no evidence of a difference between the groups in the cycle cancellation rate (OR 0.95, 95% CI 0.59 to 1.55; 11 RCTs, n = 1026 women, I^2 = 42%, low quality evidence) (Analysis 1.5). Subgroup analysis of the four studies including poor responders showed evidence of fewer cancellations in the long protocol compared with the short protocol (OR 0.31, 95% CI 0.12 to 0.76; four RCTs, n = 227 women, I^2 = 0%, low quality evidence) (Analysis 1.5).

1.6 Other outcomes

There were no studies reporting on other adverse outcomes, cost effectiveness, or acceptability of these drugs.

2. Long versus ultrashort protocol

We included two studies in this comparison (Summary of findings 2).

Primary outcome measure

2.1 Live birth and ongoing pregnancy rates

There was no evidence of a difference in live birth and ongoing pregnancy rates when a long protocol was compared with an ultrashort protocol (OR 1.78, 95% CI 0.72 to 4.36; one RCT, n = 150 women, low quality evidence) (Analysis 2.1).

Secondary outcomes

2.2 Clinical pregnancy rate

There was no evidence of a difference in the clinical pregnancy rate when a long protocol was compared with an ultrashort protocol (OR 1.56, 95% CI 0.80 to 3.06; two RCTs, n = 230 women, I^2 = 67%, low quality evidence) (Analysis 2.2).

2.3 Number of oocytes retrieved

There was no evidence of a difference in the number of oocytes recovered when a long protocol was compared with an ultrashort protocol (MD 0.53, 95% CI -0.61 to 1.66; two RCTs, n = 230 women, I^2 = 67%, low quality evidence) (Analysis 2.3).

2.4 Number of ampoules of gonadotrophins

There was no evidence of a difference in the ampoules of gonadotrophins used when a long protocol was compared with an ultrashort protocol (MD 1.10, 95% CI -1.81 to 4.01; one RCT, n = 80 women, low quality evidence) (Analysis 2.4).

2.5 Cycle cancellation

There was no evidence of a difference in the cycle cancellation rate when a long protocol was compared with a short protocol (OR 1.11, 95% CI 0.40 to 3.05; one RCT, n = 150 women, low quality evidence) (Analysis 2.5).

2.6 Other outcomes

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols.

Neither sensitivity nor subgroup analysis was done because of the low number of studies reporting on this comparison.

3. Short versus ultrashort protocol

We found only one study for this comparison (Summary of findings 3).

Primary outcome measure

3.1 Live birth and ongoing pregnancy rates

There were no studies reporting on this outcome.

Secondary outcome measures

3.2 Clinical pregnancy rate

There was no evidence of a difference in the clinical pregnancy rate when a short protocol was compared with an ultrashort protocol (OR 1.33, 95% CI 0.47 to 3.81; one RCT, n = 82 women, very low quality evidence) (Analysis 3.6).

3.3 Number of oocytes

There was no evidence of a difference in the number of oocytes recovered when a short protocol was compared with an ultrashort protocol (MD 0.70, 95% CI -1.83 to 3.23; one RCT, n = 82 women, very low quality evidence) (Analysis 3.7).

3.4 Number of ampoules of gonadotrophins

There was evidence of a difference in the ampoules of gonadotrophins used when a short protocol was compared with an ultrashort protocol (MD -13.85, 95% CI -21.49 to -6.21; one RCT, n = 82 women, very low quality evidence) (Analysis 3.8). Fewer ampoules were used in the short protocol group.

3.5 Cycle cancellation

There was no evidence of a difference in the cycle cancellation rate when a short protocol was used when compared with an ultrashort (OR 1.00, 95% CI 0.13 to 7.46; one RCT, n = 82 women, very low quality evidence) (Analysis 3.9).

3.6 Other outcomes

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols.

Neither sensitivity nor subgroup analysis was done because of the low number of studies reporting on this comparison.

4. Long lutealversus long follicular phase protocol

We included five studies in this comparison (Summary of findings 4).

Primary outcome measure

4.1 Live birth and ongoing pregnancy rates

There was no evidence of a difference in live birth and ongoing pregnancy rates when GnRHa was commenced in the luteal or follicular phase for the long protocol (OR 1.89, 95% CI 0.87 to 4.10; one RCT, n = 223 women, low quality evidence) (Analysis 4.1).

Secondary outcome measures

4.2 Clinical pregnancy rate

There was no evidence of a difference in the pregnancy rate in the luteal start of GnRHa when compared with the follicular start (OR 1.06, 95% CI 0.76 to 1.47; five RCTs, n = 750 women, I^2 = 52%, low quality evidence) (Analysis 4.2).

4.3 Number of oocytes retrieved

There was no evidence of a difference between the groups in the number of oocytes retrieved (MD -1.29, 95% CI -1.85 to 0.71; four RCTS, n = 527 women, I^2 = 74%, low quality evidence) (Analysis 4.3).

4.4 Number of ampoules of gonadotrophins

There was no evidence of a difference in the amounts of gonadotrophins required in luteal start when compared with follicular start in long protocols (MD 1.12, 95% CI -0.73 to 2.97; four RCTs, n = 527 women, I^2 = 51%, low quality evidence) (Analysis 4.4).

4.5 Cycle cancellation

There was no evidence of a difference in cycle cancellation rates in the luteal or follicular start of GnRHa groups (OR 1.45, 95% CI 0.35 to 6.01; two RCTs, n = 267 women, I^2 = 0%, low quality evidence) (Analysis 4.5).

4.6 Other outcomes

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols.

Neither sensitivity nor subgroup analysis was done because of the low number of studies reporting on this comparison for the primary outcome.

5. Long protocol (continue GnRHa versus stop GnRHa)

We included four studies in this comparison (Summary of findings 5).

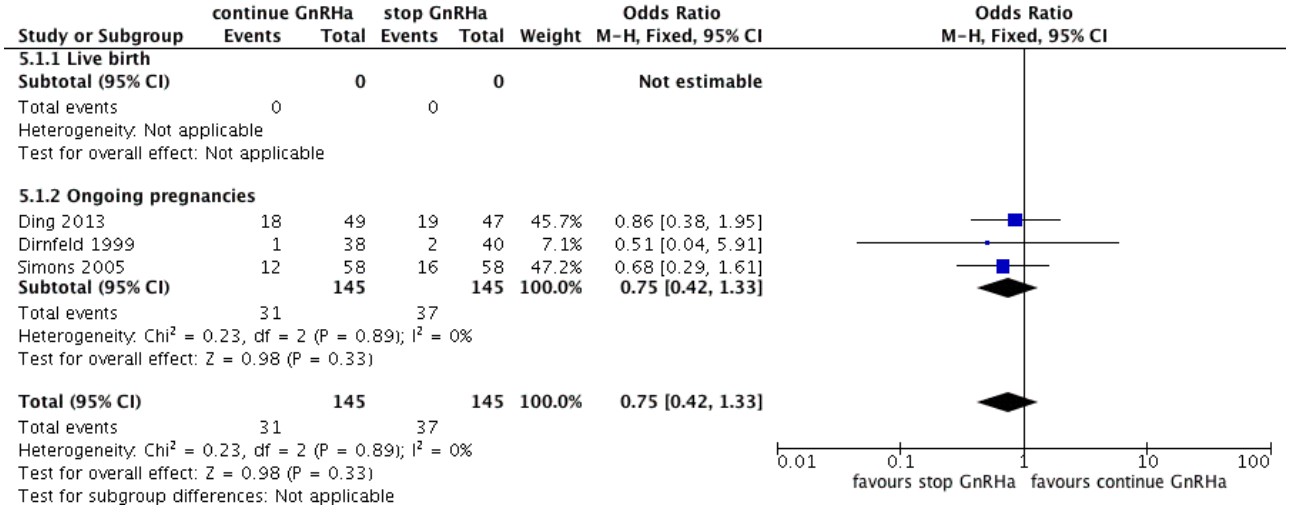
Primary outcome measure

5.1 Live birth and ongoing pregnancy rates

There was no evidence of a difference in the number of live birth and ongoing pregnancies when GnRHa was stopped compared with

when it was continued (OR 0.75, 95% CI 0.42 to 1.33; three RCTs, n = 290 women, I^2 = 0%, low quality evidence) (Analysis 5.1; Figure 7).

Figure 7. Forest plot of comparison: 5 Long protocol (continued GnRHa versus stop GnRHa), outcome: 5.1 Live birth and ongoing pregnancies.



Secondary outcomes

5.2 Clinical pregnancies

There was no evidence of a difference in the clinical pregnancy rate whether GnRHa was continued or stopped (OR 0.85, 95% CI 0.51 to 1.41; four RCTs, n = 360 women, I^2 = 0%, low quality evidence) (Analysis 5.2).

5.3 Number of oocytes

There was no evidence of a difference in the number of oocytes retrieved when GnRHa was continued compared with when it was stopped (MD -0.26, 95% CI -1.29 to 0.78; four RCTs, n = 360 women, I^2 = 73%, low quality evidence) (Analysis 5.3).

5.4 Number of ampoules of gonadotrophins

There was no evidence of a difference in the amount of gonadotrophins required in the two groups (MD -0.14, 95% CI -2.35 to 2.08; four RCTs, n = 360 women, I^2 = 65%, low quality evidence) (Analysis 5.4).

5.5 Cycle cancellation rate

There was no evidence of a difference in the cycle cancellation rate when GnRHa was stopped compared with when it was continued (OR 1.47, 95% CI 0.04 to 5.35; three RCTs, n = 264 women, I^2 = 69%, low quality evidence) (Analysis 5.5).

5.6 Other outcomes

Neither sensitivity nor subgroup analysis was done because of the low number of studies reporting on this comparison.

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols, apart from the OHSS rate (Ding 2013).

There was no evidence of a difference in rate of OHSS between the two groups compared (OR 0.47, 95% CI 0.04 to 5.35; one RCT, n = 96 women, low quality evidence) (Analysis 5.6).

6. Long protocol (continued same-dose GnRHa versus reduced-dose GnRHa)

We included four RCTs in this comparison (Summary of findings 6).

Primary outcome measure

6.1 Live birth and ongoing pregnancy rates

No study reported on this outcome.

6.2 Clinical pregnancy rate

There was no evidence of a difference in the pregnancy rate when the dose of GnRHa was reduced compared with when the same dose was continued (OR 1.02, 95% CI 0.68 to1.52; four RCTs, n = 407 women, I^2 = 0%, low quality evidence) (Analysis 6.2).

6.3 Number of oocytes

There was no evidence of a difference in the number of oocytes retrieved between groups (MD 1.03, 95% CI -0.04 to 2.10; three RCTs, n = 275 women, I^2 = 0%, low quality evidence) (Analysis 6.3).

6.4 Number of ampoules of gonadotrophins

There was no evidence of a difference in the number of ampoules of gonadotrophins required between the compared groups (MD 0.98, 95% CI -1.72 to 3.69; two RCTs, n = 228 women, I^2 = 58%, low quality evidence) (Analysis 6.4).

6.5 Cycle cancellation rate

There was no evidence of a difference in the cycle cancellation rate for the two groups (OR 1.00, 95% CI 0.14 to 7.32; two RCTs, n = 228 women, I^2 = not applicable, low quality evidence) (Analysis 6.5).

6.7 Other outcomes

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols.

Neither sensitivity nor subgroup analysis was done because of the lack of studies reporting on this comparison and addressing the primary outcome.

7. Long protocol: discontinuing versus continuing GnRHa after HCG administration

We included only one study in this comparison (Summary of findings 7).

Primary outcome measure

7.1 Live birth and ongoing pregnancy rates

There was no evidence of a difference in live birth and ongoing pregnancy rates in this comparison (OR 0.89, 95% CI 0.49 to 1.64; one RCT, n = 181 women, low quality evidence) (Analysis 7.1).

Secondary outcome measures

7.2 Clinical pregnancy rate

There was no evidence of a difference in the clinical pregnancy rate when discontinuing versus continuing GnRHa after HCG administration (OR 1.02, 95% CI 0.57 to 1.83; one RCT, n = 181 women, low quality evidence) (Analysis 7.2).

7.3 Number of oocytes retrieved

There was no evidence of a difference between the two compared groups (MD -0.90, -3.04 to 1.24; one RCT, n = 181 women, low quality evidence) (Analysis 7.3).

7.4 Number of ampoules of gonadotrophins

There was no evidence of a difference in the requirement for gonadotrophins between the two compared groups (MD 2.80, -0.55 to 6.15; one RCT, n = 181 women, low quality evidence) (Analysis 7.4).

7.5 Cycle cancellation

There was no evidence of a difference in the cycle cancellation rate in either group (OR 1.50, 95% CI 0.24 to 9.20; one RCT, n = 181 women, low quality evidence) (Analysis 7.5).

7.6 Other outcomes

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols.

Neither sensitivity nor subgroup analysis was done because of the low number of studies reporting on this comparison and addressing the primary outcome.

8. Long protocol: administration of GnRHa for two versus three weeks before stimulation

We included only one study in this comparison (Summary of findings 8).

Primary outcome measure

8.1 Live birth and ongoing pregnancy rates

There was no evidence of a difference in the live birth and ongoing pregnancy rates when administration of GnRH lasted for three or two weeks, respectively, before stimulation (OR 0.88, 95% CI 0.37 to 2.05; one RCT, n = 85 women, low quality evidence) (Analysis 8.1).

Secondary outcome measures

8.2 Clinical pregnancy rate

There was no evidence of a difference in the clinical pregnancy rate when administration of GnRH lasted for three or two weeks, respectively, before stimulation (OR 0.93, 95% CI 0.39 to 2.21; one RCT, n = 85 women, low quality evidence) (Analysis 8.2).

8.3 Total number of oocytes retrieved

There was no evidence of a difference between the groups in the number of oocytes retrieved (MD 12, 95% CI -1.90 to 2.14; one RCT, n = 85 women, low quality evidence) (Analysis 8.3).

8.4 Total dose of gonadotrophins

There was no evidence of a difference between the groups in the ampoules of gonadotrophins (MD 207.00, 95% CI -44.65 to 458.65; one RCT, n = 85 women, low quality evidence) (Analysis 8.4).

8.5 Cycle cancellation rate

There was no study reporting on this outcome.

8.6 Other outcomes

Neither sensitivity nor subgroup analysis was done because of the low number of studies reporting on this comparison and addressing the primary outcome.

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols, apart from OHSS (Lin 2013) and miscarriage rates (Lin 2013).

a. Miscarriage rate

There was no evidence of a difference in miscarriages between the two groups (OR 0.93, 95% CI 0.18 to 4.87; one RCT, n = 85 women, low quality evidence) (Analysis 8.6)

b. OHSS rate

There was no evidence of a difference in OHSS rate between the groups (OR 0.93, 95% CI 0.06 to 15.37; one RCT, n = 85 women, low quality evidence) (Analysis 8.6).

9. Short versus stop short protocol

We included only one study in this comparison (Summary of findings 9).

Primary outcome measure

9.1 Live birth and ongoing pregnancy rates

This was not reported for the comparison.

Secondary outcome measures

9.2 Clinical pregnancy rate

There was no evidence of a difference in the clinical pregnancy rate (OR 0.59, 95% CI 0.30 to 1.17; one RCT, n = 230 women, low quality evidence) when a short protocol was compared with a stop short protocol (Analysis 9.2).

9.3 Total number of oocytes retrieved

This was not reported for the comparison.

9.4 Number of ampoules of gonadotrophins

There was evidence of a difference in the requirement for gonadotrophins with a short stop protocol requiring fewer ampoules of gonadotrophins (MD -5.20, -8.11 to -2.29; one RCT, n = 230 women, low quality evidence) (Analysis 9.4).

9.5 Cycle cancellation

There was no evidence of a difference between the groups in the cycle cancellation rate (OR 0.73, 95% CI 0.34 to 1.59; one RCT, n = 230 women, low quality evidence) (Analysis 9.5).

9.7 Other outcomes

There were no studies reporting on other adverse effects, cost effectiveness, and acceptability of either of these protocols.

DISCUSSION

Summary of main results

The conclusion from the second update of this systematic review and meta-analysis is that there was no conclusive evidence that gonadotrophin-releasing hormone agonist (GnRHa)-long protocol was associated with an increase in live birth and ongoing clinical pregnancy rates in comparison with the GnRHa-short protocol, although there was moderate evidence of an increase in clinical pregnancy rates. The finding remained constant after performing sensitivity analysis, removing studies where the method of randomisation and the reporting of outcomes were unclear. Subgroup analysis including four trials studying poor responders only showed a difference in clinical pregnancy rates, number of oocytes retrieved, and cancellation rates, favouring the GnRHa-long protocol when compared with the GnRHa-short protocol.

There was no evidence of a difference in live birth and ongoing clinical pregnancy rates in comparisons of other protocols of GnRHa for pituitary down-regulation in assisted reproduction treatments.

Apart from two studies where there was evidence of a difference in the dose of gonadotrophins used when a GnRHa-short protocol was compared with a GnRHa-ultrashort protocol, and when a GnRHa-short protocol was compared with a GnRHa-stop short protocol, we found no evidence of any difference for any reproductive outcome (either primary or secondary) when GnRHa was commenced in the follicular phase compared with the luteal phase; stopped, reduced, or continued at the start of stimulation; continued or not after the oocyte triggering; or lasted for two or three weeks before stimulation.

Of note, there was very poor reporting of adverse events among studies in all comparisons, apart from cancellation rates.

Overall completeness and applicability of evidence

In the comparison of GnRH-long versus GnRH-short protocol regimens, despite the inclusion of 20 studies, there was no significant statistical heterogeneity (I^2 = 25%), but, as in many reviews in assisted reproduction, there was evidence of clinical heterogeneity.

The comparison between a luteal versus follicular start of GnRHa was based on five trials. None of them mentioned formation of a cyst, which has been shown to be associated with a follicular phase start of GnRHa (Jenkins 1996). There is controversy over whether cysts are associated with poorer outcomes. On the other hand, there is a risk of inadvertently exposing a pregnancy to GnRHa if administration is commenced in the luteal phase. Four per cent of cases of women undergoing in vitro fertilisation (IVF) have reported such a situation (Ron-El 1990). None of the studies comparing luteal or follicular phase protocols commented on these outcomes.

Furthermore, the number of studies comparing various ways of GnRHa administration in a long protocol was small: three compared the stopping versus the continuation of GnRHa at start of stimulation, four compared the reduction versus the non-reduction of the dose during stimulation, one compared the administration for two versus three weeks before stimulation, and another compared the prolongation versus the stopping after the oocyte retrieval 12 days after the embryo transfer.

Similarly, there were few studies for the rest of the comparisons: two compared GnRHa-long versus ultrashort, one for short versus ultrashort, and one for short versus stop short protocols. Hence, the evidence is insufficient for these comparisons. Also, there were no data on cost effectiveness and acceptability of these protocols to women. Importantly, and as in many systematic reviews and especially Cochrane reviews, we noticed failure of most studies to report on live birth (four out of 20 in the comparison long versus short encompassing the maximum of studies) or adverse events. Moreover, some of the findings only apply to low responders, as this is an issue of applicability.

Quality of the evidence

Although we included 37 studies in the review, most of them were very old. Only 10 were published within the last 10 years; two were published nine years ago (Fábregues 2005; Simons 2005); one, seven years ago (Isikoglu 2007); one, five years ago (Zhang 2009); one, four years (Berker 2010); and the remaining five, within the last two years (Chatillon-Boissier 2012; Ding 2013; Lin 2013; Sarhan 2013; Sunkara 2014). Because of the length of time elapsed, we were unable to contact most of the authors to get any missing data, such as the method of randomisation. Intention-to-treat analysis and an a priori power calculation were not features of any study except for very few in this review.

The general quality evidence for each comparison was low in almost all cases (see the 'Summary of findings' tables). Common limitations were failure to report live birth, risk of bias, and imprecision. Although statistical heterogeneity was not significant in most analyses, there was clinical heterogeneity, with a wide variation in the dose regimens and preparation of the GnRHa used.

For the first comparison 'long versus short protocol', the quality of the evidence was low for the primary outcome (12 studies), low for the secondary outcome 'Clinical pregnancy rate' (20 studies), and low for cancellation rate (11 studies) (Summary of findings for the main comparison). We observed a significant variation in the outcomes 'Number of oocytes retrieved' and 'Number of ampoules of gonadotrophins', most probably due to the way that these data were presented, such that no pooling of data was performed despite an adequate number of trials (10 and eight studies, respectively). Ideally, we would like to do a subgroup analysis of prognostic factors for where there was significant heterogeneity (Analysis 1.3; Analysis 1.4) based on the number of embryos transferred, previous failed cycles, maternal age, and duration of treatment.

In the rest of the comparisons, the quality of the studies was low for those reporting on the primary and secondary outcomes specified for this review, where reported (in five out of the eight remaining).

Potential biases in the review process

Through the standardised method of identification of studies, we included all relevant studies. We assessed bias according to the Cochrane 'Risk of bias' tool (Higgins 2011) and came to the conclusion that most studies were free of selective reporting. Almost all studies reported pregnancies (clinical). However, most of the studies (even the most recent) did not report live birth, which formed part of the primary outcome measure in this review. There has been considerable debate about what is the best outcome to report in assisted reproduction technology (ART) studies (Min 2004). Although the most reliable effectiveness of an intervention in ART is nowadays considered the reporting of live birth rates, in the current review, the lack of such reporting weakens the robustness of the results obtained.

Agreements and disagreements with other studies or reviews

The results for a GnRHa-long versus a GnRHa-short protocol, with pregnancy rate as the outcome, are similar to those in the previous published version of this review despite the fact that we excluded studies analysing gamete intrafallopian transfer (GIFT) cycles, cross-over trials, and quasi-randomised trials (included in the last review) in this updated review. This updated review includes further comparisons that were not part of the initial review. These referred to the GnRH-long protocol: (1) luteal versus follicular start of GnRHa; (2) stopping and reducing the dose of GnRHa versus continuing the same dose; (3) administration of GnRHa for two versus three weeks before stimulation; and (4) discontinuing versus continuing GnRHa after HCG administration, and to the GnRH-short protocol (short versus stop short).

There are no non-Cochrane reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

When long GnRHa protocols and short GnRHa protocols were compared, we found no conclusive evidence of a difference in live birth and ongoing pregnancy rates, but there was moderate quality evidence of higher clinical pregnancy rates in the long protocol group. None of the other analyses showed any evidence of a difference in birth or pregnancy outcomes between the protocols compared. There was insufficient evidence to make any conclusions regarding adverse effects.

Implications for research

As adjuvants are almost always used in ART protocols, further research with high quality trials are needed to determine an optimal protocol (when to commence and stop GnRHa and its optimal dose), further identifying the most cost-effective and acceptable regimen.

We propose comparisons of these protocols using GnRHa in women stratified by type of subfertility and age. Most importantly, for all comparisons included in this review (nine), live birth, ongoing pregnancy rates, or both, should be the primary outcome reported, along with adverse events, as GnRHa protocols have been associated with high incidence of ovarian hyperstimulation syndrome (OHSS) and miscarriage rates. Finally, further parameters should comprise the outcomes of interest, such as the acceptability of the regimens, their cost, and the woman's preference.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Acharya 1992

Methods	Randomised trial The method of allocation was not described The trial was not blinded
Participants	Couples with all causes of infertility (unexplained: 20%, male factor: 7%, endometriosis: 18%, tubal factor: 55%)
Interventions	Long follicular GnRHa protocol with buserelin acetate 200 µg I/M x 5 daily from day 2 for at least 13 days until ovarian suppression, then 4 ampoules of HMG daily x 3, then 3 ampoules x 1 day, then 2 ampoules daily thereafter and adjusted based on the response versus short GnRHa protocol with buserelin acetate (dose as above) and HMG (dose as above) commencing 1 day later
Outcomes	• Clinical pregnancy per started cycle • Multiple pregnancy • Number of oocytes retrieved (median and range) • Median number of ampoules of gonadotrophins used
Notes	Participants in the short protocol group received norethisterone 5 mg twice daily from day 21 of the previous cycle for 7 to 14 days to ensure ovarian suppression and to schedule the cycle start in such a way that the oocyte retrieval was more likely to occur on a weekday 60% of participants had 3 embryo transfers in both groups There was 1 cycle per woman

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to 1 or the other protocol using a predetermined schedule
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment

Acharya 1992 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	87 participants were randomised; all participants received treatment and were analysed
Selective reporting (reporting bias)	Unclear risk	The published report did not include any of our 2 primary outcomes (live birth/ongoing pregnancy)
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Berker 2010

Methods	Randomised trial The trial used computer-generated block randomisation with sealed envelopes
Participants	82 poor responder participants who underwent ICSI **Inclusion criteria** • At least 1 of: day 3 serum FSH level > 10 mIU/mL, < 6 total antral follicles, prior cycle cancellation, prior poor response to COH (peak E2 < 500 pg/mL, < 6 oocytes retrieved, or both) • Age > 41 **Exclusion criteria** • Participants with only 1 ovary, BMI > 30, PCOS, endometriosis stage III to IV, endocrine or metabolic disease, chromosomal disorders, and participants whose partners were azoospermic
Interventions	Participants were randomised into 2 groups: 1. the participants in the ultrashort GnRH agonist/GnRH antagonist group (n = 41) were administered leuprolide acetate at 40 microg sc/bid, started on day 2 of menses and continued for 3 consecutive days, followed by gonadotrophins, which were initiated on the last day of leuprolide administration with maximal doses continuing until HCG day. Once the leading follicle had reached a size of 14 mm, co-treatment was initiated with the GnRH antagonist cetrorelix at 0.25 mg/day, which was continued up to HCG injection 2. the participants in the microdose group (n = 41) started to use 40 microg sc/bid leuprolide acetate on day 2 of menses, and 2 days after initiation of GnRHa, gonadotropin stimulation was initiated and continued until HCG day The starting dose of recombinant FSH depended on the age, BMI, and ovarian response to the previous cycle and increased to a maximum of 450 IU/day depending on the ovarian response. Dosage of rFSH was individualised after day 5 according to ultrasonographic and hormonal follow-up Luteal support was initiated on the day of oocyte retrieval and continued until the day of pregnancy testing with vaginal progesterone
Outcomes	• Number of mature oocytes • Clinical pregnancy rate • Fertilisation rate • Implantation rate • Grade A embryo rate

Berker 2010 *(Continued)*

	• Cycle cancellation rate
Notes	Cycle cancellation rates were similar in the groups There was 1 cycle per woman The population was selective group (poor responders)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation was computer generated using sealed envelopes
Allocation concealment (selection bias)	Low risk	On the day of stimulation initiation, a nurse who assigned participants to their groups opened sealed envelopes with treatment allocation instructions
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not mention blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 82 poor responder participants underwent 78 COH-ICSI cycles. Of these participants, 41 received the ultrashort GnRH agonist/GnRH antagonist protocol, and 41 received the microdose flare-up protocol. Cycle cancellation was carried out for 2 participants in ultrashort GnRH agonist/GnRH antagonist protocol group
Selective reporting (reporting bias)	Low risk	Most of the outcomes of interest except live birth were reported
Other bias	Low risk	We suspected no other bias

Cedrin-Durnerin 2000

Methods	Randomised trial
Participants	230 infertile women undergoing new or repeated IVF cycles **Exclusion criteria** • Women age 43 or older and those who had chronic anovulation
Interventions	Daily subcutaneous injection of Dtrp6-GnRH (decapeptyl, 100 µg/day) from day 1 of IVF cycle followed by ovarian stimulation with exogenous gonadotrophins 150 IU I/m, with the dose being adjusted according to response Women were randomised into 2 groups: 1. GnRHa being injected daily from day 1 of IVF cycle to the time of HCG administration 2. GnRH agonist administration of agonist being stopped on the 7th day of the IVF cycle
Outcomes	• Number of HMG ampoules • Number of oocytes • Pregnancy rate per started cycle • Miscarriage rate

Cedrin-Durnerin 2000 *(Continued)*

Notes	2 variants of the short protocol were used There was 1 cycle per woman

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	230 women were randomised and received therapy. 30 cycles were cancelled, and analysis was presented for 200 women. The paper thoroughly presented reasons for cancellation
Selective reporting (reporting bias)	Unclear risk	The published report did not include any of our 2 primary outcomes (live birth/ongoing pregnancy)
Other bias	High risk	An important group of IVF participants (participants with chronic anovulation) were excluded from participation. Besides, 2 variants of short protocol were used

Chatillon-Boissier 2012

Methods	Prospective randomised trial
Participants	44 "poor responder" participants undergoing an IVF cycle
Interventions	Participants were randomised into 2 groups: 1. long agonist half-dose group (20 participants) 2. short agonist group (19 participants) COH with rFSH 300 to 450 UI/d
Outcomes	• Number of retrieved oocytes • Total number of embryos • Pregnancy rate per cycle • Pregnancy rate per retrieval • Live birth rate
Notes	There was 1 cycle per woman There was no pretreatment prior to initiation of GnRHa in both groups This was a special category of participants (poor responders)

Risk of bias

Chatillon-Boissier 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised from a computer-generated list of pseudo-random permutation of blocks of variable size
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	44 participants were randomised; 39 participants received treatment (reasons specifically mentioned)
Selective reporting (reporting bias)	Low risk	The paper reported most outcomes of interest
Other bias	Low risk	We suspected no other bias

Chen 1992

Methods	Randomised trial The method of allocation was not described
Participants	Infertile couples with tubal factor (70%), male factor (10%), endometriosis (18%), and oocyte donation (2%) Average female age: 33 years
Interventions	1. Long follicular GnRHa protocol with leuprolide acetate 1 mg s.c. daily from day 2 or 3 until ovarian suppression, then FSH 2 ampoules and HMG 2 to 4 ampoules daily in divided doses adjusted depending on the response 2. Ultrashort GnRHa protocol with leuprolide acetate (as above) from day 3. Luteal support with HCG: 1500 IU X 3 and progesterone in oil 50 mg I/M daily
Outcomes	• Clinical pregnancy rate • Number of oocytes retrieved • Number of ampoules of gonadotrophins
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	The paper did not describe allocation concealment
Blinding (performance bias and detection bias)	High risk	The trial was not blinded

Chen 1992 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting of attrition/exclusions to permit a judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	The paper did not report ongoing pregnancy and live birth, but they were not the planned outcome measures
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Dal Prato 2001

Methods	Prospective randomised
Participants	132 women undergoing COH for IVF/ICSI, aged between 25 and 38 years with infertility caused by tubal idiopathic and male factor infertility **Exclusion criteria** • Cases with active endometriosis or only 1 ovary, or with FSH concentration > 15 IU/L on day 3 of menstrual cycles • Women with previous COH requiring high doses of gonadotrophins in a long GnRHa protocol or conversely a known history of risk of severe hyperstimulation
Interventions	1. In group 1 (66 women), pituitary desensitisation was performed with single I/M injection of triptorelin, 3.75 mg starting from day 21 of the cycle preceding treatment 2. In group 2, 66 women received daily s.c injections of 100 µg triptorelin starting from day 21 of the preceding cycle. At the onset of menses (start time for FSH stimulation), the dose was reduced to 50 µg s.c daily until the day of HCG administration Luteal support - natural progesterone in oil
Outcomes	• Pregnancy rate per women • Number of oocytes • Number of ampoules of gonadotrophins • Miscarriage rates
Notes	Pregnancy was defined as the presence of gestational sac on ultrasound scan performed 4 weeks after embryo transfer There was 1 woman per cycle

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation was done using sealed envelopes containing the name of 1 of the 2 groups
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding (performance bias and detection bias)	High risk	Participants were not blinded to the treatment

Dal Prato 2001 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	132 women were randomised; all women received treatment as allocated
Selective reporting (reporting bias)	Unclear risk	The published report did not include our primary outcome
Other bias	Low risk	We suspected no other bias

De Placido 1991

Methods	Randomised trial
Participants	Information not provided
Interventions	1. Long luteal GnRHa protocol with subcutaneous buserelin acetate (0.3 mg x 2 daily from the luteal phase) 2. Short GnRHa protocol with the same dose of buserelin acetate using a short protocol
Outcomes	• Clinical pregnancy rate per started cycle
Notes	This trial was a randomised comparison of depot versus daily GnRHa formulation; it was assumed that allocation to the long or short GnRHa protocol was also randomised. No data were provided on the number of participants undergoing oocyte retrieval and embryo transfer Gonadotrophin administration, method of oocyte retrieval, and luteal phase management was not described Most of the information in the bias table is incomplete as this was an abstract. We wrote to the authors and did not receive any reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	The paper did not describe allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not describe blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting of attrition/exclusions to permit a judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	High risk	Only the clinical pregnancy rate per started cycle was reported
Other bias	High risk	Data regarding the number of participants and other inclusion criteria were lacking

Ding 2013

Methods	Prospective randomised trial
Participants	96 participants with high response to gonadotrophin stimulation compared with reference concentrations undergoing IVF/ICSI cycle **Inclusion criteria** • Infertility participants with 8 or more subcapsular follicles of 2 to 8 mm in diameter in 1 plane in either ovary undergoing IVF treatments **Exclusion criteria** • Basal FSH > 10 IU/l • Age > 35 years • BMI > 30 kg/m2 • Ovarian surgery radiotherapy or chemotherapy • Ovarian dysfunction • Endometriosis • Hyperprolactinaemia thyroid dysfunction • Presence of organic pelvic diseases
Interventions	96 participants were allocated to 2 independent groups: 1. GnRH agonist withdrawal group (47 participants): triptorelin was initiated during the luteal phase of the previous cycle (day 21), 0.1 mg/day for 10 days followed by 0.05 mg/day until the concentration of serum oestradiol <= 40 pg/ml. Once the serum oestradiol concentration was 40 pg/ml, the stimulation of the ovaries was initiated using recombinant FSH (doses ranging from 150 to 250 IU/day). When the diameter of 1 or more follicles was 14 mm, triptorelin (0.05 mg/day) was withdrawn for 2 (15/47) or 3 (32/47) days 2. control group (49 participants): triptorelin was administered as in group (1), but administration of triptorelin (0.05 mg/day) was continued to the day of triggering ovulation rFSH administration was administered until the triggering of ovulation in both groups
Outcomes	• Implantation rate per transferred embryo • Clinical pregnancy rate per transfer cycle • Ongoing pregnancy rate per transfer cycle • Multiple pregnancy rate per pregnancy • OHSS (moderate/severe)
Notes	Clinical pregnancy was determined by observing a gestational sac by means of echographic screening at 7 weeks of pregnancy Ongoing pregnancy was defined as a conception cycle with at least 1 foetal sac with a positive heartbeat reaching beyond 12 weeks of amenorrhoea There was 1 cycle per participant ET in 29 out of 47 participants in group (1) ET in 26 out of 49 participants in group (2)

Risk of bias

Bias	Authors' judgement	Support for judgement

Ding 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was done by computer software
Allocation concealment (selection bias)	Low risk	The trial used closed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not mention blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	This study enrolled 96 participants Oocyte retrieval cycles: 47/47 and 49/49. The number of retrieved oocytes was reported, but only 54 out of 96 reached ET because on day 3 (18 cycles in the GnRH agonist withdrawal group and 23 cycles in the control group), all embryos were cryopreserved. The criteria for this choice was not mentioned
Selective reporting (reporting bias)	Low risk	ET occurred in 29 out of 47 participants in group (1), and for 26 out of 49 participants in group (2), ET was not reported. However, the ongoing pregnancy rate was reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Dirnfeld 1991

Methods	Randomised controlled trial
Participants	Infertile couples with a previously cancelled or unsuccessful IVF cycle owing to inadequate response Mean female age: 33.5 (range = 26 to 40)
Interventions	1. Long GnRHa protocol with buserelin acetate 1000 µg intranasal daily for 15 to 30 days until ovarian suppression, then reduced to 600 µg daily and HMG 2 to 3 ampoules daily 2. Short GnRHa protocol with buserelin acetate 600 µg intranasal daily from day 1 and HMG 2 to 3 ampoules from day 3 Luteal support from day of oocyte retrieval with progesterone oil 100 mg I/M daily
Outcomes	• Number of oocytes • Number of ampoules of gonadotrophins • Clinical pregnancy rate per cycle • Ongoing pregnancy rate per cycle
Notes	We contacted the author. Long GnRH protocol was commenced in either luteal or follicular phase, although no explanation was given regarding how this decision was made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random numbered table was used

Dirnfeld 1991 *(Continued)*

Allocation concealment (selection bias)	High risk	Allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	54 participants were randomised and received treatment
Selective reporting (reporting bias)	Low risk	The paper reported most of our prespecified relevant outcomes
Other bias	High risk	We contacted the authors. Long GnRH protocol was commenced in either the luteal or follicular phase

Dirnfeld 1999

Methods	Prospective randomised controlled trial
Participants	63 participants with previous poor response to COH, high basal FSH (> 8 mIU/ml), or both, undergoing 78 IVF-ET cycles All causes of infertility were included **Exclusion criteria** • Participants > 42 years of age • Participants with irregular menstrual cycles (> 42 or < 21 days)
Interventions	1. Group 1 received 1000 µg/day of nasal spray or 0.1 mg/day of s.c. D-trp-LHRH (Decapeptyl). Treatment with GnRHa was started in the mid-luteal phase and ended at down-regulation 2. In group 2, ovarian down-regulation was performed in an identical manner and was continued through the follicular phase until the HCG administration
Outcomes	• Number of oocytes • Number of ampoules of gonadotrophins • Clinical pregnancy rate per cycle • Ongoing pregnancy rate per cycle
Notes	There was more than 1 cycle per participant. Outcomes were described as per cycle Clinical pregnancy was defined as presence of intrauterine gestational sac on first trimester USG, and ongoing pregnancy was defined as 1 that progressed beyond 20 weeks' gestation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although the authors mentioned that a random number table was used to generate random sequence, it was not clear how the table was created
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment

Dirnfeld 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	63 women agreed to participate in the trial, but 78 were included in analysis (78 cycles). It was not clear if 63 or 78 participants were randomised
Selective reporting (reporting bias)	Unclear risk	Neither adverse outcomes were mentioned nor live birth rates
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Fenichel 1988

Methods	Randomised trial Allocation was done by drawing lots
Participants	**Inclusion criteria** • Women with tubal factor infertility • No more than 3 previous IVF cycles • Female aged < 38 years (mean: 31 years) • Partner with normal semen analysis
Interventions	1. Long luteal GnRHa protocol with depot triptorelin 3.75 mg i.m. then 15 days later HMG 4 ampoules daily x 4 days, then dose adjusted according to response 2. Short protocol with triptorelin 0.1 mg s.c. daily from cycle day 2 with HMG starting the same day 2 to 4 ampoules x 2 days, then dose adjusted according to response, luteal phase support 1500 IU HCG i.m. x 2
Outcomes	• Clinical pregnancy rate per started cycle • Number of oocytes retrieved • Number of ampoules of gonadotrophins used
Notes	The study also included an arm treated with clomiphene citrate and HMG without GnRHa

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generation was achieved through drawing lots
Allocation concealment (selection bias)	High risk	The paper did not conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias)	Low risk	30 women were randomised; all received treatment

Fenichel 1988 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Our primary outcome was not reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Foulot 1988

Methods	Randomised trial Allocation was done by drawing lots The trial was not blinded
Participants	Infertile couples Mean female age: 32 years **Exclusion criteria** • Women with polycystic ovaries
Interventions	1. Long follicular GnRHa protocol with buserelin 0.3 ml subcutaneously daily for 14 days, then HMG 2 to 4 ampoules daily 2. Short GnRHa protocol with buserelin (same dose) from day 2 and HMG 1 ampoule on days 2 and 3, then 2 ampoules daily from day 4 Luteal phase support with uterogestan from day of oocyte retrieval
Outcomes	• Clinical and ongoing pregnancy rate per started cycle/per oocyte retrieval/per embryo transfer • Number of oocytes retrieved • Number of ampoules of gonadotrophins
Notes	A measure of variance was not given for the number of oocytes and ampoules of gonadotrophins

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation was done by drawing lots
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not report blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 participants were randomised; all received treatment
Selective reporting (reporting bias)	Low risk	The ongoing pregnancy rate was reported, but adverse outcomes were not

Foulot 1988 *(Continued)*

Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Frydman 1988

Methods	Randomised controlled trial
Participants	186 infertile couples with predominantly tubal factor (90%) **Exclusion criteria** • Poor responders in previous IVF cycles (defined by cancelled cycles because of low estradiol)
Interventions	1. In group 1, pituitary desensitisation was obtained by s.c. injection of buserelin (300 µgm twice daily) from day 2 followed by HMG or FSH 2 ampoules twice daily for 7 days, then adjusted based on response 2. Short GnRHa protocol: DTRP6-LHRH 0.1 mg s.c. daily from day 1 or 2 followed by HMG or FSH 2 ampoules daily from day 3 Luteal phase support with dydrogesterone 30 mg daily
Outcomes	• Clinical and ongoing pregnancy rate • Miscarriage • Number of oocytes retrieved
Notes	Participants were randomised to receive HMG and FSH in both protocols (2 interventions) We included the article after internal discussion with SB (as other systematic reviews have shown that FSH and HMG are equivalent) Although outcomes measured the number of oocytes retrieved, we did not include in meta-analysis as there was a statistically significant difference in the oocytes retrieved in both groups in the HMG and FSH group within the long and short protocol group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of allocation was not described; we wrote to the trial authors but did not receive any reply
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	186 participants were randomised; all received treatment. Our outcomes were reported
Selective reporting (reporting bias)	Low risk	Most relevant outcomes were reported (ongoing pregnancy rate was reported, but adverse outcomes were not)
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Fábregues 2005

Methods	Prospective randomised study
Participants	150 consecutive infertile women undergoing their first cycle of IVF/ICSI fulfilling **Inclusion criteria** • Regularly menstruating (26 to 33 days) • Aged 26 to 40 years with a normal BMI (19.5 to 28.0) All women had normal ovaries and no previous surgery; none of them had occult ovarian failure on the basis of their basal FSH < 12 IU/L
Interventions	1. Group 1: pituitary desensitisation was achieved by subcutaneous administration of triptorelin acetate (decapeptyl 0.1 mg/day) started in the mid-luteal phase of the previous cycle and continued until administration of HCG 2. Group II: standard daily dose of triptorelin acetate was reduced to 0.05 mg once the ovarian suppression was confirmed and stimulation with recombinant FSH was commenced
Outcomes	• Clinical pregnancy • Number of oocytes
Notes	Intention-to-treat analysis was not done There was 1 cycle per woman A total dose of gonadotropin with variance was given rather than number of ampoules

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	150 women were randomised; all received treatment (13 cycles were cancelled due to low response - there were analyses for 137 women). Although there were 75 women in each group, full data was only reported for 68 and 69 women, respectively
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Low risk	Although the paper gave an a priori sample size calculation, there was insufficient information to assess whether an important risk of bias existed

Garcia-Velasco 2000

Methods	Prospective randomised controlled trial
Participants	70 women who were undergoing stimulation for IVF/ICSI cycles and were previous low responders **Inclusion criteria** • Women had to have at least 1 previous cycle cancelled due to poor response and FSH < 12 IU/ml **Exclusion criteria** • There was no exclusion criteria or age limit
Interventions	1. GnRHa was started in the luteal phase of the previous cycle (leuprolide acetate 1 mg/day s.c.) on day 21 and was continued in group 1 up until the day of HCG 2. In group 2, GnRHa was stopped as soon as gonadotrophins were commenced. On day 1 and 2 of stimulation, 3 ampoules of HMG were administered together with 5 ampoules of FSH. On days 3, 4, and 5 of ovarian stimulation, 2 ampoules of HMG and 3 ampoules of FSH were administered
Outcomes	• Pregnancy per cycle/per woman • Pregnancy per transfer • Number of cancellations due to poor response • Number of oocytes obtained
Notes	There was 1 cycle per woman This was a special category of participants (poor responders)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computerised random number list was used
Allocation concealment (selection bias)	Unclear risk	The paper did not describe the method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not report blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	70 women were randomised; all women were included in analysis
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Hazout 1993

Methods	Randomised trial Allocation was done by using permutation blocks of 8

Hazout 1993 *(Continued)*

Participants	**Inclusion criteria** • New or repeat IVF participants with either unexplained infertility (31%) or tubal factor (69%) • Females aged less than 38 years and duration of infertility < 4 years
Interventions	1. Long follicular GnRHa protocol with decapeptyl, 3.75 mg depot, administered cycle day 2 then 18 days later or when estradiol suppression was achieved, HMG at 4 ampoules daily (or dose based on participant's response in previous cycles) for 5 days with dose adjusted thereafter depending on the response 2. Short protocol with decapeptyl 0.1 mg daily for 7 days starting cycle day 2, then starting cycle day 4, HMG 3 ampoules daily for 5 days, with dose adjusted thereafter depending on the response. Luteal phase support with HCG 1500 IU on day of transfer and 4 days later (if estradiol < 2500 pg/ml) or with progesterone suppositories 300 mg daily (if estradiol > 2500 pg/ml)
Outcomes	• Clinical pregnancy rate per cycle started, per oocyte retrieval, per embryo transfer • Number of oocytes mature retrieved • Number of ampoules of gonadotrophins used/cycle
Notes	The number of pregnancies in the short protocol group was estimated from the pregnancy rates given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was done by using a permutation block of 8
Allocation concealment (selection bias)	High risk	Allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not report blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	182 women were randomised. 96 received the long protocol. 84 reported in the text versus 86 in the table received the 7-day protocol. There were no cancellations mentioned for the 7-day group
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Hedon 1988

Methods	Randomised trial
Participants	Infertile couples (tubal factor: 53%, unexplained: 19%, endometriosis: 7%, combined cause: 22%), excluding those with male factor infertility and ovulation disorders
Interventions	1. Long follicular GnRHa protocol with buserelin 0.3 ml s.c. x 2 daily days 2 to 14, then HMG 4 ampoules x 3 days, 2 ampoules x 2 days, then dose adjusted based on response 2. Short GnRHa protocol with buserelin (as above) from day 2 together with HMG 1 ampoule x 2, 1.67 ampoules x 3 days, then dose adjusted based on response

Hedon 1988 *(Continued)*

	Luteal support HCG 1500 IU x 2
Outcomes	• Clinical and ongoing pregnancy rate per started cycle/per oocyte retrieval/per embryo transfer • Number of oocytes retrieved • Number of ampoules of gonadotrophins used
Notes	A measure of variance was not given for the number of oocytes retrieved and number of gonadotropin ampoules

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Although 120 women were randomised, data were available for only 112 women; we wrote to the authors but did not receive any reply. 120 participants were randomised, but 56 participants received treatment in each group = 8 participants were not included due to the reasons mentioned
Selective reporting (reporting bias)	Low risk	Most relevant outcomes, including 1 of the primary outcomes in this review, were reported except adverse outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Isikoglu 2007

Methods	Prospective randomised trial
Participants	181 women undergoing IVF/ICSI
Interventions	GnRHa was administered from the 21st day of the preceding cycle. Participants were divided into 2 groups: 1. (n = 90 participants): participants were continuously administered GnRHa for 12 days after embryo transfer 2. (n = 91 participants): GnRHa was stopped on the day of human chorionic gonadotropin administration
Outcomes	• Number of gonadotropin ampoules used • Number of mature oocytes recovered • Rates of testicular sperm usage • Number of embryos transferred • Cycle and transfer cancellation rates • Clinical pregnancy rate • Implantation rate

Isikoglu 2007 *(Continued)*

	• Live birth rate
Notes	Participants were randomised by a computer-generated list

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved by a computer-generated list
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Only embryologists were reported to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	181 participants were randomised; all participants were included and mentioned in the analysis
Selective reporting (reporting bias)	Low risk	All our outcomes were mentioned
Other bias	Low risk	We suspected no other bias

Kingsland 1992

Methods	Randomised trial Allocation was concealed using sealed envelopes
Participants	Couples with all causes of infertility (tubal factor: 50%, unexplained: 29%, male factor: 14%, endometriosis: 5%) undergoing their first IVF attempt
Interventions	1. 2 ampoules per day of HMG were administered by i.m. injection (starting from day 2 of the cycle, 3 ampoules were administered if the woman was over 35 years of age) 2. In addition to regimen in group A, participants were given clomiphene citrate 100 mg/day from day 2 to 6 of the menstrual cycle 3. Ultrashort GnRHa protocol with buserelin 500 µg s.c on days 2, 3, and 4 and HMG from day 3 versus 4. Long follicular GnRHa protocol with buserelin 200 µg s.c. daily from day 1 until pituitary desensitisation, then HMG 3, 4, or 5 ampoules daily (for participants ≤ 35 years, > 35 years, and > 40 years, respectively), versus luteal phase support with HCG 2000 IU i.m. x 2
Outcomes	• Clinical pregnancy and live birth rate per cycle/per embryo transfer • Number of oocytes • Number of ampoules of gonadotrophins
Notes	Women were randomised into 4 groups: A + B without GnRHa and C + D with GnRHa

Risk of bias

Bias	Authors' judgement	Support for judgement

Kingsland 1992 *(Continued)*

Random sequence generation (selection bias)	Low risk	A random number table was used
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	308 women were randomised into 4 groups; all participants received treatment. The number of cancelled cycles was reported
Selective reporting (reporting bias)	Low risk	Most of our outcomes were reported
Other bias	Low risk	We suspected no other bias

Kondaveeti-Gordon 1996

Methods	Randomised prospective study
Participants	Women undergoing IVF/ICSI (first cycle only)
Interventions	1. Down-regulation (buserelin acetate intranasal spray 6 times daily - total daily dose of 1200 µg) commenced on day 1 or day 21 of the cycle
Outcomes	• Pregnancy rate • Number of oocytes obtained
Notes	There was 1 cycle per woman. Although an a priori power calculation was done, the study was powered only to detect difference in the use of gonadotrophins

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated with a permuted block
Allocation concealment (selection bias)	High risk	Allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	86 participants were randomised; all participants received treatment and analysed
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes

Kondaveeti-Gordon 1996 *(Continued)*

Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Lin 2013

Methods	Prospective randomised controlled study
Participants	100 participants undergoing IVF/ICSI cycle **Inclusion criteria** • Subfertile participants undergoing first IVF/(ICSI) with tubal factor, male factor, or unexplained factor • Undertaking a luteal long protocol • Basal FSH levels 10 IU/L • Aged 35 years **Exclusion criteria** • Endometriosis • Adenomyosi • Polycystic ovarian syndrome
Interventions	In both groups, a single dose of long-acting GnRHa (Diphereline®, 1.25 mg, 3.75 mg/ampoule) was administered on days 20 to 22 of the mid-luteal phase. Participants were divided into 2 groups: 1. group A: initiation of gonadotrophins occurred on the 21st day 2. group B: initiation of gonadotrophins on the 14th day after GnRHa administration Ovarian stimulation was performed with an initial gonadotropin dose of 75 to 300 IU (recombinant FSH (rFSH) or human menopausal gonadotropin (HMG))
Outcomes	1. Clinical pregnancy rate 2. Implantation rate 3. Live birth rate 4. Miscarriage rate 5. Moderate OHSS rate
Notes	Clinical pregnancy was defined as a positive serum HCG result, with US evidence of a gestational sac and foetal heartbeat Miscarriage rate was defined as the proportion of participants with an initially positive pregnancy test and US evidence of a gestational sac with a foetal pole where pregnancy failed to develop by 12 weeks of gestation Live birth rate was defined as pregnancies over 28 weeks per treatment cycle of ET Luteal phase support was started immediately after oocyte retrieval

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved by computer-generated random numbers 2 weeks after GnRHa administration

Lin 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 participants from random visits who met the inclusion criteria were recruited. 85 participants were included in analysis. However, all reasons and numbers mentioned for the 15 participants were missing (6 cycles were cancelled due to low response or privacy reasons; ET was cancelled in 6 cycles due to no useable embryos or high risk OHSS - there was no extra justification)
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Low risk	We suspected no other bias

Loumaye 1989

Methods	Randomised trial The method of allocation was not described
Participants	**Inclusion criteria** • Couples with tubal factor infertility • Females aged < 40 years
Interventions	1. Long luteal GnRHa protocol with buserelin 300 µg intranasally, 3 times daily, then HMG 3 ampoules daily from day 3 of subsequent menses 2. Short GnRHa protocol with buserelin (as above) from day 1 followed by 3 ampoules of HMG daily from day 3 Luteal phase support with HCG 1500 IU intramuscular on days 6 and 9 after retrieval
Outcomes	• Clinical pregnancy rate • Ongoing pregnancy rate • Number of oocytes obtained
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded

Loumaye 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	18 participants were randomised; all received therapy. Cancellation was not mentioned; 17 out of 18 transferred
Selective reporting (reporting bias)	Low risk	Our prespecified relevant outcomes were reported, including ongoing pregnancy
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Pellicer 1989

Methods	Randomised trial The method of randomisation was not known
Participants	Women undergoing IVF between 15 January and 31 May 1998 **Inclusion criteria** • Women who had both ovaries and normal ovarian function prior to IVF
Interventions	Pituitary desensitisation was achieved with 300 µgm of buserelin twice a day 1. Group 1 and 2 commenced GnRHa in luteal phase (group 1: 4 to 7 days after ovulation, whereas group 2 commenced 8 to 10 days after ovulation) 2. Group 3 commenced GnRHa in the follicular phase HMG + FSH were used for stimulation. Standard dose was used up to day 5, which was then modified according to individual response
Outcomes	• Number of oocytes • Clinical pregnancy
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocation into groups, but it was not clear how this was done
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The total number of participants randomised was not mentioned in the methods. In the results section, 44 participants were mentioned as receiving treatment after randomisation
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes

Pellicer 1989 *(Continued)*

Other bias	High risk	Group 1 and 2 commenced GnRHa on different days, although both were in the luteal phase

Ron-El 1990

Methods	Random allocation into 2 groups
Participants	216 consecutive women undergoing IVF/ICSI
Interventions	1. GnRHa (3.2 mg decapeptyl single intramuscular injection) was given either on day 1 to 3 of the menstrual cycle (group A) or on day 22 (Group B) HMG was used for stimulation with a standard dose for the first 4 days followed by individual adjustment of doses
Outcomes	• Number of oocytes retrieved • Ampoules of gonadotrophins required • Clinical pregnancy
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Although the paper reported random allocation, it did not describe the exact method
Allocation concealment (selection bias)	Unclear risk	The paper did not describe allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	216 women were randomised; all were mentioned to have received treatment
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

San Roman 1992

Methods	Randomised trial
Participants	55 women undergoing IVF-ET regardless of previous cycle response or number of previous cycles undertaken

San Roman 1992 *(Continued)*

Interventions	1. Group 1 received GnRHa (lupron) 1 mg/day s.c. for 10 days commencing on cycle day 21. After 10 days, if serum estradiol was ≤ 184 pmol/L the GnRHa dose was reduced to 0.5 mg/day s.c. and HMG was administered 225 IU I/M. GnRHa was continued until HCG (long protocol) 2. Group 2 commenced concurrent therapy with GnRHa 0.5 mg/day s.c. and HMG 225 IU I/M beginning on menstrual cycle day 3. Concurrent treatment with GnRHa + HMG was continued for 5 days. GnRHa was continued until HCG (short protocol)
Outcomes	• Cycle cancellation • Number of ampoules of gonadotrophins • Clinical pregnancy • Live birth
Notes	A clinical pregnancy was defined as USG visualisation of gestational sac or pathological evidence of trophoblast GnRHa dose was reduced at the start of stimulation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	High risk	Allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	55 women were recruited and randomised. All women received treatment; outcomes were not reported for 5 of them (low response)
Selective reporting (reporting bias)	Low risk	Our prespecified relevant outcomes were reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Sarhan 2013

Methods	Prospective randomised controlled study
Participants	181 infertile participants undergoing ICSI cycles
Interventions	All participants started treatment with subcutaneous daily injections of GnRHa (triptorelin). Participants were divided into 2 groups: 1. group A (66 participants): treatment with the agonist was started on the first or second day of the menstrual period 2. group B (115 participants): treatment with the agonist was started on day 20 to 22 of the cycle In both groups, the agonist treatment was continued until the day of HCG administration

Sarhan 2013 *(Continued)*

Outcomes	• Days of stimulation • Number of ampoules of gonadotrophins used • Number of oocytes retrieved per cycle • Number of embryos per cycle • Fertilisation rate • Cleavage rate • Pregnancy rate • Clinical pregnancy rate per cycle and per ET
Notes	Clinical pregnancy was defined by the presence of intrauterine gestational sac(s) with pulsating heart beats on trans-vaginal ultrasound scan at 5 to 6 weeks' gestation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using closed envelopes
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not report blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	181 participants were randomised. All participants were mentioned as included in analysis
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Simon 1994

Methods	Prospective randomised trial
Participants	42 women undergoing a fresh cycle of IVF due to tubal obstruction **Inclusion criteria** • Women less than 39 years old who had 2 ovaries and normal ovarian function **Exclusion criteria** • Suspected male factor
Interventions	After pituitary down-regulation (serum estradiol < 30 pg/ml, serum progesterone < 0.5 ng/ml, and the absence of any ovarian follicle > 10 mm in size), participants were allocated into 2 groups: 1. group A continued to receive the standard dose of 0.5 mg/day LHRHa 2. group B were given a reduced dose of 0.1 mg/day of LHRHa

Simon 1994 *(Continued)*

	Luteal support was provided with intramuscular progesterone injection in oil
Outcomes	• Number of oocytes retrieved per woman • Clinical pregnancies/woman • Implantation rate • Pregnancy per ET
Notes	There was 1 cycle per woman

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	In the text, it was reported that 43 women were randomised and received treatment, while in the abstract and tables, it is reported that 42 women received treatment
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was an insufficient rationale or evidence that an identified problem would introduce bias

Simons 2005

Methods	Double-blind, randomised, multicentre study
Participants	178 women undergoing IVF/ICSI treatment, history of spontaneous regular cycle between 24 and 35 days **Inclusion criteria** • Aged 18 to 38 years at the time of screening • BMI < 33 **Exclusion criteria** • Women with either a history of PCO or incipient ovarian failure • Ovulation induction treatment or an IVF/ICSI attempt in the 2 months before the study • Poor response to stimulation in previous cycle
Interventions	1. Group L received the traditional long protocol, i.e., mid-luteally started triptorelin was continued until the day of HCG injection 2. In group M, triptorelin continued up to and including the fourth day of HMG treatment 3. In group S, triptorelin was stopped at the first day of HMG treatment

Simons 2005 *(Continued)*

Outcomes	1. Occurrence of premature LH surge 2. Number of oocytes, implantation rate, clinical and ongoing pregnancy, dose of triptorelin
Notes	Comparison groups for this review: group L versus group S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated
Allocation concealment (selection bias)	Low risk	Allocation was concealed in a sealed envelope in a central locker
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and personnel blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	178 participants were randomised; 18 participants were not included in the analysis. (Reasons and numbers were mentioned thoroughly: discontinuation during the stimulation phase or missing LH data)
Selective reporting (reporting bias)	Low risk	All our prespecified relevant outcomes were reported
Other bias	Low risk	There was insufficient rationale or evidence that an identified problem would introduce bias

Sunkara 2014

Methods	Prospective randomised controlled trial
Participants	111 women with previous poor ovarian response undergoing IVF **Exclusion criteria** • Women aged > 40 years and women with a single ovary
Interventions	Women were allocated to 3 groups: 1. long GnRH agonist group: pituitary down-regulation with nafarelin nasal spray 400 mg twice daily was commenced in the midluteal phase of the menstrual cycle and continued for 2 weeks. Ovarian stimulation was commenced with gonadotropin injections at a dose of 450 IU/day and continued with a reduced dose of nafarelin 200 mg twice daily until the administration of HCG injection 2. short GnRH agonist group: nafarelin nasal spray was commenced on day 2 or 3 of the cycle. Nafarelin was administered at a dose of 200 mg twice daily followed by gonadotropin injections at a dose of 450 IU/day commenced 1 day later. Both nafarelin and gonadotropin injections were continued until the administration of HCG 3. GnRH antagonist group
Outcomes	1. Number of oocytes retrieved 2. Mature oocytes retrieved 3. Clinical pregnancy rates 4. Ongoing pregnancy rates

Sunkara 2014 *(Continued)*

	5. Gonadotropin consumption 6. Duration of stimulation 7. Cycle cancellation rate 8. Fertilisation rate 9. Cycles reaching ET
Notes	Participants were allocated to 1 of the 3 study groups by a third party, distant, internet-based block randomisation to ensure complete allocation concealment. The clinician performing the OR and the embryologist involved were blinded to the treatment allocation The participants were poor responders

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computerised
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding (performance bias and detection bias) All outcomes	Low risk	The clinician performing the OR and the embryologist involved were blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	111 women were randomised. 19 women did not receive the allocated intervention (reasons mentioned: 3 conceived spontaneously; 16 decided to postpone IVF treatment)
Selective reporting (reporting bias)	Low risk	All our planned outcomes were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Tan 1992

Methods	Randomised trial
Participants	Couples with all causes of infertility (unexplained: 25%, male factor: 11%, endometriosis: 5%, tubal factor: 58%) undergoing their first cycle of IVF
Interventions	1. Long follicular GnRHa protocol with buserelin acetate 200 µg subcutaneous daily from day 1 for at least 14 days until ovarian suppression, then HMG 3, 4 or 5 ampoules daily based on age 2. Short protocol GnRHa protocol with buserelin (as above) from day 2 and HMG from day 3 Luteal support with HCG 2000 IU x 2
Outcomes	• Clinical pregnancy rate • Number of oocytes retrieved • Number of ampoules of gonadotrophins
Notes	Significantly more cleaved embryos were available for transfer in participants on the long versus the short protocol

Tan 1992 *(Continued)*

	A measure of variance was not given for the number of oocytes retrieved and number of ampoules of gonadotrophins

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random tables were used
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	91 women were randomised and received treatment
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Tasdemir 1995

Methods	Randomised trial
Participants	Couples with all causes of infertility (tubal factor: 40%, male factor: 29%, unexplained: 19%, endometriosis: 10%) undergoing their first IVF cycle
Interventions	1. Long luteal protocol with buserelin acetate 900 µg intranasal daily then cycle day 2 2. Short GnRHa protocol with buserelin (as above) from cycle day 1 and HMG as above Luteal phase support with 2000 IU HCG x 3
Outcomes	1. Clinical pregnancy rate 2. Live birth rate
Notes	The trial author confirmed that the study was randomised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The exact method of randomisation was not known
Allocation concealment (selection bias)	Unclear risk	The paper did not describe allocation concealment
Blinding (performance bias and detection bias)	High risk	The trial was not blinded

Tasdemir 1995 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	90 participants were randomised. The number of participants allocated to each group was not mentioned in the text or tables either. The number of participants receiving treatment and analysed was not mentioned
Selective reporting (reporting bias)	Low risk	Live birth rate was reported
Other bias	High risk	The median number of embryos transferred was 4 with the long GnRHa protocol and 1 with the short protocol. We obtained confirmation of randomisation in the original review. We did not receive any reply to further queries. There was no power calculation and no mention of the exact number of participants in each group

Urbancsek 1996

Methods	Prospective randomised trial
Participants	124 women undergoing IVF due to tubal factor or unexplained infertility
Interventions	1. Buserelin acetate (intranasally 300 µg 4 times a day) starting on day 1 of cycle or in the mid-luteal phase for pituitary down-regulation
Outcomes	1. Live birth 2. Clinical pregnancy 3. Ongoing pregnancy
Notes	There was more than 1 cycle per participant A measure of variance for the number of oocytes was not given Only unexplained infertility and tubal factor were included There was more than 1 cycle per woman; data for only 1 cycle were not available separately

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was centrally prepared
Allocation concealment (selection bias)	Unclear risk	The paper did not report allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was not done
Selective reporting (reporting bias)	Low risk	Live birth and other prespecified outcomes were reported

Urbancsek 1996 *(Continued)*

Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

van de-Helder 1990

Methods	Randomised trial
Participants	**Inclusion criteria** • Infertile women with blocked tubes and regular cycles • Female aged < 41 years (mean age: 32; range = 23 to 40 years) • Partners with normal semen analysis
Interventions	1. Long luteal GnRHa protocol with buserelin 200 µg intranasally daily (3 times) from the mid-luteal phase until ovarian suppression was confirmed (after which stimulation with HMG was started) 2. Short GnRHa protocol with buserelin from day 1 at the same dose (with start of stimulation with HMG from day 4) Buserelin was continued until the day of HCG administration
Outcomes	• Clinical and ongoing pregnancy rates, per started cycle, per oocyte recovery, per embryo transfer • Number of oocytes retrieved • Number of ampoules of gonadotrophins used
Notes	The trial included a third group that was randomised not to receive GnRHa. Clinical pregnancy was defined as foetal heart activity seen on ultrasound A measure of variance was not provided for the average number of gonadotrophins ampoules and average number of oocytes retrieved

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	152 participants were randomised; 152 participants received treatment - there were 23 cancellations, all due to low response
Selective reporting (reporting bias)	Low risk	Our prespecified outcomes, including ongoing pregnancy rate, were reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Weissman 2003

Methods	Randomised prospective study
Participants	60 low responders (from previous cycle) who were undergoing IVF Poor responders were defined as fewer than 5 oocytes retrieved, 3 or fewer follicles 16 mm or larger on the day of cancellation or serum E2 less than 500 pg/ml on the day of HCG administration Only participants with FSH less than 20 IU/L were included
Interventions	1. Short protocol (high dose GnRHa (500 µg/day) was administered for first 4 days followed by a standard agonist dose (100 µg/day) 2. Long protocol (standard GnRHa dose (100 µg/day) used until pituitary down-regulation after which the agonist dose was halved during stimulation)
Outcomes	• Number of oocytes retrieved • Number of cancellation • Implantation rate • Clinical pregnancy
Notes	Both short and long protocols were modified protocols 1 cycle per woman

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	60 participants were randomised; treatment was allocated to all of them
Selective reporting (reporting bias)	Low risk	Most outcomes of interest were reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Yang 1996

Methods	Randomised trial
Participants	Couples with all causes of infertility except severe male factor and polycystic ovarian syndrome (tubal factor: 52%, unexplained: 28%, endometriosis: 17%, male factor: 3%)

Yang 1996 *(Continued)*

Interventions	1. Long GnRHa protocol with leuprolide acetate 1 mg subcutaneously daily until ovarian suppression, then dose reduced to 0.5 mg daily together with HMG 3 to 6 ampoules intramuscular daily x 5 days then HMG dose reduced according to the response 2. A modified short protocol with decapeptyl 0.1 mg s.c. daily from cycle day 1 to 7 with HMG (as above) starting cycle day 3 Luteal support with progesterone vaginal suppositories 200 mg x 2 daily with HCG 1500 IU intramuscular x 4
Outcomes	• Clinical pregnancy rate per cycle started • Number of oocytes retrieved • Number of ampoules of gonadotrophins required
Notes	Long GnRHa was commenced in either the luteal or follicular phase There was 1 cycle per woman

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described; we wrote to the trial authors but received no reply
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not report blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	60 participants were randomised; all received treatment, and no cancellations were reported
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Ye 2001

Methods	Prospective randomised trial
Participants	109 infertile couples undergoing IVF
Interventions	1. GnRHa long protocol (GnRHa taken by nasal spray 0.9 mg/day starting on day 21 of previous menstrual cycle; gonadotrophins were started once pituitary suppression was achieved) 2. Short protocol (GnRH agonist 0.45 mg per day commenced on day 2 of the menstrual cycle, and gonadotrophins were commenced on the same day)
Outcomes	• Ampoules of gonadotrophins required • Number of oocytes retrieved • Pregnancy rate

Ye 2001 *(Continued)*

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation was used
Allocation concealment (selection bias)	High risk	Allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	109 participants were randomised; all received therapy as shown in the tables
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Zhang 2009

Methods	Prospective randomised trial
Participants	88 participants with infertility due to tubal factor **Inclusion criteria** • Aged < 35 years of age, BMI: 18 ˜ 29 kg/m2, duration of menstrual cycle (25 ˜ 35 days), spontaneous ovulation • Existence of both ovaries and uterus • Adequate male sperm quality feasible for IVF fertilisation **Exclusion criteria** • Polycystic ovary syndrome, endometriosis, or severe male factor • Systemic, endocrine, or metabolic disease • Undergoing radiotherapy and chemotherapy • Smokers • Those taking narcotics
Interventions	Participants were divided into 2 groups: 1. short GnRHa group (44 participants) 2. long GnRHa group (44 participants)
Outcomes	• Total dose of gonadotrophins • Number of oocytes retrieved, cleavage and fertilisation rates • Clinical pregnancy and miscarriage rates

Zhang 2009 *(Continued)*

	• Concentrations of IGF-II and IGFBP-4 in the follicular fluid
Notes	The article was in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not mentioned
Allocation concealment (selection bias)	Unclear risk	The paper did not mention allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The paper did not mention blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	88 participants were randomised; all participants received treatment. Analyses were mentioned for 88 participants (data derived from tables)
Selective reporting (reporting bias)	Unclear risk	There was no mention of our primary outcomes
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

BMI: body mass index.
COH: controlled ovarian hyperstimulation.
E2: estradiol.
ET: embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.
GnRHa: gonadotrophin-releasing hormone agonists.
HCG: human chorionic gonadotrophin.
HMG: human menopausal gonadotrophin.
I/M: intramuscular.
ICSI: intracytoplasmic sperm injection.
IGFBP-4: insulin-like growth factor binding protein-4.
IGF-II: insulin-like growth factor II.
IVF: in vitro fertilisation.
IVF-ET: in vitro fertilisation pre-embryo transfer.
LH: luteinising hormone.
OHSS: ovarian hyperstimulation syndrome.
OR: oocyte retrieval
PCOS: polycystic ovary syndrome.
rFSH: recombinant follicle-stimulating hormone.
s.c.: subcutaneously.
US/USG: ultrasonography.

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

Study	Reason for exclusion
Abd Rabo 2012	This paper evaluated the effect of using letrozole in improvement of the results of ICSI/ET in women with endometriosis using a long agonist protocol

Study	Reason for exclusion
Aflatoonian 2012	This paper assessed the efficacy of low dose HCG in the late follicular phase in controlled ovarian stimulation using a GnRH agonist protocol
Albuquerque 2013	This was a Cochrane review from the *Cochrane Database of Systematic Reviews*
Antoine 1990	This paper compared GnRHa with no GnRHa
Azem 2010	There were no data for comparison after repeated attempts to reach the authors. Only the abstract was available
Beckers 2000	Participants were randomised into 3 groups. 2 interventions were compared stopping GnRHa on day 3 of stimulation as well as luteal support
Bloch 2011	This paper used the same study population as in Azem 2010, assessing phycological outcomes
Braendle 1989	Allocation to a short or long protocol was sequential and not random
Buvat 1993	Quasi-randomisation was used (randomised by year of birth)
Cambiaghi 2011	This paper compared 2 different regimens of long protocols
Check 1992	This was a randomised trial (allocation was based on the last digit of the participant's social security number) comparing long versus ultrashort protocol, but we excluded as it had a cross-over design
Cheon 2008	This paper compared 2 regiments for the same GnRHa protocol
Corson 1992	This study compared 3 protocols ((a) stopping GnRHa at start of stimulation, (b) reducing GnHa at start of stimulation, (c) no GnRHa at all for both IVF as well as GIFT cycles). We could not extract data on IVF cycles separately. We contacted the authors, but separate data were not available, as the study was very old
Dessolle 2011	This was a prospective non-randomised study
Devroey 1994	This was a non-randomised pilot study
Dor 1992	This study compared GnRHa with no GnRHa
Eftekhar 2013	This trial compared daily injection with a single intramuscular dose of GnRHa
Elgendy 1998	This paper reported quasi-randomisation (alternate IVF numbers)
Faber 1998	This was a non-randomised study
Ferraretti 1996	This was a retrospective data analysis
Fujii 1997	This paper reported quasi-randomisation (group allocated based on day of visit to the unit)
Garcia 1990	The method of allocation to short or long luteal GnRHa protocol was stated to be prospective, but no information was provided on whether randomisation was used. We attempted to contact the authors, but received no reply
Gersak 1994	The paper compared GnRHa with no GnRHa
Gianaroli 1994	This study compared 3 different long protocols: (a) buserelin 0.5 mg s.c. twice a day 15 days prior to ovarian stimulation, (b) a single dose of long-acting triptorelin (3.75 mg) 15 days before ovari-

Study	Reason for exclusion
	an stimulation, (c) long-acting triptorelin 4 weeks prior to ovarian stimulation followed by daily administration of 0.1 mg agonist until HCG injection. This did not follow any of the defined comparisons in the protocol
Gizzo 2014	Randomisation was according to the luteal phase supplementation
Harrison 1994	This paper compared GnRHa with no GnRHa
Huang 2012	This was a retrospective study
Jinno 1996	This paper was an evaluation of bromocryptine in 1 of 2 groups
Jinno 2009	This paper compared different doses of the same GnRH agonist
Ku 2005	This was a retrospective study
Kubik 1990	The paper compared GnRHa with no GnRHa
Kuc 2011	This was a retrospective study
Li 2012	This paper compared 2 different doses of Lupron Depot in GnRH analogues in a long 21 protocol
Liu 2012	This was a non-RCT
Lorusso 2004	This was a non-randomised study
Loutradis 1998	This paper compared 2 regiments in long protocols
Marcus 1993	This was a randomised trial (allocation was by the last digit of the medical file number) comparing long versus ultrashort protocol. We excluded it because of its cross-over design
Maroulis 1991	192 women who were referred for IVF. Randomly allocated to group A (protocol with pure FSH-HMG), group B (received GnRHa in the luteal phase), or group C (received GnRHa in the follicular phase). During the first 9 months, participants were randomly allocated between protocol A and B (in 2:1 ratio) whereas for the last 11 months between protocols A, B, and C
McKenna 1989	Allocation was not random
Mochtar 2011	Allocation depended on the size of leading follicles
NCT00436319	This was a stopped trial (personal communication with authors)
NCT02342197	The primary outcome was the number of oocytes retrieved (not the prespecified outcomes of our review)
Neuspiller 1998	This was a study on oocyte donors
Norman 1991	Allocation to a short or long luteal GnRHa protocol was not random, but based on clinical grounds
Padilla 1991	Participants were allocated to 5 different protocols based on the results of the Lupron screening test. Those with pattern C were randomised into 1 of 3 protocols in phase 1: (1) no GnRHa, (2) double dose GnRHa with flare protocol (not clear whether this was short or ultrashort protocol), or (3) luteal phase GnRHa. In phase 2, they were all given luteal phase GnRHa
Pantos 1994	This study was quasi-random (alternate)

Study	Reason for exclusion
Remorgida 1989	We excluded as only GIFT cycles were included
Rodrigues 2014	This was a non-RCT
Ron-El 1992	Allocation to ultrashort GnRHa protocol was based on the ability of the participant to attend the clinic on day 1 or 2. These participants were matched by age and indication for IVF to participants having the long GnRHa protocol
Sarhan 2012	This paper compared 3 GnRH analogues in long protocols
Sathanandan 1989	This comprised of long luteal GnRHa protocol with leuprolide in participants identified as having poor or abnormal response in a previous stimulation cycle versus short GnRHa protocol with leuprolide in participants undergoing their first cycle of treatment or who had had a satisfactory response in a previous cycle. Allocation was not random, and participant groups were not similar
Smitz 1992	Quasi-randomisation (allocated to groups according to year of birth)
Smitz 1992a	The method of allocation to short or long GnRHa protocol was not stated. Pregnancy was not the outcome in this study because none of the participants had embryo transfer owing to complete failure of fertilisation
Stenbæk 2013	This trial compared a short antagonist versus long agonist protocol
Suganuma 1996	This paper reported pseudo-randomisation (alternate participants were allocated into the groups). Some participants had cross-over of groups
Tanaka 2014	The was not an RCT
Tarin 1990	That study was a cytogenetic analysis of human unfertilised oocytes
Tarlatzis 1993	Although the study was designed to have random allocation, in practice the randomisation was incomplete as it was done according to the stimulation protocol, the scheduling convenience, and the cost of the analogue used
Tarlatzis 1994	Although the study was designed to have random allocation, in practice the randomisation was incomplete as it was done according to the stimulation protocol, the scheduling convenience, and the cost of the analogue used
Tehraninejad 2010	The paper compared daily doses versus Lupron Depot of GnRH in a long 21 protocol
van de-Helder 1990b	The paper compared GnRHa with no GnRHa
Wu 2012	Participants were assigned to 4 groups according to serum progesterone and oestradiol concentrations on the day of HCG administration
Yang 1991	The paper compared GnRHa with no GnRHa

FSH-HMG: follicle stimulating hormone-human menopausal gonadotrophin.
GIFT: gamete intra-fallopian transfer.
GnRHa: gonadotrophin-releasing hormone agonists.
HCG: human chorionic gonadotrophin.
ICSI/ET: intracytoplasmic sperm injection/embryo transfer.
IVF: in vitro fertilisation.
RCT: randomised controlled trial.
s.c.: subcutaneously.

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

NCT01006954

Trial name or title	Comparison of Micro Dose Gonadotropin-Releasing Hormone (GnRH) Agonist Flare up & Flare Protocol in Poor Responders in Assisted Reproductive Technology (ART) Cycle
Methods	Allocation: randomised Endpoint Classification: efficacy Study Intervention Model: parallel assignment Masking: single blind (participant) Primary purpose: treatment
Participants	**Inclusion criteria** • Poor responders **Exclusion criteria** • Male factor • Myoma ≥ 6 cm • 1 way ovary • Tumour or cyst > 13 mm • Age > 42
Interventions	1. Microflare and flare up protocols
Outcomes	• Primary outcome measure: pregnancy rate • Secondary outcome measures: cycle cancellation rates, number of oocytes generated, number of embryos generated, implantation rate
Starting date	September 2008
Contact information	Endocrinology and Female Infertility Department Reproductive Medicine Research Centre Royan Institute Academic Center for Education, Culture and Research (ACECR) Tehran Islamic Republic of Iran 14114
Notes	This study has been completed. No data were published

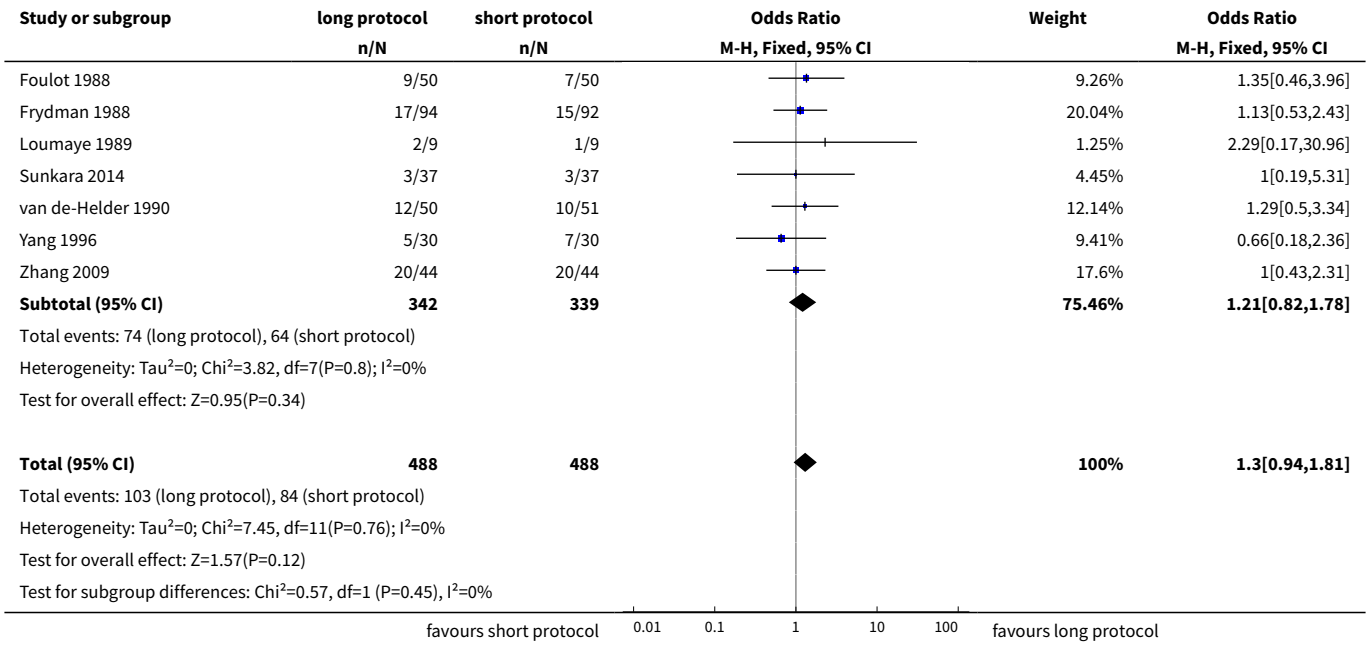
DATA AND ANALYSES

Comparison 1. Long versus short protocol

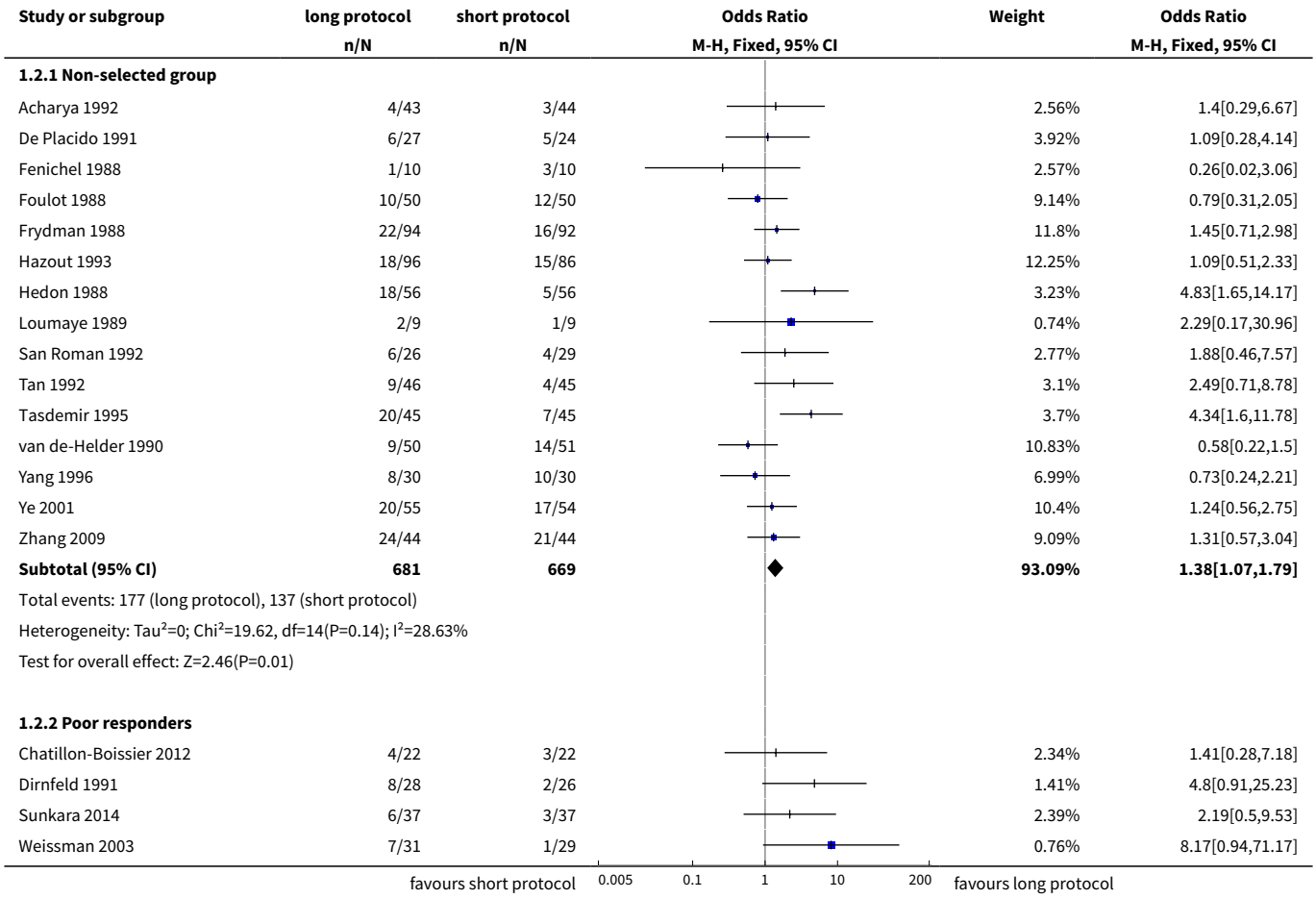
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancies	12	976	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.94, 1.81]
1.1 Live birth	4	295	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.85, 3.03]
1.2 Ongoing pregnancies	8	681	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.82, 1.78]
2 Clinical pregnancies	19	1582	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [1.18, 1.92]
2.1 Non-selected group	15	1350	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [1.07, 1.79]
2.2 Poor responders	4	232	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [1.39, 7.02]
3 Number of oocytes	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Non-selected group	6	512	Mean Difference (IV, Fixed, 95% CI)	2.47 [2.21, 2.72]
3.2 Poor responders	4	227	Mean Difference (IV, Fixed, 95% CI)	1.40 [0.75, 2.06]
4 Dose of gonadotrophins	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Non-selected group	4	439	Mean Difference (IV, Fixed, 95% CI)	15.64 [14.05, 17.22]
4.2 Poor responders	4	227	Mean Difference (IV, Fixed, 95% CI)	7.07 [3.06, 11.08]
5 Cycle cancellation	11	1026	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.55]
5.1 Non-selected group	7	799	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.92, 3.23]
5.2 Poor responders	4	227	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.12, 0.76]

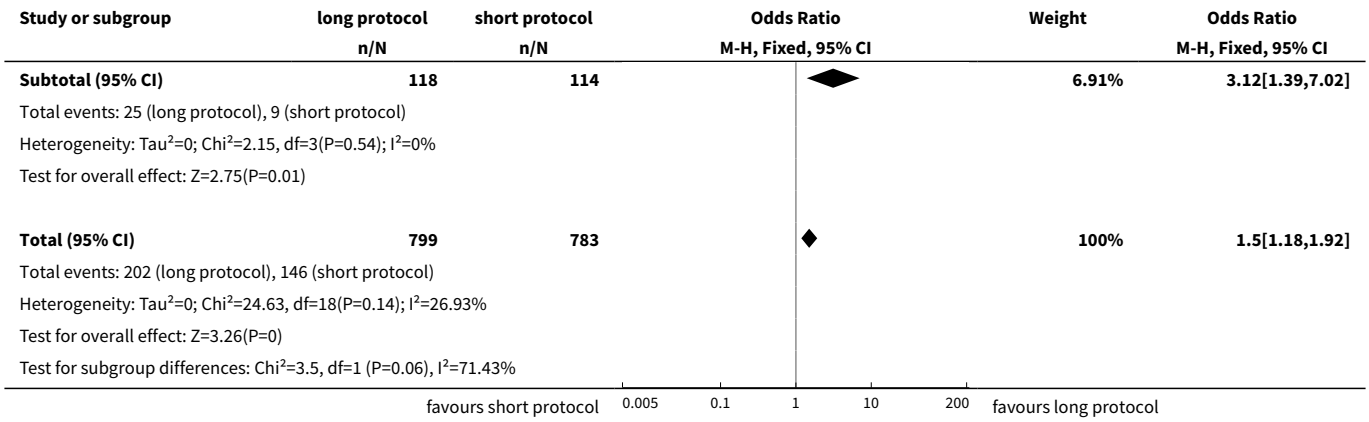
Analysis 1.1. Comparison 1 Long versus short protocol, Outcome 1 Live birth/ongoing pregnancies.

Study or subgroup	long protocol n/N	short protocol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Live birth					
Acharya 1992	4/43	3/44		4.34%	1.4[0.29,6.67]
Chatillon-Boissier 2012	2/22	3/22		4.4%	0.63[0.1,4.22]
San Roman 1992	6/26	1/29		1.17%	8.4[0.94,75.31]
Ye 2001	17/55	13/54		14.62%	1.41[0.61,3.29]
Subtotal (95% CI)	**146**	**149**		**24.54%**	**1.6[0.85,3.03]**
Total events: 29 (long protocol), 20 (short protocol)					
Heterogeneity: Tau^2=0; Chi^2=3.23, df=3(P=0.36); I^2=7.08%					
Test for overall effect: Z=1.46(P=0.14)					
1.1.2 Ongoing pregnancies					
Dirnfeld 1991	6/28	1/26		1.31%	6.82[0.76,61.12]
			0.01 0.1 1 10 100		
			favours short protocol		favours long protocol

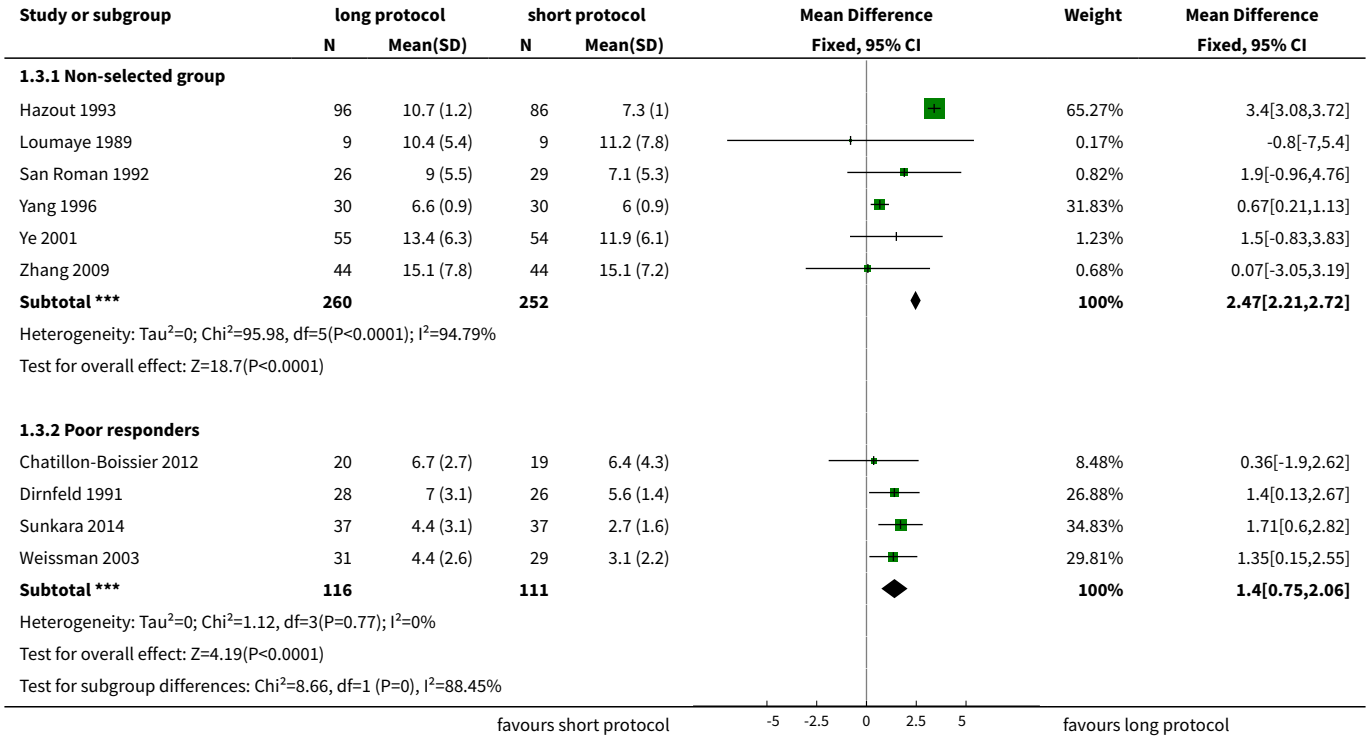


Analysis 1.2. Comparison 1 Long versus short protocol, Outcome 2 Clinical pregnancies.

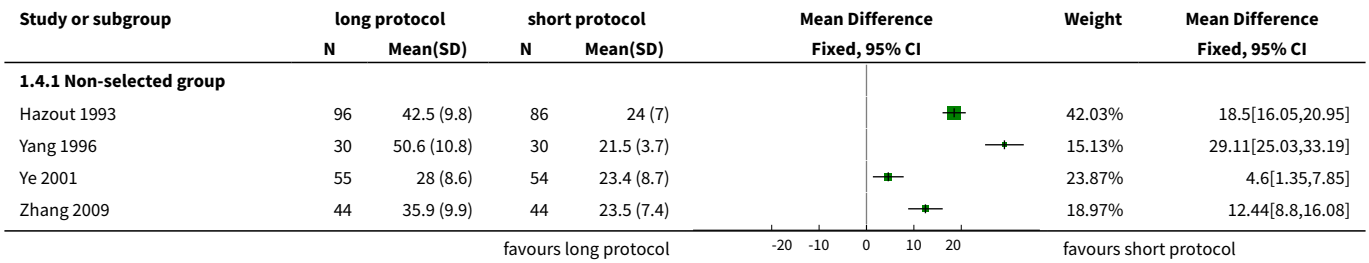


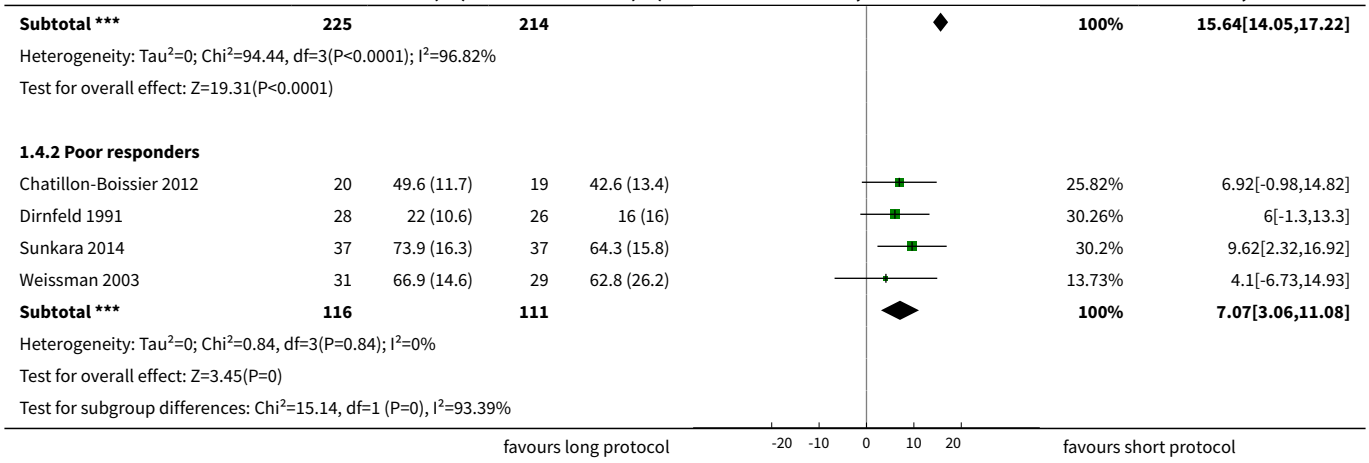


Analysis 1.3. Comparison 1 Long versus short protocol, Outcome 3 Number of oocytes.

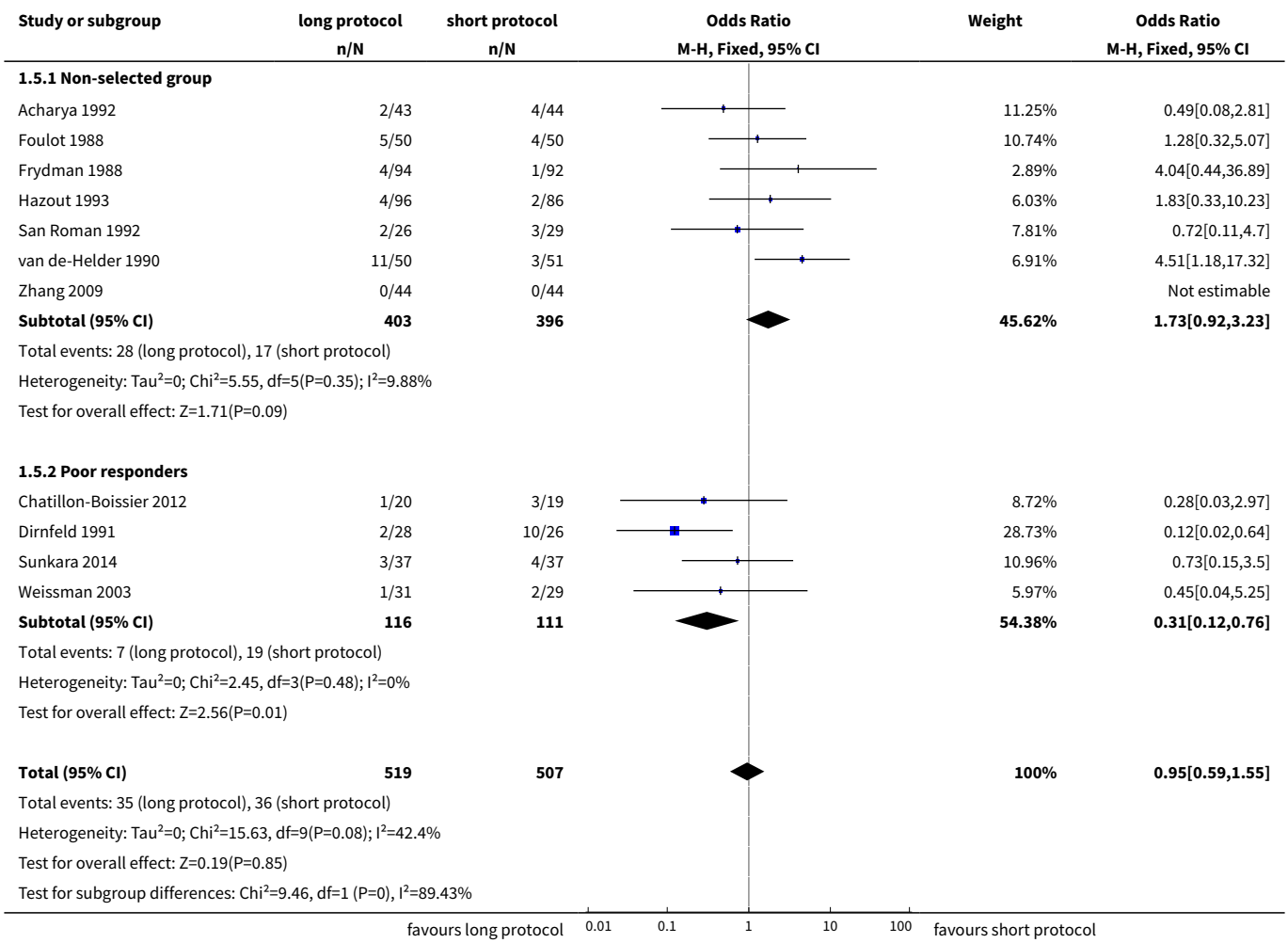


Analysis 1.4. Comparison 1 Long versus short protocol, Outcome 4 Dose of gonadotrophins.





Analysis 1.5. Comparison 1 Long versus short protocol, Outcome 5 Cycle cancellation.



Comparison 2. Long protocol versus ultrashort protocol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Clinical pregnancies	2	230	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.80, 3.06]
3 Number of oocytes	2	230	Mean Difference (IV, Fixed, 95% CI)	0.53 [-0.61, 1.66]
4 Dose of gonadotrophins	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Cycle cancellation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

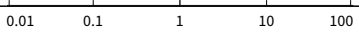
Analysis 2.1. Comparison 2 Long protocol versus ultrashort protocol, Outcome 1 Live birth and ongoing pregnancies.

Study or subgroup	long protocol n/N	ultrashort protocol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kingsland 1992	15/76	9/74		0%	1.78[0.72,4.36]

favours u/short protocol — favours long protocol

Analysis 2.2. Comparison 2 Long protocol versus ultrashort protocol, Outcome 2 Clinical pregnancies.

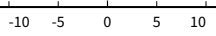
Study or subgroup	long protocol n/N	ultrashort protocol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen 1992	7/37	8/43		43.69%	1.02[0.33,3.15]
Kingsland 1992	18/76	10/74		56.31%	1.99[0.85,4.65]
Total (95% CI)	**113**	**117**		**100%**	**1.56[0.8,3.06]**
Total events: 25 (long protocol), 18 (ultrashort protocol)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=1.31(P=0.19)					



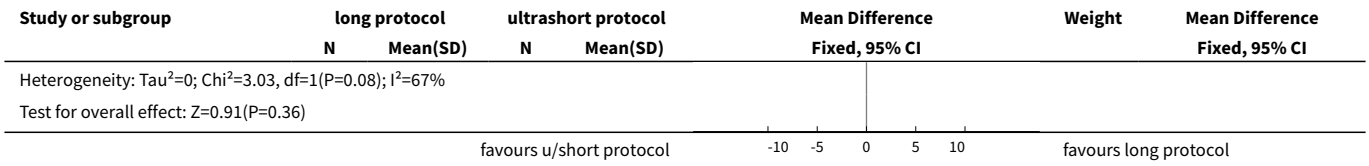
favours u/short protocol — favours long protocol

Analysis 2.3. Comparison 2 Long protocol versus ultrashort protocol, Outcome 3 Number of oocytes.

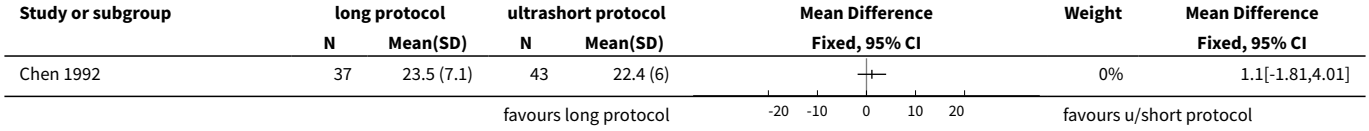
Study or subgroup	long protocol N	Mean(SD)	ultrashort protocol N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Chen 1992	37	7.9 (4.7)	43	8.8 (4.2)		33.35%	-0.9[-2.87,1.07]
Kingsland 1992	76	7.6 (4)	74	6.4 (4.7)		66.65%	1.24[-0.15,2.63]
Total ***	**113**		**117**			**100%**	**0.53[-0.61,1.66]**



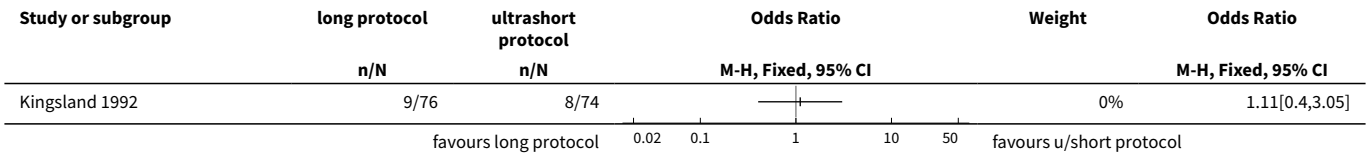
favours u/short protocol — favours long protocol



Analysis 2.4. Comparison 2 Long protocol versus ultrashort protocol, Outcome 4 Dose of gonadotrophins.



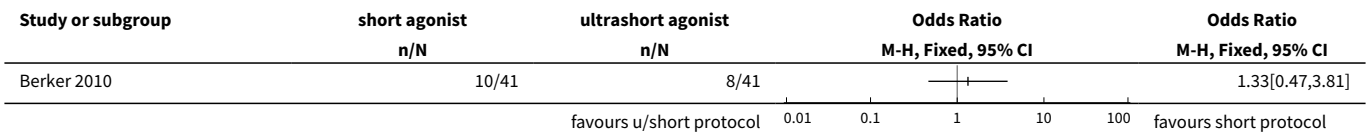
Analysis 2.5. Comparison 2 Long protocol versus ultrashort protocol, Outcome 5 Cycle cancellation.



Comparison 3. Short versus ultrashort protocol

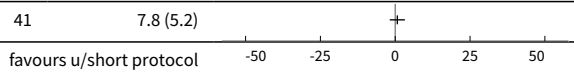
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Number of oocytes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Dose of gonadotrophins	1	82	Mean Difference (IV, Fixed, 95% CI)	-13.85 [-21.49, -6.21]
5 Cycle cancellation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.2. Comparison 3 Short versus ultrashort protocol, Outcome 2 Clinical pregnancies.



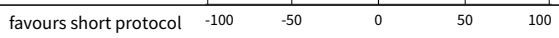
Analysis 3.3. Comparison 3 Short versus ultrashort protocol, Outcome 3 Number of oocytes.

Study or subgroup	short		ultrashort		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Berker 2010	41	8.5 (6.4)	41	7.8 (5.2)		0.7[-1.83,3.23]



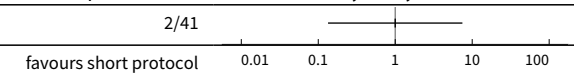
Analysis 3.4. Comparison 3 Short versus ultrashort protocol, Outcome 4 Dose of gonadotrophins.

Study or subgroup	short		ultrashort		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Berker 2010	41	31 (12.4)	41	44.9 (21.7)		100%	-13.85[-21.49,-6.21]
Total ***	**41**		**41**			**100%**	**-13.85[-21.49,-6.21]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.55(P=0)							



Analysis 3.5. Comparison 3 Short versus ultrashort protocol, Outcome 5 Cycle cancellation.

Study or subgroup	short agonist	ultrashort agonist	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Berker 2010	2/41	2/41		1[0.13,7.46]



Comparison 4. Long protocol (luteal versus follicular)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Clinical pregnancies	5	750	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.76, 1.47]
3 Number of oocytes	4	527	Mean Difference (IV, Fixed, 95% CI)	-1.29 [-1.86, -0.71]
4 Dose of gonadotrophins	4	527	Mean Difference (IV, Fixed, 95% CI)	1.12 [-0.73, 2.97]
5 Cycle cancellation	2	267	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.35, 6.01]

Analysis 4.1. Comparison 4 Long protocol (luteal versus follicular), Outcome 1 Live birth and ongoing pregnancies.

Study or subgroup	luteal start n/N	follicular start n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Urbancsek 1996	17/96	13/127		0%	1.89[0.87,4.1]

favours follicular start | favours luteal start

Analysis 4.2. Comparison 4 Long protocol (luteal versus follicular), Outcome 2 Clinical pregnancies.

Study or subgroup	luteal start n/N	follicular start n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kondaveeti-Gordon 1996	12/48	9/38		11.19%	1.07[0.4,2.9]
Pellicer 1989	4/29	6/15		10.13%	0.24[0.05,1.05]
Ron-El 1990	24/108	29/108		33.5%	0.78[0.42,1.45]
Sarhan 2013	38/115	21/66		26.54%	1.06[0.55,2.02]
Urbancsek 1996	26/96	20/127		18.65%	1.99[1.03,3.83]
Total (95% CI)	**396**	**354**		**100%**	**1.06[0.76,1.47]**
Total events: 104 (luteal start), 85 (follicular start)					
Heterogeneity: Tau^2=0; Chi^2=8.36, df=4(P=0.08); I^2=52.14%					
Test for overall effect: Z=0.32(P=0.75)					

favours follicular start | favours luteal start

Analysis 4.3. Comparison 4 Long protocol (luteal versus follicular), Outcome 3 Number of oocytes.

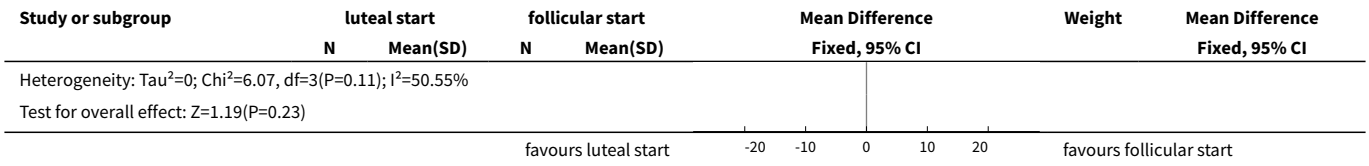
Study or subgroup	luteal start N	luteal start Mean(SD)	follicular start N	follicular start Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kondaveeti-Gordon 1996	48	12 (8)	38	10.3 (7)		3.27%	1.7[-1.47,4.87]
Pellicer 1989	29	6.9 (1.1)	15	8.7 (1.1)		69.99%	-1.8[-2.49,-1.11]
Ron-El 1990	108	7.1 (4.9)	108	7.9 (4.4)		21.33%	-0.8[-2.04,0.44]
Sarhan 2013	115	13.3 (9.3)	66	11.7 (7.4)		5.42%	1.6[-0.87,4.07]
Total ***	**300**		**227**			**100%**	**-1.29[-1.86,-0.71]**
Heterogeneity: Tau^2=0; Chi^2=11.41, df=3(P=0.01); I^2=73.71%							
Test for overall effect: Z=4.4(P<0.0001)							

favours follicular start | favours luteal start

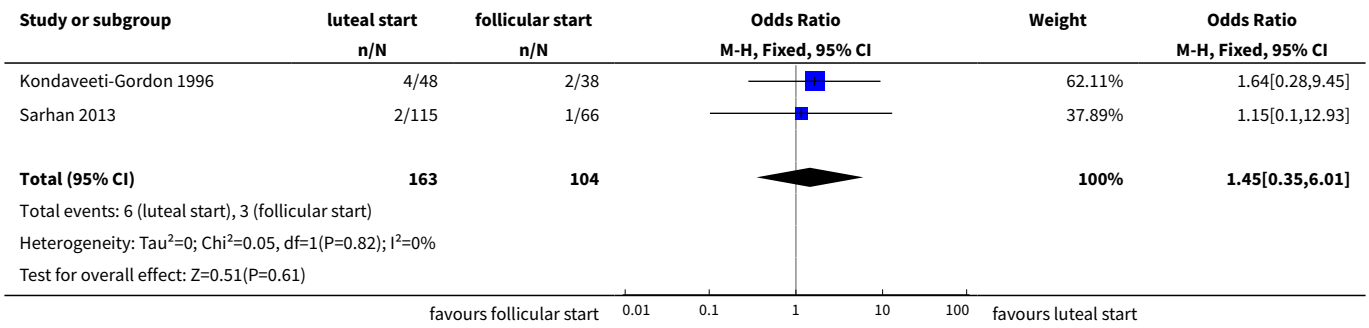
Analysis 4.4. Comparison 4 Long protocol (luteal versus follicular), Outcome 4 Dose of gonadotrophins.

Study or subgroup	luteal start N	luteal start Mean(SD)	follicular start N	follicular start Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kondaveeti-Gordon 1996	48	62 (9.4)	38	58 (10.1)		19.64%	4[-0.17,8.17]
Pellicer 1989	29	34.6 (10.2)	15	36.1 (8.9)		10%	-1.5[-7.34,4.34]
Ron-El 1990	108	45 (15)	108	41.5 (13)		24.36%	3.5[-0.24,7.24]
Sarhan 2013	115	39.3 (9.5)	66	40.1 (8.7)		46.01%	-0.8[-3.52,1.92]
Total ***	**300**		**227**			**100%**	**1.12[-0.73,2.97]**

favours luteal start | favours follicular start



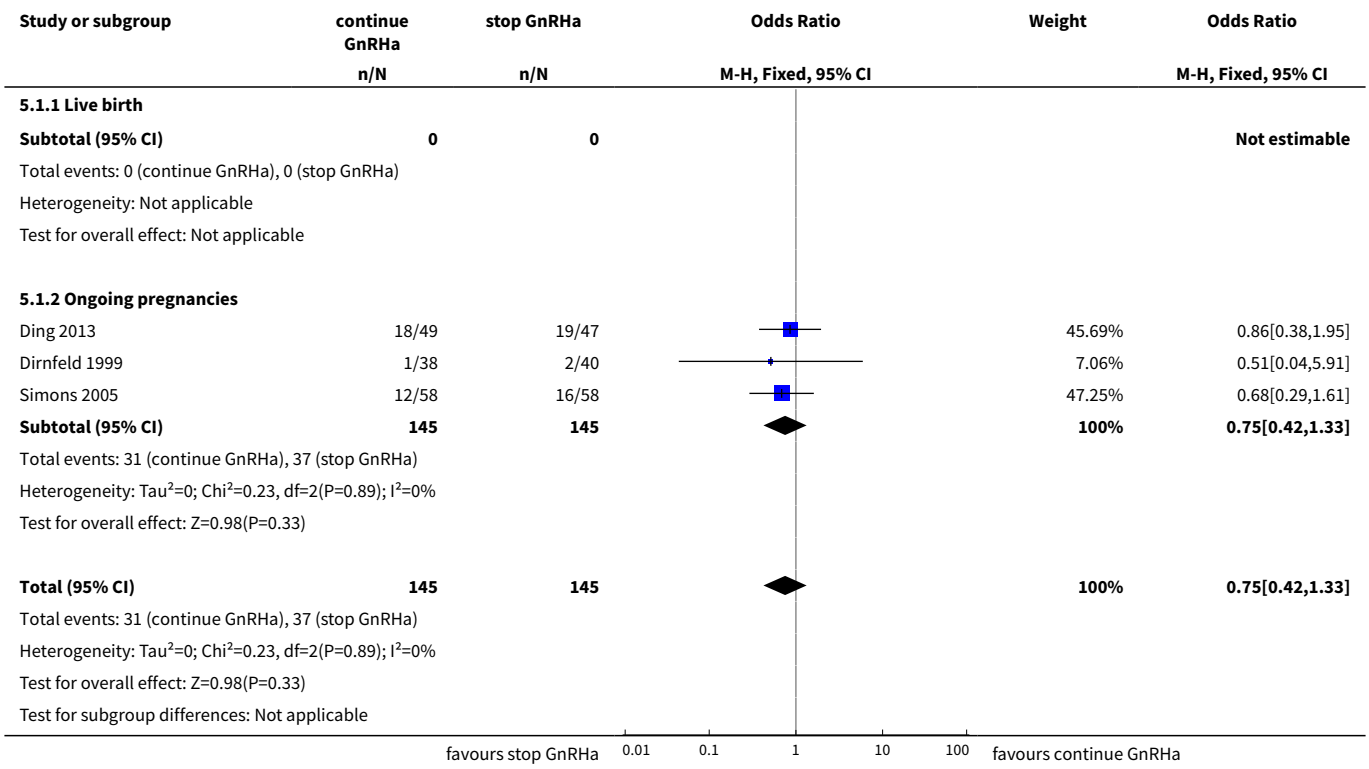
Analysis 4.5. Comparison 4 Long protocol (luteal versus follicular), Outcome 5 Cycle cancellation.



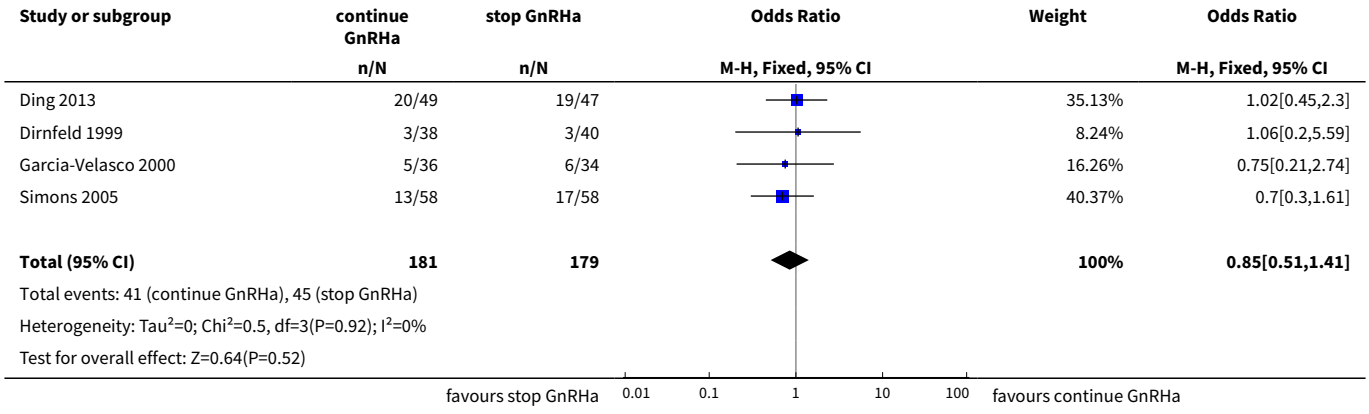
Comparison 5. Long protocol (continued GnRHa versus stop GnRHa)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	3	290	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.42, 1.33]
1.1 Live birth	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Ongoing pregnancies	3	290	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.42, 1.33]
2 Clinical pregnancies	4	360	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.51, 1.41]
3 Number of oocytes	4	360	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-1.29, 0.78]
4 Dose of gonadotrophins	4	360	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-2.35, 2.08]
5 Cycle cancellation	3	264	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.56, 3.56]
6 Other outcomes - OHSS	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

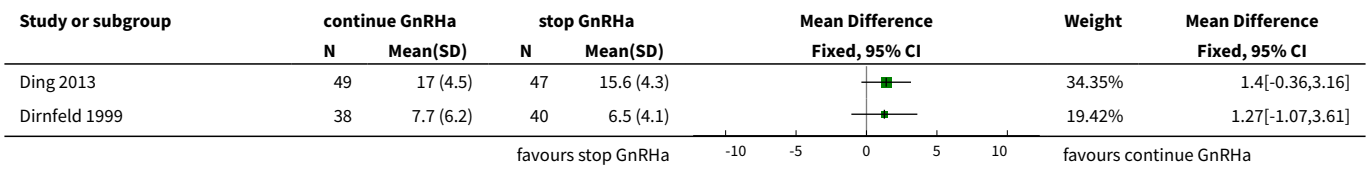
Analysis 5.1. Comparison 5 Long protocol (continued GnRHa versus stop GnRHa), Outcome 1 Live birth and ongoing pregnancies.

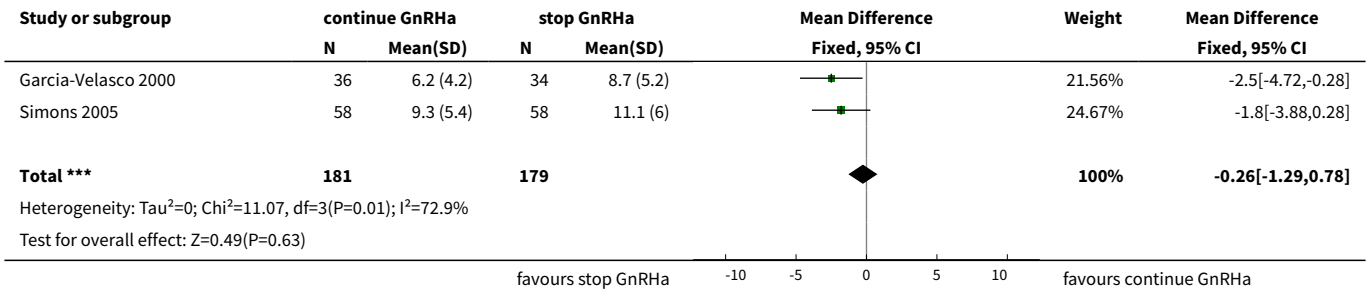


Analysis 5.2. Comparison 5 Long protocol (continued GnRHa versus stop GnRHa), Outcome 2 Clinical pregnancies.

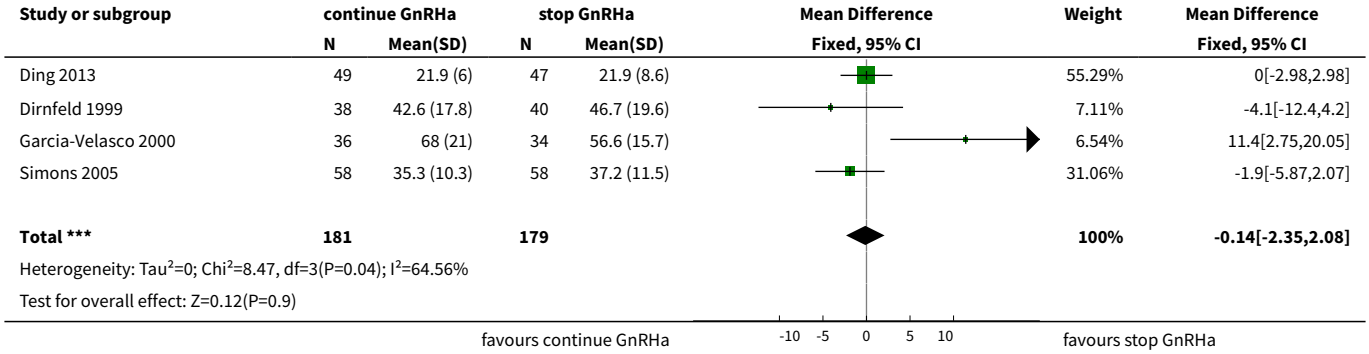


Analysis 5.3. Comparison 5 Long protocol (continued GnRHa versus stop GnRHa), Outcome 3 Number of oocytes.

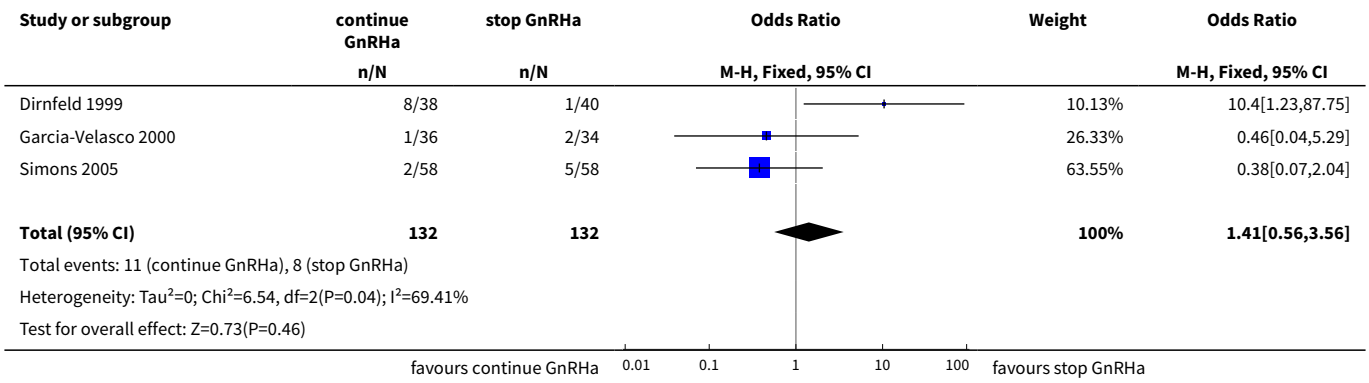




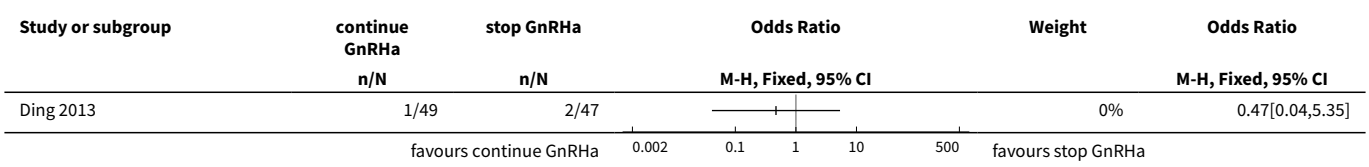
Analysis 5.4. Comparison 5 Long protocol (continued GnRHa versus stop GnRHa), Outcome 4 Dose of gonadotrophins.



Analysis 5.5. Comparison 5 Long protocol (continued GnRHa versus stop GnRHa), Outcome 5 Cycle cancellation.



Analysis 5.6. Comparison 5 Long protocol (continued GnRHa versus stop GnRHa), Outcome 6 Other outcomes - OHSS.

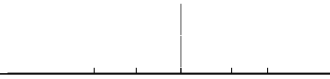


Comparison 6. Long protocol (continued same versus reduced dose GnRHa)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical pregnancies	4	407	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.52]
3 Number of oocytes	3	275	Mean Difference (IV, Fixed, 95% CI)	1.03 [-0.04, 2.10]
4 Dose of gonadotrophins	2	228	Mean Difference (IV, Fixed, 95% CI)	0.98 [-1.72, 3.69]
5 Cycle cancellation	2	228	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 7.32]

Analysis 6.2. Comparison 6 Long protocol (continued same versus reduced dose GnRHa), Outcome 2 Clinical pregnancies.

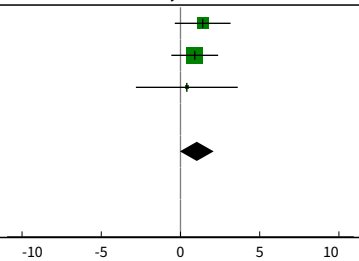
Study or subgroup	continue same dose GnRHa n/N	decreased dose of GnRHa n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Dal Prato 2001	24/66	22/66		29.64%	1.14[0.56,2.34]
Ding 2013	20/49	19/47		24.3%	1.02[0.45,2.3]
Fábregues 2005	27/68	28/69		35.48%	0.96[0.49,1.91]
Simon 1994	7/22	7/20		10.58%	0.87[0.24,3.13]
Total (95% CI)	**205**	**202**		**100%**	**1.02[0.68,1.52]**
Total events: 78 (continue same dose GnRHa), 76 (decreased dose of GnRHa)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=3(P=0.98); I^2=0%					
Test for overall effect: Z=0.09(P=0.92)					



favours decreased dose GnRHa — favours continue same dose GnRHa

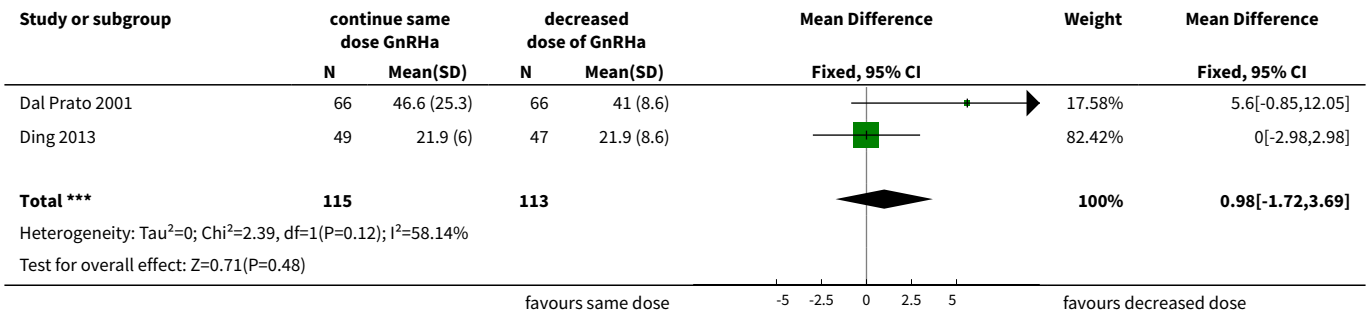
Analysis 6.3. Comparison 6 Long protocol (continued same versus reduced dose GnRHa), Outcome 3 Number of oocytes.

Study or subgroup	continue same dose GnRHa N	Mean(SD)	decreased dose of GnRHa N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ding 2013	49	17 (4.5)	47	15.6 (4.3)		36.75%	1.4[-0.36,3.16]
Fábregues 2005	68	10.4 (5.7)	69	9.5 (2.5)		52.22%	0.9[-0.58,2.38]
Simon 1994	22	13.3 (4.7)	20	12.9 (5.8)		11.03%	0.4[-2.81,3.61]
Total ***	**139**		**136**			**100%**	**1.03[-0.04,2.1]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=2(P=0.84); I^2=0%							
Test for overall effect: Z=1.89(P=0.06)							

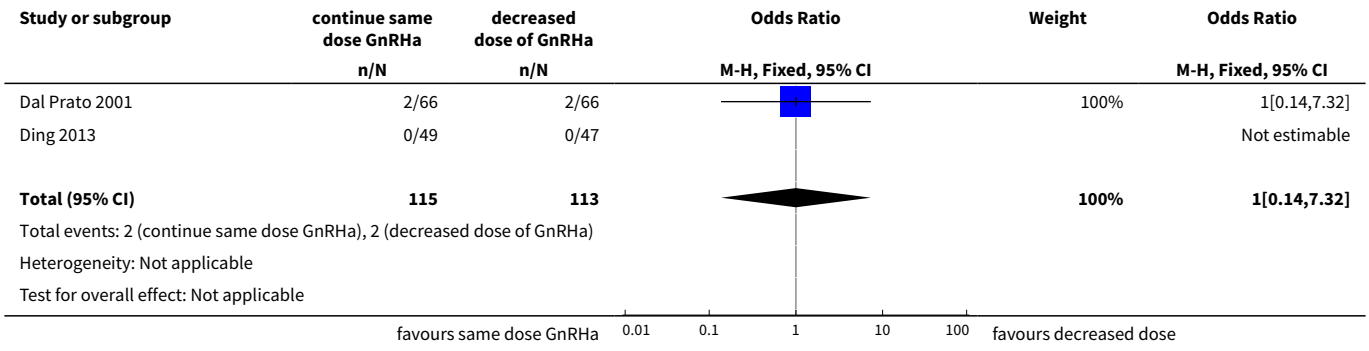


favours decreased dose GnRHa — favours same dose GnRHa

Analysis 6.4. Comparison 6 Long protocol (continued same versus reduced dose GnRHa), Outcome 4 Dose of gonadotrophins.



Analysis 6.5. Comparison 6 Long protocol (continued same versus reduced dose GnRHa), Outcome 5 Cycle cancellation.

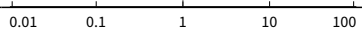


Comparison 7. Long protocol (GnRHa until HCG versus extended GnRHa 12 days after HCG)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Clinical pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Number of oocytes	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Dose of gonadotrophins	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Cycle cancellation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 7.1. Comparison 7 Long protocol (GnRHa until HCG versus extended GnRHa 12 days after HCG), Outcome 1 Live birth and ongoing pregnancies.

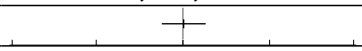
Study or subgroup	GnRHa until hCG n/N	GnRHa extend 12d after hC n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Isikoglu 2007	32/91	34/90		0%	0.89[0.49,1.64]



favours GnRHa 12 days after ET — favours GnRHa until HCG

Analysis 7.2. Comparison 7 Long protocol (GnRHa until HCG versus extended GnRHa 12 days after HCG), Outcome 2 Clinical pregnancies.

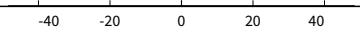
Study or subgroup	GnRHa until HCG n/N	GnRHa extend 12d after HCG n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Isikoglu 2007	45/91	44/90		0%	1.02[0.57,1.83]



favours GnRHa 12 days after ET — favours GnRHa until HCG

Analysis 7.3. Comparison 7 Long protocol (GnRHa until HCG versus extended GnRHa 12 days after HCG), Outcome 3 Number of oocytes.

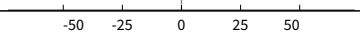
Study or subgroup	GnRHa until HCG N	Mean(SD)	GnRHa extend 12d after HCG N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Isikoglu 2007	91	12.4 (7.8)	90	13.3 (6.9)		0%	-0.9[-3.04,1.24]



favours GnRHa 12 days after ET — favours GnRHa until HCG

Analysis 7.4. Comparison 7 Long protocol (GnRHa until HCG versus extended GnRHa 12 days after HCG), Outcome 4 Dose of gonadotrophins.

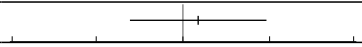
Study or subgroup	GnRHa until HCG N	Mean(SD)	GnRHa extend 12d after HC N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Isikoglu 2007	91	55.9 (11.4)	90	53.1 (11.6)		0%	2.8[-0.55,6.15]



favours GnRHa until HCG — favours GnRHa12days after

Analysis 7.5. Comparison 7 Long protocol (GnRHa until HCG versus extended GnRHa 12 days after HCG), Outcome 5 Cycle cancellation.

Study or subgroup	GnRHa until HCG n/N	GnRHa extend 12d after HC n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Isikoglu 2007	3/91	2/90		0%	1.5[0.24,9.2]



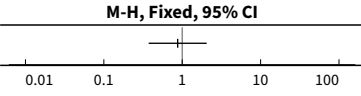
favours GnRHa until HCG — favours GnRHa12daysafter

Comparison 8. Long protocol (GnRHa for 2 weeks versus 3 weeks before stimulation)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Number of oocytes	1	85	Mean Difference (IV, Fixed, 95% CI)	0.12 [-1.90, 2.14]
4 Dose of gonadotrophins	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Cycle cancellation	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Other outcomes	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Miscarriages	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 OHSS	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

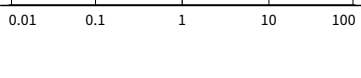
Analysis 8.1. Comparison 8 Long protocol (GnRHa for 2 weeks versus 3 weeks before stimulation), Outcome 1 Live birth and ongoing pregnancies.

Study or subgroup	GnRHa for 3 weeks n/N	GnRHa for 3 weeks n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lin 2013	20/44	20/41		0.88[0.37,2.05]



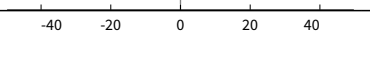
Analysis 8.2. Comparison 8 Long protocol (GnRHa for 2 weeks versus 3 weeks before stimulation), Outcome 2 Clinical pregnancies.

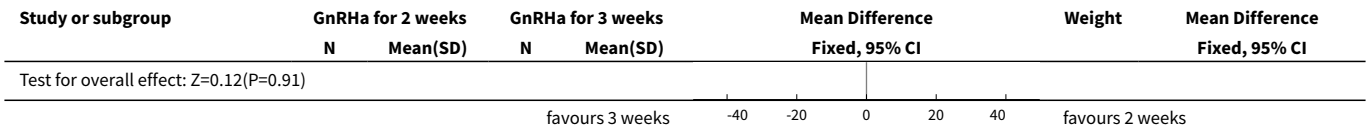
Study or subgroup	GnRHa for 2 weeks n/N	GnRHa for 3 weeks n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lin 2013	25/44	24/41		0.93[0.39,2.21]



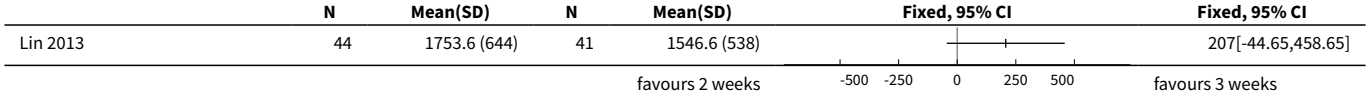
Analysis 8.3. Comparison 8 Long protocol (GnRHa for 2 weeks versus 3 weeks before stimulation), Outcome 3 Number of oocytes.

Study or subgroup	GnRHa for 2 weeks N	GnRHa for 2 weeks Mean(SD)	GnRHa for 3 weeks N	GnRHa for 3 weeks Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Lin 2013	44	12.3 (5.5)	41	12.2 (4)		100%	0.12[-1.9,2.14]
Total ***	**44**		**41**			**100%**	**0.12[-1.9,2.14]**
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$							

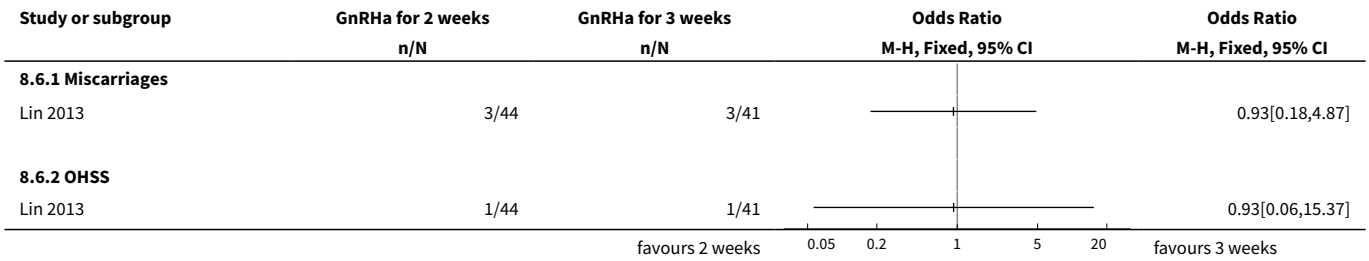




Analysis 8.4. Comparison 8 Long protocol (GnRHa for 2 weeks versus 3 weeks before stimulation), Outcome 4 Dose of gonadotrophins.



Analysis 8.6. Comparison 8 Long protocol (GnRHa for 2 weeks versus 3 weeks before stimulation), Outcome 6 Other outcomes.



Comparison 9. Short versus stop short protocol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth and ongoing pregnancies	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical pregnancies	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Number of oocytes	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Dose of gonadotrophins	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Cycle cancellation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 9.2. Comparison 9 Short versus stop short protocol, Outcome 2 Clinical pregnancies.

Study or subgroup	short protocol n/N	stop short protocol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Cedrin-Durnerin 2000	17/115	26/115		0%	0.59[0.3,1.17]

favours stop short 0.01 0.1 1 10 100 favours short

Analysis 9.4. Comparison 9 Short versus stop short protocol, Outcome 4 Dose of gonadotrophins.

Study or subgroup	short protocol N	short protocol Mean(SD)	stop short protocol N	stop short protocol Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cedrin-Durnerin 2000	115	30.2 (11.2)	115	35.4 (11.3)		0%	-5.2[-8.11,-2.29]

favours short -10 -5 0 5 10 favours stop short

Analysis 9.5. Comparison 9 Short versus stop short protocol, Outcome 5 Cycle cancellation.

Study or subgroup	short protocol n/N	stop short protocol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Cedrin-Durnerin 2000	13/115	17/115		0%	0.73[0.34,1.59]

favours short 0.01 0.1 1 10 100 favours stop short

APPENDICES

Appendix 1. Menstrual Disorders and Subfertility database search

Search strategy for SD265 09.04.14:

Keywords CONTAINS "IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection" or "controlled ovarian hyperstimulation" or "controlled ovarian stimulation" or"COH" or"embryo transfer" or"ovarian hyperstimulation"or "ovarian stimulation" or Title CONTAINS "IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection"or "controlled ovarian hyperstimulation" or "controlled ovarian stimulation" or"COH" or"embryo transfer" or"ovarian hyperstimulation"or "ovarian stimulation"

AND

Keywords CONTAINS "Gonadorelin" or "Gonadotrophin releasing agonist"or "Gonadotrophin releasing hormones"or "gonadotropin releasing hormone agonist" or "Goserelin" or "goserelin acetate" or "goserelin pretreatment" or"Gosereline "or "buserelin"or "busereline"or"leuprolide "or"leuprolin"or"leuprorelin"or"nafarelin"or"triptorelin"or"Lupron"or "Zoladex"or"deslorelin"or "GnRH agonist"or "GnRH a"or"GnRH agonists"or"GnRHa"or"GnRH analog"or"GnRH analogue"or"GnRH analogues"or"Luteinising hormone releasing hormone"or"luteinizing hormone supplementation"or"Lutenising hormone releasing hormone"or"menotropin"or"menotrophin"or"human menopausal gonadotrophin"or"human menopausal gonadotrophins"or "human menopausal gonadotrophins"or Title CONTAINS "Gonadorelin" or "Gonadotrophin releasing agonist"or "Gonadotrophin releasing hormones"or "gonadotropin releasing hormone agonist"

AND

Keywords CONTAINS "desensitisation vs flareup"or"long agonist protocol"or "long-long protocol"or "long protocol"or"long-term GnRHa treatment"or"long v short protocol"or"short interval"or"short protocol"or"ultra long protocol"or"ultra-short protocol"or"reduced dose"or"down regulation"or"follicular phase"or"high dose"or"high dose protocol"or"stop protocol"or"prolonged stimulation"or"day

7"or "continuous"or"early v late"or"early versus late"or"daily"or or"dosage"or"dose"or "long-term"or"flare-up"or "flare-up GnRH agonist"or"flare-up protocol"or"Protocols"or"dose-response study"or"dosing regimen

Appendix 2. CENTRAL search

EBM Reviews - Cochrane Central Register of Controlled Trials <March 2015>
Search Strategy:

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/ or exp in vitro oocyte maturation techniques/ (1765)

2 embryo transfer.tw. (1066)

3 in vitro fertili?ation.tw. (1571)

4 intracytoplasmic sperm injection$.tw. (518)

5 (ivf or icsi).tw. (2756)

6 exp Infertility, Female/ (930)

7 exp Primary Ovarian Insufficiency/ (68)

8 exp Infertility/ (1664)

9 (ovar$ adj2 stimulat$).tw. (976)

10 (ovar$ adj2 hyperstimulat$).tw. (675)

11 COH.tw. (162)

12 or/1-11 (5354)

13 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin pamoate/ (1885)

14 gonadotropin-releasing hormone$.tw. (835)

15 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (1330)

16 (Lupron or Suprefact or Suprecor).tw. (45)

17 (histrelin or Supprelin).tw. (1)

18 (Zoladex or deslorelin).tw. (236)

19 (Suprelorin or Ovuplant).tw. (0)

20 Synarel.tw. (3)

21 GnRHa.tw. (236)

22 GnRH-a.tw. (1393)

23 GnRH agonist$.tw. (796)

24 GnRH analog$.tw. (313)

25 luteinizing hormone releasing agonist$.tw. (1)

26 exp Menotropins/ (358)

27 human menopausal gonadotropin$.tw. (239)

28 or/13-27 (3595)

29 desensiti?ation.tw. (1004)

30 (long adj2 protocol).tw. (335)

31 (short adj2 protocol).tw. (122)

32 (ultra short adj2 protocol).tw. (3)

33 (long adj2 follicular).tw. (10)

34 (ultrashort adj2 protocol).tw. (3)

35 reduced dos$.tw. (840)

36 down regulat$.tw. (923)

37 downregulat$.tw. (587)

38 (follicular adj5 luteal).tw. (293)

39 high dose$.tw. (13920)

40 stop versus non stop.tw. (1)

41 prolonged protocol.tw. (1)

42 7 day.tw. (3291)

43 continu$ versus stop$.tw. (2)

44 short acting.tw. (1380)

45 early cessation.tw. (36)

46 early follicular.tw. (198)

47 different phase$.tw. (173)

48 daily.tw. (78531)

49 long acting.tw. (3713)

50 long luteal.tw. (13)

51 desensiti?e.tw. (31)

52 suppression.tw. (7910)

53 suppress.tw. (1966)

54 (inhibition or inhibit).tw. (16876)

55 (long adj2 protocol$).tw. (375)

56 (short adj2 protocol$).tw. (142)

57 or/29-56 (119095)

58 12 and 28 and 57 (722)

Appendix 3. MEDLINE search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/ or exp in vitro oocyte maturation techniques/ (32710)
2 embryo transfer.tw. (7668)
3 in vitro fertili?ation.tw. (16760)
4 intracytoplasmic sperm injection$.tw. (4912)
5 (ivf or icsi).tw. (18836)
6 exp Infertility, Female/ (23368)
7 exp Primary Ovarian Insufficiency/ (1673)
8 exp Infertility/ (52626)
9 (ovar$ adj2 stimulat$).tw. (4982)
10 (ovar$ adj2 hyperstimulat$).tw. (3842)
11 COH.tw. (1130)
12 or/1-11 (89231)
13 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin pamoate/ (28527)
14 gonadotropin-releasing hormone$.tw. (11008)
15 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (4078)
16 (Lupron or Suprefact or Suprecor).tw. (168)
17 (histrelin or Supprelin).tw. (46)
18 (Zoladex or deslorelin).tw. (560)
19 (Suprelorin or Ovuplant).tw. (22)
20 Synarel.tw. (12)
21 GnRHa.tw. (1094)
22 GnRH-a.tw. (900)
23 GnRH agonist$.tw. (3408)
24 GnRH analog$.tw. (2085)
25 luteinizing hormone releasing agonist$.tw. (5)
26 exp Menotropins/ (3017)
27 human menopausal gonadotropin$.tw. (1344)
28 or/13-27 (36003)
29 desensiti?ation.tw. (19633)
30 (long adj2 protocol).tw. (843)
31 (short adj2 protocol).tw. (406)
32 (ultra short adj2 protocol).tw. (5)
33 (long adj2 follicular).tw. (47)
34 (ultrashort adj2 protocol).tw. (11)
35 reduced dos$.tw. (3057)
36 down regulat$.tw. (89044)
37 downregulat$.tw. (64084)
38 (follicular adj5 luteal).tw. (2798)
39 high dose$.tw. (101864)
40 stop versus non stop.tw. (1)
41 prolonged protocol.tw. (5)
42 7 day.tw. (15537)
43 continu$ versus stop$.tw. (3)
44 short acting.tw. (5630)
45 early cessation.tw. (285)
46 early follicular.tw. (1652)
47 different phase$.tw. (7846)
48 daily.tw. (348977)
49 long acting.tw. (16507)
50 long luteal.tw. (52)
51 desensiti?e.tw. (1409)
52 suppression.tw. (170539)
53 suppress.tw. (64930)
54 (inhibition or inhibit).tw. (789675)

55 (long adj2 protocol$).tw. (1017)
56 (short adj2 protocol$).tw. (526)
57 or/29-56 (1536670)
58 12 and 28 and 57 (2202)
59 randomized controlled trial.pt. (370469)
60 controlled clinical trial.pt. (88141)
61 randomized.ab. (290565)
62 randomised.ab. (58371)
63 placebo.tw. (157118)
64 clinical trials as topic.sh. (169329)
65 randomly.ab. (210657)
66 trial.ti. (124866)
67 (crossover or cross-over or cross over).tw. (60254)
68 or/59-67 (936052)
69 exp animals/ not humans.sh. (3921813)
70 68 not 69 (863309)
71 58 and 70 (696)

Appendix 4. EMBASE search

Database: Embase <1980 to 2015 Week 16>

Search Strategy:

1 exp embryo transfer/ or exp infertility therapy/ (75966)
2 exp female infertility/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (71995)
3 embryo transfer.tw. (10480)
4 in vitro fertili?ation.tw. (20223)
5 intracytoplasmic sperm injection$.tw. (6184)
6 (ivf or icsi).tw. (28413)
7 exp premature ovarian failure/ (2247)
8 (ovar$ adj2 stimulat$).tw. (6983)
9 (ovar$ adj2 hyperstimulat$).tw. (5230)
10 COH.tw. (1444)
11 or/1-10 (108706)
12 exp gonadorelin/ or exp gonadorelin agonist/ (36886)
13 exp buserelin acetate/ or exp buserelin/ (4583)
14 exp goserelin/ (5701)
15 exp leuprorelin/ (8556)
16 exp nafarelin acetate/ or exp nafarelin/ (1328)
17 exp triptorelin/ (3972)
18 gonadotrop?in-releasing hormone$.tw. (14213)
19 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (5269)
20 (Lupron or Suprefact or Suprecor).tw. (2488)
21 (histrelin or Supprelin).tw. (114)
22 (Zoladex or deslorelin).tw. (2138)
23 (Suprelorin or Ovuplant).tw. (31)
24 Synarel.tw. (319)
25 GnRHa.tw. (1457)
26 GnRH-a.tw. (1070)
27 GnRH agonist$.tw. (4596)
28 GnRH analog$.tw. (2744)
29 luteinizing hormone releasing agonist$.tw. (7)
30 exp human menopausal gonadotropin/ (7971)
31 human menopausal gonadotrop?in$.tw. (2022)
32 or/12-31 (57973)
33 11 and 32 (13889)
34 desensiti?ation.tw. (21946)
35 (long adj2 protocol).tw. (1285)
36 (short adj2 protocol).tw. (584)
37 (ultra short adj2 protocol).tw. (8)
38 (long adj2 follicular).tw. (61)

39 (ultrashort adj2 protocol).tw. (13)
40 reduced dos$.tw. (4136)
41 down regulat$.tw. (108195)
42 downregulat$.tw. (79715)
43 (follicular adj5 luteal).tw. (2948)
44 high dose$.tw. (125377)
45 stop versus non stop.tw. (1)
46 prolonged protocol.tw. (5)
47 7 day.tw. (18760)
48 continu$ versus stop$.tw. (3)
49 short acting.tw. (7235)
50 early cessation.tw. (343)
51 early follicular.tw. (1874)
52 different phase$.tw. (8761)
53 daily.tw. (436352)
54 long acting.tw. (20976)
55 long luteal.tw. (76)
56 desensiti?e.tw. (1555)
57 suppression.tw. (186085)
58 suppress.tw. (72208)
59 (inhibition or inhibit).tw. (859108)
60 (long adj2 protocol$).tw. (1526)
61 (short adj2 protocol$).tw. (742)
62 or/34-61 (1754598)
63 33 and 62 (3688)
64 Clinical Trial/ (829568)
65 Randomized Controlled Trial/ (338773)
66 exp randomization/ (61524)
67 Single Blind Procedure/ (18032)
68 Double Blind Procedure/ (112415)
69 Crossover Procedure/ (38335)
70 Placebo/ (236318)
71 Randomi?ed controlled trial$.tw. (95890)
72 Rct.tw. (13384)
73 random allocation.tw. (1288)
74 randomly allocated.tw. (19790)
75 allocated randomly.tw. (1896)
76 (allocated adj2 random).tw. (707)
77 Single blind$.tw. (13937)
78 Double blind$.tw. (138097)
79 ((treble or triple) adj blind$).tw. (351)
80 placebo$.tw. (193550)
81 prospective study/ (245030)
82 or/64-81 (1339414)
83 case study/ (25067)
84 case report.tw. (253821)
85 abstract report/ or letter/ (883698)
86 or/83-85 (1157110)
87 82 not 86 (1302183)
88 63 and 87 (1219)

Appendix 5. CINAHL search

EBSCO: 01.01.08 to 23.04.14.

S33	S18 AND S32	70
S32	S19 OR S20 or S21 or S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	955,673

(Continued)

S31	TX allocat* random*	4,250
S30	(MH "Quantitative Studies")	13,306
S29	(MH "Placebos")	9,184
S28	TX placebo*	33,672
S27	TX random* allocat*	4,250
S26	(MH "Random Assignment")	39,015
S25	TX randomi* control* trial*	86,166
S24	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	764,433
S23	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	114
S22	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	0
S21	TX clinic* n1 trial*	171,126
S20	PT Clinical trial	77,731
S19	(MH "Clinical Trials+")	186,401
S18	S8 AND S17	157
S17	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	1,371
S16	TX (gonadotropin releasing hormone agonist*)	190
S15	TX (Luteinising hormone releasing hormone)	34
S14	TX GnRH a	129
S13	TX buserelin or TX leuprolin or TX leuprorelin or TX nafarelin or TX triptorelin or TX Lupron or TX Zoladex or TX deslorelin	124
S12	TX (GnRH agonist*)	159
S11	TX Gonadorelin OR TX Leuprolide	1,015
S10	TX Goserelin	237
S9	(MM "Gonadorelin") OR (MM "Leuprolide") OR (MM "Goserelin")	590
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	3,731
S7	TX embryo* N3 transfer*	771
S6	TX ovar* N3 hyperstimulat*	336
S5	TX ovari* N3 stimulat*	246

(Continued)

S4	TX IVF or TX ICSI	1,249
S3	(MM "Fertilization in Vitro")	1,446
S2	TX vitro fertilization	2,852
S1	TX vitro fertilisation	266

Appendix 6. Information from the studies selected for the review

Trial characteristics

(1) Method and timing of randomisation:

- randomisation was adequate (e.g., by computer, random number tables, or drawing lots); or
- not clear (e.g., stated but not further described, or did not fall into one of the randomisation categories).

(2) Allocation concealment.

(3) Duration, timing, and location of the trial (single centre or multicentre trial), duration of follow up, and:

- outcome data used for primary analysis were complete (follow up to live birth), all randomised women were accounted for with an intention-to-treat analysis;
- completeness of data uncertain; or
- outcome data incomplete, with 5% of the cycles commenced missing some outcome data.

(4) Co-intervention:

- other care provided with the intervention under study was equivalent in the treatment and control groups;
- issue of co-intervention was not considered; or
- co-intervention variations definitely existed.

(5) The presence of a power calculation:

(a) yes (prospective and valid or not valid); or
(b) no.

Baseline characteristics of the studied groups

(a) Cause and duration of pre-existing subfertility
(b) Age of the women and parity
(c) Investigative work-up prior to in vitro fertilisation (IVF)
(d) Previously administered treatment(s)

Intervention

(a) Type of intervention and control comparator
(b) Dose and type of regime

(c) We differentiated between whether the studied population included all women undergoing assisted reproduction technology (ART) or was limited to women who had responded poorly in a previous attempt or were expected to have a diminished response. As different drug regimes of ovarian stimulation can lead to a variable ovarian response, data on the drugs employed was also extracted.

Outcomes

(a) Outcomes reported
(b) How outcomes were defined
(c) Timing of outcome measurement

WHAT'S NEW

Date	Event	Description
24 July 2015	New citation required but conclusions have not changed	The addition of 8 new studies did not lead to a change in the conclusions of this review.
24 July 2015	New search has been performed	8 studies were added in this update, and 1 co-author was added. The text was thoroughly changed according to current Menstrual Disorders and Subfertility Group guidelines. New included studies: Berker 2010; Chatillon-Boissier 2012; Ding 2013; Isikoglu 2007; Lin 2013; Sarhan 2013; Sunkara 2014; and Zhang 2009.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 8, 2011

Date	Event	Description
11 January 2009	Amended	Original review has been withdrawn, and a new protocol has been published. Title changed back from 'Long versus short gonadotropin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles' to 'Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive treatment'. 11 December 2008: Title changed from 'Gonadotrophin-releasing hormone agonist protocols for pituitary down regulation in assisted reproductive treatment' to 'Long versus short gonadotropin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles'.
12 November 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AM: initiated and conceptualised the protocol; undertook data searching, selection of studies, data extraction, drafting of the first update of the review, assessment of studies for inclusion, interpretation and analysis of data, and editing of the second update.
CS: co-drafted the protocol; undertook data searching, selection of studies, and data extraction, and wrote the second update.
AG: co-drafted the protocol; undertook data searching, selection of studies, and data extraction.
GB: undertook data searching, selection of studies, and data extraction in the second update.
SB: overall supervision and editing of the review.

Timeline

A new search for RCTs will be performed every two years with the review updated accordingly.

DECLARATIONS OF INTEREST

Charalampos S Siristatidis: nothing to declare.
Ahmed Gibreel: nothing to declare.
George Basios: nothing to declare.
Abha Maheshwari: nothing to declare.

Siladitya Bhattacharya: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Assisted Reproduction Unit, University of Aberdeen, UK.
- Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, University of Athens, Greece.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Our protocol mentioned one of the comparison groups as gonadotrophin-releasing hormone agonists (GnRHa) versus placebo. However, there is a review of randomised controlled trials (RCTs) on this topic (Fields 2013) suggesting that use of GnRHa is associated with a better outcome in assisted reproduction technology (ART). The current review intended to explore which protocol was better.

A short protocol versus a short stop protocol was not listed in the initial comparison groups. However, since we were looking at all protocols for GnRHa for pituitary down-regulation, we felt it was appropriate to include studies comparing these groups.

The original review was withdrawn, and a new protocol was published.

11 December 2008: The title changed from 'Long versus short gonadotropin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles' to 'Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive treatment'.

A further title change from 'Gonadotrophin-releasing hormone agonist protocols for pituitary down regulation in assisted reproductive treatment' to 'Gonadotropin releasing hormone agonist protocols for pituitary suppression in assisted reproduction' was agreed in 2011.

31 August 2014: we added two comparisons:

- long protocol: discontinuing versus continuing GnRHa after HCG administration; and
- long protocol: administration of GnRHa for fewer than versus more than 18 days before stimulation.

INDEX TERMS

Medical Subject Headings (MeSH)

*Reproductive Techniques, Assisted; Buserelin [administration & dosage]; Clinical Protocols; Drug Administration Schedule; Fertility Agents, Female [*administration & dosage]; Gonadotropin-Releasing Hormone [*agonists]; Leuprolide [administration & dosage]; Live Birth [epidemiology]; Luteinizing Hormone [*antagonists & inhibitors] [metabolism]; Ovulation Induction [*methods]; Pituitary Gland [*drug effects]; Pregnancy Rate; Randomized Controlled Trials as Topic; Triptorelin Pamoate [administration & dosage]

MeSH check words

Female; Humans; Pregnancy