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Luteal phase support for assisted reproduction cycles (Review)

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TABLE OF CONTENTS

[Intervention Review]

Luteal phase support for assisted reproduction cycles

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ABSTRACT

Background

Progesterone prepares the endometrium for pregnancy by stimulating proliferation in response to human chorionic gonadotropin (hCG) produced by the corpus luteum in the luteal phase of the menstrual cycle. In assisted reproduction techniques (ART), progesterone and/or hCG levels are low, so the luteal phase is supported with progesterone, hCG or gonadotropin-releasing hormone (GnRH) agonists to improve implantation and pregnancy rates.

Objectives

To determine the relative effectiveness and safety of methods of luteal phase support provided to subfertile women undergoing assisted reproduction.

Search methods

We searched databases including the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and trial registers up to November 2014. Further searches were undertaken in August 2015.

Selection criteria

Randomised controlled trials (RCTs) of luteal phase support using progesterone, hCG or GnRH agonist supplementation in ART cycles.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcome was live birth or ongoing pregnancy. The overall quality of the evidence was assessed using GRADE methods.

Main results

Ninety-four RCTs (26,198 women) were included. Most studies had unclear or high risk of bias in most domains. The main limitations in the evidence were poor reporting of study methods and imprecision due to small sample sizes.

1. hCG vs placebo/no treatment (five RCTs, 746 women)

Findings suggested benefit for the hCG group in live birth or ongoing pregnancy rates when data were analysed with a fixed-effect model (OR 1.76, 95% CI 1.08 to 2.86, three RCTs, 527 women, I^2 = 24%, very low-quality evidence) but there was no clear evidence of a difference

using a random-effects model (OR 1.67, 95% CI 0.90 to 3.12). hCG may increase ovarian hyperstimulation syndrome (OHSS) rates (OR 4.28, 95% CI 1.91 to 9.6, one RCT, 387 women, low-quality evidence).

2. Progesterone vs placebo/no treatment (eight RCTs, 875 women)

Findings suggested benefit for the progesterone group in live birth or ongoing pregnancy rates when data were analysed with a fixed-effect model (OR 1.77, 95% CI 1.09 to 2.86, five RCTs, 642 women, I^2 = 35%, very low-quality evidence) but there was no clear evidence of a difference using a random-effects model (OR 1.77, 95% CI 0.96 to 3.26). OHSS was not reported.

3. Progesterone vs hCG regimens (16 RCTs, 2162 women)

hCG regimens included hCG alone and hCG with progesterone. There was no evidence of a difference between progesterone and hCG regimens in live birth or ongoing pregnancy rates (OR 0.95, 95% CI 0.65 to 1.38, five RCTs, 833 women, I^2 = 0%, low-quality evidence). Progesterone was associated with lower OHSS rates than hCG regimens (OR 0.46, 95% CI 0.30 to 0.71, 5 RCTs, 1293 women , I^2=48%).

4. Progesterone vs progesterone with oestrogen (16 RCTs, 2577 women)

There was no evidence of a difference between the groups in rates of live birth or ongoing pregnancy (OR 1.12, 95% CI 0.91 to 1.38, nine RCTs, 1651 women, I^2 = 0%, low-quality evidence) or OHSS (OR 0.56, 95% CI 0.2 to 1.63, two RCTs, 461 women, I^2 = 0%, low-quality evidence).

5. Progesterone vs progesterone + GnRH agonist (seven RCTs, 1708 women)

Live birth or ongoing pregnancy rates were lower in the progesterone-only group than the progesterone plus GnRH agonist group (OR 0.62, 95% CI 0.48 to 0.81, nine RCTs, 2861 women, I^2 = 55%, random effects, low-quality evidence). Statistical heterogeneity was high but the direction of effect was consistent across studies. OHSS was reported in one study only; there was no evidence of a difference between the groups (OR 1.00, 95% CI 0.33 to 3.01, one RCT, 300 women, very low quality evidence).

6. Progesterone regimens (45 RCTs, 13,814 women)

There were nine different comparisons between progesterone regimens. Findings for live birth or ongoing pregnancy were as follows: intramuscular (IM) versus oral: OR 0.71, 95% CI 0.14 to 3.66 (one RCT, 40 women, very low-quality evidence); IM versus vaginal/rectal: OR 1.37, 95% CI 0.94 to 1.99 (seven RCTs, 2309 women, I^2 = 71%, random effects, very low-quality evidence); vaginal/rectal versus oral: OR 1.19, 95% CI 0.83 to 1.69 (four RCTs, 857 women, I^2 = 32%, low-quality evidence); low-dose versus high-dose vaginal: OR 0.97, 95% CI 0.84 to 1.11 (five RCTs, 3720 women, I^2 = 0%, moderate-quality evidence); short versus long protocol: OR 1.04, 95% CI 0.79 to 1.36 (five RCTs, 1205 women, I^2 = 0%, low-quality evidence); micronised versus synthetic: OR 0.9, 95% CI 0.53 to 1.55 (two RCTs, 470 women, I^2 = 0%, low-quality evidence); vaginal ring versus gel: OR 1.09, 95% CI 0.88 to 1.36 (one RCT, 1271 women, low-quality evidence); subcutaneous versus vaginal gel: OR 0.92, 95% CI 0.74 to 1.14 (two RCTs, 1465 women, I^2 = 0%, low-quality evidence); vaginal versus rectal: OR 1.28, 95% CI 0.64 to 2.54 (one RCT, 147 women, very low-quality evidence). OHSS rates were reported for only two comparisons: IM versus oral, and low versus high-dose vaginal; there was no evidence of a difference between the groups.

7. Progesterone and oestrogen regimens (two RCTs, 1195 women)

The included studies compared two different oestrogen protocols. There was no evidence of a difference in live birth or ongoing pregnancy rates between a short or long protocol (OR 1.08, 95% CI 0.81 to 1.43, one RCT, 910 women, low-quality evidence) or between a low or high dose of oestrogen (OR 0.65, 95% CI 0.37 to 1.13, one RCT, 285 women, very low-quality evidence). Neither study reported OHSS.

Authors' conclusions

hCG or progesterone given during the luteal phase may be associated with higher rates of live birth or ongoing pregnancy than placebo or no treatment, but the evidence is not conclusive. The addition of GnRHa to progesterone appears to improve outcomes. hCG may increase the risk of OHSS compared to placebo. Moreover hCG, with or without progesterone, is associated with higher rates of OHSS than progesterone alone. Neither the addition of oestrogen nor the route of progesterone administration appears to be associated with an improvement in outcomes.

PLAIN LANGUAGE SUMMARY

Luteal phase support for assisted reproduction

Review question

Many different interventions, dosages and administration routes of luteal phase support have been investigated. We made seven different comparisons to prepare a complete overview of this topic.

Background

After ovulation, the luteal phase of the menstrual cycle starts, and continues until the next menstruation. Remnants of the ovulated egg in the ovary are known as 'corpus luteum', or yellow body. The yellow body produces hormones, including progesterone. Progesterone stimulates proliferation of the lining of the uterus to prepare for implantation.

During assisted reproduction, the woman's pituitary gland is desensitised with medications so that the ovaries can be stimulated in a controlled manner. This results in more mature eggs, which can be harvested and fertilised outside the woman's body. Hyperstimulation of the ovaries causes a luteal phase defect, as the corpus luteum is unable to produce sufficient progesterone.

As a low progesterone level may lower the chance of implantation, the luteal phase needs to be supported. This may involve oral, vaginal or intramuscular progesterone, human chorionic gonadotropin (hCG) (which stimulates progesterone production) or gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists stimulate the production of GnRH, a hormone responsible for follicle-stimulating hormone (FSH), and luteinising hormone (LH), which triggers ovulation and develops the yellow body. GnRH agonists are thought to restore LH levels and support the luteal phase naturally.

Study characteristics

We found 94 randomised controlled trials comparing different luteal phase support regimens in a total of 26,198 women. Our primary outcome was live birth or ongoing pregnancy. Other outcomes were clinical pregnancy, ovarian hyperstimulation syndrome (OHSS), miscarriage and multiple pregnancy. The evidence is current to August 2015.

Key results

hCG or progesterone given during the luteal phase may be associated with higher rates of live birth or ongoing pregnancy than placebo or no treatment, but the evidence is not conclusive. The addition of GnRHa to progesterone appears to improve outcomes. hCG may increase the risk of OHSS compared to placebo. Moreover hCG, with or without progesterone, is associated with higher rates of OHSS than progesterone alone. Neither the addition of oestrogen nor the route of progesterone administration appears to be associated with an improvement in outcomes.

Quality of the evidence

Evidence for most comparisons was of low or very low quality. The main limitations in the evidence were poor reporting of study methods and imprecision due to small sample sizes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. hCG compared with placebo/no treatment for assisted reproduction cycles

hCG compared with placebo/no treatment for assisted reproduction cycles

Population: subfertile women
Setting: assisted reproduction
Intervention: hCG
Comparison: placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/No treatment	hCG				
Live birth or ongoing pregnancy	120 per 1000	194 per 1000 (128 to 281)	OR 1.76 (1.08 to 2.86)	527 (3 RCTs)	⊕⊝⊝⊝ Very low[a,b,c,f]	
Clinical pregnancy	155 per 1000	192 per 1000 (141 to 256)	OR 1.3 (0.9 to 1.88)	746 (5 RCTs)	⊕⊕⊝⊝ Very low[a,b,c,d]	
OHSS	41 per 1000	155 per 1000 (76 to 292)	OR 4.28 (1.91 to 9.6)	387 (1 RCT)	⊕⊕⊝⊝ Low[a,c,e]	

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

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

[a]Serious risk of bias due to inadequate reporting of study methods. Risk of bias unclear in most domains of most studies.
[b]Serious imprecision with low event rate.
[c]Number of studies was not sufficient for assessment of publication bias.
[d]Findings compatible with meaningful benefit for hCG group, or with no effect.
[e]Serious imprecision; single study with low event rate.

[f]Findings not statistically significant when random-effects model was used (OR 1.67, 95% CI 0.90 to 3.12), or when analysis was restricted to studies reporting live birth.

Summary of findings 2. Progesterone compared with placebo/no treatment for assisted reproduction cycles

Progesterone compared with placebo/no treatment for assisted reproduction cycles

Population: subfertile women
Setting: assisted reproduction
Intervention: progesterone
Comparison: placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Progesterone				
Live birth or ongoing pregnancy	39 per 1000	66 per 1000 (42 to 103)	OR 1.77 (1.09 to 2.86)	642 (5 RCTs)	⊕⊝⊝⊝ Very low[a,b,c,d]	
Clinical pregnancy	100 per 1000	174 per 1000 (126 to 234)	OR 1.89 (1.3 to 2.75)	841 (7 RCTs)	⊕⊕⊝⊝ Low[a,b,c]	
OHSS	Not reported in any included studies					

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

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

[a]Serious risk of bias due to inadequate reporting of study methods. Risk of bias unclear in most domains of most studies.
[b]Serious imprecision with low event rate.
[c]Number of studies was not sufficient for assessment of publication bias.
[d] Findings not statistically significant when random-effects model was used (OR 1.77, 95% CI 0.96 to 3.26), or when analysis was restricted to studies reporting live birth.

Summary of findings 3. Progesterone compared with hCG regimens for assisted reproduction cycles

Progesterone compared with hCG regimens for assisted reproduction cycles

Population: subfertile women
Setting: assisted reproduction
Intervention: progesterone
Comparison: hCG (alone or with progesterone)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	hCG (alone or with progesterone)	Progesterone				
Live birth or ongoing pregnancy	198 per 1000	190 per 1000 (138 to 254)	OR 0.95 (0.65 to 1.38)	833 (5 RCTs)	⊕⊕⊝⊝ Low[a,b,c,d]	
Clinical pregnancy	284 per 1000	300 per 1000 (263 to 340)	OR 1.08 (0.9 to 1.3)	2355 (16 RCTs)	⊕⊕⊕⊝ Moderate[a]	
OHSS	118 per 1000	58 per 1000 (39 to 87)	OR 0.46 (0.30 to 0.71)	1293 (5 studies)	⊕⊕⊝⊝ Low[a,c,e]	

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

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

[a]Serious risk of bias due to inadequate reporting of study methods. Risk of bias unclear in most domains of most studies.
[b]Serious imprecision with low event rate.
[c]Number of studies was not sufficient for assessment of publication bias.
[d]Findings compatible with meaningful benefit for either group, or with no effect
e Some inconsistency: I^2=48% overall, I^2=60% in progesterone vs hCG subgroup

Summary of findings 4. Progesterone compared with progesterone + oestrogen for assisted reproduction cycles

Progesterone compared with progesterone + oestrogen for assisted reproduction cycles

Population: subfertile women
Setting: assisted reproduction
Intervention: progesterone
Comparison: progesterone + oestrogen (route of oestrogen: oral, transdermal, vaginal or oral + transdermal)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Progesterone + oestrogen	Progesterone				
Live birth or ongoing pregnancy	367 per 1000	393 per 1000 (345 to 444)	OR 1.12 (0.91 to 1.38)	1651 (9 RCTs)	⊕⊕⊖⊖ Low[a, b, c]	
Clinical pregnancy	433 per 1000	397 per 1000 (355 to 443)	OR 0.86 (0.72 to 1.04)	2169 (14 RCTs)	⊕⊕⊖⊖ Low[a, d, f]	
OHSS	51 per 1000	30 per 1000 (11 to 82)	OR 0.58 (0.2 to 1.68)	461 (2 RCTs)	⊕⊕⊖⊖ Low[b, c, e]	

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

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

[a]Serious risk of bias due to inadequate reporting of study methods. Risk of bias unclear in most domains of most studies.
[b]Serious imprecision with low event rate.
[c]Number of studies was not sufficient for assessment of publication bias.
[d]Serious inconsistency with substantial statistical heterogeneity (I^2 = 56%). Limiting analysis to the 9 studies using oral oestrogen yielded OR of 1.01 (95% CI 0.80 to 1.27) and reduced heterogeneity (I^2 = 16%).
[e]Serious risk of bias due to inadequate reporting of study methods. Risk of bias both 'high risk' and 'low risk'
[f]Two studies with an outlying result.

Summary of findings 5. Progesterone compared with progesterone + GnRH agonist for assisted reproduction cycles

Progesterone compared with progesterone + GnRH agonist for assisted reproduction cycles

Population: women who had undergone IVF/ICSI
Setting: clinic
Intervention: progesterone luteal support
Comparison: progesterone + 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				
	Progesterone + GnRH agonist	Progesterone luteal support				
Live birth or ongoing pregnancy	356 per 1000	255 per 1000 (209 to 309)	OR 0.62 (0.48 to 0.81)	2861 (9 RCTs)	⊕⊖⊖⊖ Very low[a,b]	
Clinical pregnancy	405 per 1000	310 per 1000 (258 to 367)	OR 0.66 (0.51 to 0.85)	2435 (8 RCTs)	⊕⊕⊖⊖ Low[c,d]	
OHSS	50 per 1000	50 per 1000 (17 to 137)	OR 1.00 (0.33 to 3.01)	300 (1 study)	⊕⊖⊖⊖ Very low[e,f,]	

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

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

[a] Evidence of significant heterogeneity I^2 = 69%
[b] Only three of the studies reported on live birth as an outcome
[c] Evidence of heterogeneity I^2=47%
[d] Some studies used multiple doses and some used single doses. We have used subgroup analysis to explore this further
[e] Lack of detail to make a judgement of risk of bias
[f] Evidence based on a single trial

Summary of findings 6. Progesterone regimens for assisted reproduction cycles

Progesterone regimens for assisted reproduction cycles

Population: subfertile women
Setting: assisted reproduction
Comparisons of progesterone regimens

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Comparison	Intervention				
Live birth or ongoing pregnancy IM vs oral	200 per 1000	151 per 1000 (34 to 478)	OR 0.71 (0.14 to 3.66)	40 (1 RCT)	⊕⊝⊝⊝ Very low[a,b,c]	
Live birth or ongoing pregnancy IM vs vaginal/rectal	266 per 1000	310 per 1000 (272 to 353)	OR 1.24 (1.03 to 1.5)	2309 (7 RCTs)	⊕⊝⊝⊝ Very low[a,c,d]	
Live birth or ongoing pregnancy Vaginal/rectal vs oral	205 per 1000	235 per 1000 (176 to 303)	OR 1.19 (0.83 to 1.69)	857 (4 RCTs)	⊕⊕⊝⊝ Low[a,c,e]	
Live birth or ongoing pregnancy Low dose vaginal vs high dose vaginal	301 per 1000	295 per 1000 (266 to 324)	OR 0.97 (0.84 to 1.11)	3720 (5 RCTs)	⊕⊕⊕⊝ Moderate[a,c]	
Live birth or ongoing pregnancy Short protocol vs long protocol	664 per 1000	672 per 1000 (609 to 728)	OR 1.04 (0.79 to 1.36)	1205 (5 RCTs)	⊕⊕⊕⊝ Low[a,c,e]	
Live birth or ongoing pregnancy Micronised vs synthetic	220 per 1000	203 per 1000 (130 to 305)	OR 0.9 (0.53 to 1.55)	470 (2 RCTs)	⊕⊕⊝⊝ Low[b,c,e]	
Live birth or ongoing pregnancy Vaginal ring vs vaginal gel	441 per 1000	462 per 1000 (409 to 517)	OR 1.09 (0.88 to 1.36)	1271 (1 RCT)	⊕⊕⊝⊝ Low[c,f,g]	
Live birth or ongoing pregnancy	358 per 1000	339 per 1000 (292 to 388)	OR 0.92 (0.74 to 1.14)	1465 (2 RCTs)	⊕⊕⊝⊝ Low[c,g,h]	

Subcutaneous vs vaginal gel					
Live birth or ongoing pregnancy Vaginal vs rectal	306 per 1000	360 per 1000 (220 to 528)	OR 1.28 (0.64 to 2.54)	147 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]
OHSS IM vs oral	50 per 1000	50 per 1000 (3 to 475)	OR 1.00 (0.06 to 17.18)	40 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]
OHSS Low dose vaginal vs high dose vaginal	60 per 1000	55 per 1000 (35 to 86)	OR 0.91 (0.57 to 1.46)	1251 (2 RCTs)	⊕⊕⊕⊖ Low[b,c,g]
OHSS rates not reported for other comparisons.					

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

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

[a]Serious risk of bias due to inadequate reporting of study methods. Risk of bias unclear in most study domains.
[b]Very serious imprecision with low event rate; findings compatible with meaningful benefit in either arm or with no effect.
[c]Number of studies was not sufficient for assessment of publication bias.
[d]Very serious inconsistency with varying directions of effect (I^2 = 71%). Findings not statistically significant when random-effects model was used, or when analysis was restricted to studies reporting live births.
[e]Serious imprecision with low event rate; findings compatible with meaningful benefit in the oral arm or with no effect.
[f]Serious imprecision; findings compatible with meaningful benefit in the gel arm or with no effect.
[g]Serious risk of bias due to inadequate reporting of study methods in 1 or more studies.
[h]Serious imprecision; findings compatible with meaningful benefit in the subcutaneous arm or with no effect.

Summary of findings 7. Progesterone + oestrogen regimens for assisted reproduction cycles

Progesterone + oestrogen regimens for assisted reproduction cycles
Population: subfertile women **Setting:** assisted reproduction Comparisons of progesterone and oestrogen regimens

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Comparison	Progesterone regimens				
Live birth/ongoing pregnancy - short vs long protocol	293 per 1000	309 per 1000 (251 to 372)	OR 1.08 (0.81 to 1.43)	910 (1 RCT)	⊕⊕⊖⊖ Low[a,b,c]	
Live birth/ongoing pregnancy - low vs high dose protocol	342 per 1000	253 per 1000 (161 to 370)	OR 0.65 (0.37 to 1.13)	285 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d]	
OHSS - short vs long protocol	Not reported in any studies					
OHSS - low vs high dose protocol	Not reported in any studies					

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

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

[a]Serious risk of bias due to inadequate reporting of study methods. Risk of bias unclear in most study domains.
[b]Serious imprecision; findings compatible with meaningful benefit in either arm or with no effect.
[c]Number of studies was not sufficient for assessment of publication bias.
[d]Very serious imprecision with low event rate; findings compatible with meaningful benefit in either arm or with no effect.

BACKGROUND

Description of the condition

Assisted reproductive technology (ART), such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), is used increasingly to assist couples to have a family. In cases of fertility treatment during which one or more embryos were transferred, less than one-third of cases resulted in a live birth (CDC 2009; de Mouzon 2010; Macaldowie 2014). These figures suggest that implantation failure is an important limiting factor in the outcomes of ART.

The endometrium, which lines the uterus, prepares for implantation of the embryo. This process starts in the proliferative phase (from menstruation to ovulation) and extends throughout the luteal phase (from ovulation until menstruation). The luteal phase begins on the day of the luteinising hormone (LH) surge, which causes ovulation. The luteal phase ends at the onset of the next menstruation and usually lasts 12 to 16 days. During the luteal phase, the corpus luteum undergoes morphological and biochemical changes known as 'luteinisation'. Under the influence of LH, specific cells called granulosa cells produce progesterone. This in turn induces the secretory transformation of the endometrium, preparing it for implantation by thickening and increasing vascularisation to facilitate implantation (Farquhar 2010). Implantation occurs six days after fertilisation in natural cycles.

After implantation, trophoblastic tissue of the placenta secretes human chorionic gonadotropin (hCG), which acts on the ovary. hCG maintains and stimulates the corpus luteum, the remnant of the follicle, to produce oestradiol and progesterone (Pabuccu 2005). This is important in maintaining the pregnancy until the placenta takes over steroid hormone production at approximately seven weeks.

From the early phase of assisted reproduction, it has been clear that the luteal phase in ART is not sufficient, although the underlying mechanism is unclear (Edwards 1980). Several theories have been proposed to explain the deficient luteal phase in ART. In ART cycles, the corpus luteum is formed from the remnants of aspirated follicles under the influence of LH and produces progesterone and oestradiol (Messinis 2009). It was first thought that oocyte retrieval caused a luteal phase defect and, in particular, steroid secretion, but this theory was rejected when Kerin (Kerin 1981) demonstrated that aspiration of a single follicle did not lead to impaired steroid function. Another theory was that gonadotropin-releasing hormone (GnRH) agonist co-treatment caused prolonged pituitary recovery, which resulted in lack of LH; thus the corpus luteum did not develop fully (Smitz 1992a). Lack of LH was thought to be caused by a short-loop negative feedback mechanism after hCG administration for oocyte maturation. This theory was also rejected, as long-loop negative feedback by ovarian oestrogens has a greater effect on LH levels (Miyake 1979), and hCG does not lower LH secretion in non-stimulated, normal ovulating women (Tavaniotou 2003). Currently it is thought that LH levels are lowered by high steroid levels (Fatemi 2009). Steroid levels are high because of the multiple corpora lutea, which produce more steroids than are produced in a natural cycle. This causes negative feedback on the pituitary gland and lowers LH levels. In this way, the luteal phase is shortened (known as premature luteolysis), and chances of pregnancy are reduced. In summary, premature luteolysis results from high concentrations of steroids caused by higher numbers of corpora lutea (secondary to controlled ovarian stimulation) during the early luteal phase, which in turn inhibit LH release directly by negative feedback.

In 2005, GnRH was introduced as a new means of providing luteal phase support. GnRH blocks the LH surge, and it was assumed that GnRH agonists might maintain their stimulatory effect throughout the luteal phase and restore LH levels - a process that would support the luteal phase (Pirard 2006a). In 2004, Tesarik reported on the use of GnRH agonists six days after ICSI amongst oocyte donors. This study showed that single-dose agonist administration increased the implantation rate without affecting miscarriage and abortion rates, resulting in an improved birth rate. However the multiple pregnancy rate was also increased (Tesarik 2004).

Adequate luteal phase support is therefore essential during IVF and ICSI for improving implantation and pregnancy rates. This can be achieved by substituting deficient LH with GnRH agonists or hCG, which has a longer half-life, or directly by using progesterone with or without oestrogen. The ideal method of luteal phase supplementation remains a matter of debate and is the focus of this review.

Description of the intervention

The following agents can be used during the luteal phase.

1. Progesterone (including micronised progesterone or synthetic progestogens such as dydrogesterone, which have higher bioavailability (Schindler 2009)), administered by the following routes.
   a. Intramuscular (IM).
   b. Oral.
   c. Vaginal - an oral progesterone supplement administered by the vaginal route can lead to higher serum progesterone concentrations (Choavaratana 2004). Progesterone can also be administered vaginally by a gel or cream, which can generate high concentrations by bypassing the first-pass effect through the liver (Geber 2007a).
   d. Rectal.
2. Human chorionic gonadotropin (hCG) is similar to LH in its mode of action and physiological effects. Molecular structure is also similar. However hCG differs from LH in that elevated sialic acid residues are responsible for the longer serum half-life and potency (Balasch 2004). Two types of hCG have been used: human derived and recombinant (Mochtar 2007). hCG is administered by the following routes.
   a. Intramuscular (IM).
   b. Subcutaneous (SC). It has been suggested that the bioavailability of hCG is lower after SC injections than after IM injections, but this remains unclear (Chan 2003;Mannaerts 1998; Saal 1991; Wikland 1995).
3. Oestrogen: oral, transdermal or vaginal administration in combination with progesterone.
4. GnRH agonists.
   a. Intranasal.
   b. Intramuscular (IM).
   c. Subcutaneous (SC).

How the intervention might work

In ART, levels of progesterone in the luteal phase are insufficient (see above); therefore the levels of progesterone need to be increased. The progesterone level can be increased directly by giving progesterone, or progesterone and oestrogen in combination, or indirectly by giving hCG, which in turn stimulates progesterone secretion. Addition of a GnRH agonist is thought to restore LH levels during the luteal phase.

Why it is important to do this review

Less than one-third of all cases involving an embryo result in a live birth. Luteal phase support has a positive effect on the outcome of ART compared with no treatment (van der Linden 2011). Many randomised trials have compared different methods of administration and different preparations to identify the best method of providing luteal phase support. This updated Cochrane review examines all currently available evidence on hCG, progesterone, oestrogen and GnRH analogues as agents for luteal phase support in ART.

OBJECTIVES

To determine the relative effectiveness and safety of methods of luteal phase support provided to subfertile women undergoing assisted reproduction.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing any of the agents used for luteal phase support during the luteal phase of an ART cycle. We included cross-over trials in the review for completeness but used only first phase data in the analysis. We did not include quasi-RCTs. We excluded studies investigating luteal phase support involving intrauterine insemination (IUI).

Types of participants

We included all subfertile women undergoing treatment with ART, including IVF or ICSI. We did not take the cause of subfertility into account. We excluded studies including women who had cycles of gamete intrafallopian transfer (GIFT) or zygote intrafallopian transfer (ZIFT), unless these treatments took place in less than 20% of cycles, as pregnancy outcomes with GIFT and ZIFT are less than with IVF. This 20% threshold was arbitrary.

Types of interventions

We included trials if they investigated or included:

1. any type, dose or route of progesterone, provided at least five doses were given during the luteal phase, to ensure the inclusion of true luteal phase support studies;
2. any type, dose or route of hCG, provided at least two doses were given during the luteal phase, to ensure the inclusion of true luteal phase support studies;
3. progesterone combined with oestrogen;
4. progesterone combined with hCG; or
5. GnRH agonist during the luteal phase.

We considered all ovarian stimulation protocols.

We excluded trials if they investigated or included:

1. luteal phase support after frozen embryo transfer;
2. luteal phase support after embryo transfer from donated oocytes;
3. luteal phase support after embryo transfer from frozen oocytes or frozen ovarian tissue;
4. luteal phase support after in vitro maturation (IVM) cycles; or
5. luteal phase support after intrauterine insemination (IUI) cycles.

Types of outcome measures

Primary outcomes

1. Live birth rate (LBR) or ongoing pregnancy per woman ('live birth' defined as the delivery of one or more living infants; 'ongoing pregnancy' defined as a pregnancy beyond 12 weeks' gestation).

Secondary outcomes

2. Clinical pregnancy rate (CPR) per woman (defined as the presence of a gestational sac, with or without a foetal heartbeat, on ultrasonography).

3. Miscarriage rate (MR) per woman.

4. Ovarian hyperstimulation syndrome (OHSS) per woman.

5. Multiple pregnancy rate per woman (counted as one).

Search methods for identification of studies

This review used information provided in the Cochrane Menstrual Disorder and Subfertility Group (MDSG) module regarding search strategies (www.mrw.interscience.wiley.com/cochrane/clabout/articles/MENSTR/frame.html). We sought all published and unpublished RCTs that described progesterone or hCG, or both, for luteal support in women undergoing ART. We used indexed and free-text terms. We designed search strategies in consultation with the MDSG Trials Search Co-ordinator. All searches were run from inception until 05.08.15

Electronic searches

We searched the following databases.

1. MDSG Specialised Register (see Appendix 1).
2. Cochrane Central Register of Controlled Trials (CENTRAL) (see Appendix 2).
3. MEDLINE (see Appendix 3).
4. EMBASE (see Appendix 4).
5. PsycINFO (see Appendix 5).
6. Cumulative Index to Nursing and Allied Health Literature (CINAHL) (see Appendix 6).
7. Database of Abstracts of Reviews of Effects (DARE) (see Appendix 7).

The MDSG Specialised Register has been prepared through handsearching.

We combined the MEDLINE search with the Cochrane highly sensitive search strategy for identifying randomised trials, which

appears in the *Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0, Chapter 6, 6.4.11 (Higgins 2011).

We combined the EMBASE search with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/mehodology/filters.html#random).

We imposed no language restrictions on the searches.

Searching other resources

We searched the following.

1. ClinicalTrials.gov (http://clinicaltrials.gov/ct2/home) for ongoing and registered trials (Appendix 8)
2. The World Health Organization International Trials Registry Platform (www.who.int/trialsearch/Default.aspx) for ongoing and registered trials (Appendix 8)
3. Conference abstracts on the Web of Science (http://wokinfo.com) (see Appendix 9).
4. OpenSigle for grey literature from Europe (http://opensigle.inist.fr), using the search string "((chorionic gonadotropin) OR (progesterone)) AND (luteal phase)".
5. Latin American Caribbean Health Sciences Literature (LILACS) (http://regional.bvsalud.org/php/index.php?lang=en), using the keywords "luteal phase support".

Data collection and analysis

Selection of studies

Two review authors (MvdL, MM) independently screened titles and abstracts to exclude studies that were clearly irrelevant. We retrieved the full texts of potentially eligible studies for further independent scrutiny by two review authors (MvdL, MM) and checked compliance with the inclusion criteria by using the study eligibility form (see Appendix 10). We provided reasons for exclusion in the 'Characteristics of excluded trials' table. When it was unclear whether a study was eligible, we contacted the original study authors. We resolved disagreements through consultation with a third review author (CF).

Data extraction and management

We extracted data using a data extraction form (see Appendix 11) that was designed and pilot-tested by the review authors. In the case of multiple publications, we referenced studies by their main trial report and linked the references. We contacted the original study authors if further information was required. Three review authors (MvdL, MM, KB) independently extracted data and resolved disagreements through consultation with the other review authors.

Assessment of risk of bias in included studies

We assessed risk of bias with regard to sequence generation, allocation, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting and other potential sources of bias. We summarised conclusions in a 'Risk of bias' table (see Appendix 12). Review authors judged all six domains as at 'low risk', 'high risk' or 'unclear risk' of bias and described in the table the methods used. When information was missing, we contacted study authors.

1. Random sequence generation (selection bias).
   a. Proper methods included use of a computer random number generator, coin tossing, dice throwing and shuffling of cards or envelopes.
   b. Allocation by judgement of clinician, preference of participant, lab tests, date of birth, record number and inadequate sequence generation such as day of the week was not sufficient.
2. Allocation concealment (selection bias).
   a. Proper methods required sequentially numbered drug containers of identical appearance, numbered opaque sealed envelopes or secure third party randomisation such as by telephone or computer allocation.
   b. Prior knowledge of the allocation because of an open random allocation schedule or alternation, rotation, etc, was not sufficient.
3. Blinding of participants and personnel (performance bias).
   a. Review authors assigned low risk of bias when blinding of clinicians and participants (when possible) was ensured, or when incomplete blinding had no effect on the outcome measurement.
   b. When no blinding was provided and this had an influence on the outcome measurement, review authors identified the study as having risk of bias.
4. Blinding of outcome assessment (detection bias).
   a. Review authors assigned low risk of bias when blinding of researchers (when possible) was ensured, or when incomplete blinding had no effect on the outcome measurement.
   b. When no blinding was provided and this had an influence on the outcome measurement, review authors identified the study as having risk of bias.
5. Incomplete outcome data (attrition bias).
   a. Review authors assigned low risk of bias when missing outcome data were unlikely to be related to true outcomes, or when all outcome data were complete.
   b. High risk of bias indicated that missing outcome data were likely to be related to true outcomes, or that the proportion of missing outcome results compared with observed event risk was sufficient to induce clinically relevant bias in observed effect size.
6. Selective reporting (reporting bias).
   a. Review authors assigned low risk of bias when all prespecified outcomes that were of interest or described in the protocol were reported.
   b. High risk of bias indicated that not all prespecified outcomes were mentioned, reported outcomes were not prespecified or a key outcome that would be expected was not reported.
7. Free of other bias.
   a. Risk of other bias (e.g. embryo transfer policies different in different arms of the study) showed extreme baseline imbalance.

When risk of bias tables had been completed, we generated a risk of bias summary figure (Higgins 2011).

Measures of treatment effect

We retrieved only dichotomous data for this review; thus we calculated Peto odds ratios (ORs) with 95% confidence intervals (CIs).

Unit of analysis issues

The primary analysis was per woman randomly assigned. We counted multiple live births as one live birth and included cross-over data from the first phase of the study. When information were missing, we contacted the study authors.

Dealing with missing data

To obtain complete data, as much as possible, we contacted the original study authors. In case data could not be obtained, we undertook imputation for the primary outcome and assumed that no live birth occurred when this was not reported. When data for secondary outcomes were missing, we analysed only available data.

Assessment of heterogeneity

We assessed heterogeneity by examining a forest plot and the I^2 statistic according to guidelines set forth in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we detected substantial heterogeneity, that is, $I^2 \geq 50\%$, we performed a sensitivity analysis to explore possible explanations.

Assessment of reporting biases

We assessed publication bias by examining a funnel plot if more than 10 studies were included. An asymmetrical funnel plot indicates possible publication bias, although the asymmetry may have other causes. We assessed within-study reporting bias if study protocols were available, and if we noted differences between outcomes in the protocol and in the subsequent publication.

Data synthesis

We combined the data from primary studies by using a fixed-effect model in the following comparisons.

1. hCG versus placebo or no treatment.
2. Progesterone versus placebo or no treatment.
3. Progesterone versus hCG regimens.
   a. Progesterone versus hCG.
   b. Progesterone versus progesterone and hCG.
4. Progesterone versus progesterone and oestrogen.
   a. Oral oestrogen.
   b. Transdermal oestrogen.
   c. Vaginal oestrogen.
   d. Oral and transdermal oestrogen.
5. Progesterone versus progesterone and GnRH agonist.
   a. Single dose.
   b. Multiple dose.
6. Progesterone regimens.
   a. IM progesterone versus oral progesterone.
   b. IM progesterone versus vaginal or rectal progesterone.
   c. Vaginal or rectal progesterone versus oral progesterone.
   d. Low-dose vaginal progesterone (≤ 100 mg) versus high-dose vaginal progesterone (> 100 mg).
   e. Short protocol versus long protocol.
   f. Micronised progesterone versus synthetic progesterone.
   g. Vaginal ring versus vaginal gel.
   h. Subcutaneous versus vaginal gel.
   i. Vaginal progesterone versus rectal progesterone.
7. Progesterone + oestrogen regimens.
   a. Short protocol versus long protocol.
   b. Low-dose oestrogen (≤ 2 mg) versus high-dose oestrogen (> 2 mg).

When studies contributed to more than one comparison in a pooled analysis, we split as equally as possible comparisons data from the group that appeared in both comparisons. When data were split in this way, we provided details in a footnote in the forest plot.

Subgroup analysis and investigation of heterogeneity

We analysed data in the following subgroups as well.

1. Ovarian stimulation protocols including:
   a. clomiphene citrate alone without GnRH agonists;
   b. human gonadotropins with clomiphene citrate without GnRH agonists;
   c. human gonadotropins with or without GnRH agonists; and
   d. human gonadotropins with or without GnRH antagonists.
2. Participants with previously failed cycles.
   a. ≤ 2 failed ART cycles.
   b. > 2 failed ART cycles.
3. Duration of progesterone.
   a. Stop at day of positive pregnancy test.
   b. Given up to 12 weeks for women who conceive.
4. Number of embryos transferred.
   a. Single embryo transfer.
   b. > one embryo transferred.

Sensitivity analysis

We performed a sensitivity analysis for the primary outcome to determine differences in results caused by:

1. eligibility restricted to studies without high risk of bias;
2. alternative imputation strategies that had been adopted;
3. use of risk ratio rather than odds ratio as the effect estimate; or
4. use of a random-effects rather than a fixed-effect analysis.

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

We prepared 'Summary of findings' tables using GRADEPRO software. These tables evaluate the overall quality of the body of evidence for the primary review outcomes, using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). We have justified, documented and incorporated into reporting of results for each outcome judgements about evidence quality (high, moderate or low).

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We conducted our searches on 05 August 2015 (using the strings reported in the appendices (Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 1; Appendix 6; Appendix 7; Appendix 8; Appendix 9), and in Open System for Information on Grey Literature in Europe (OpenSigle) and Latin American Caribbean Health Sciences Literature (LILACS). We identified 2441 studies and found six studies by using other methods such as handsearching.

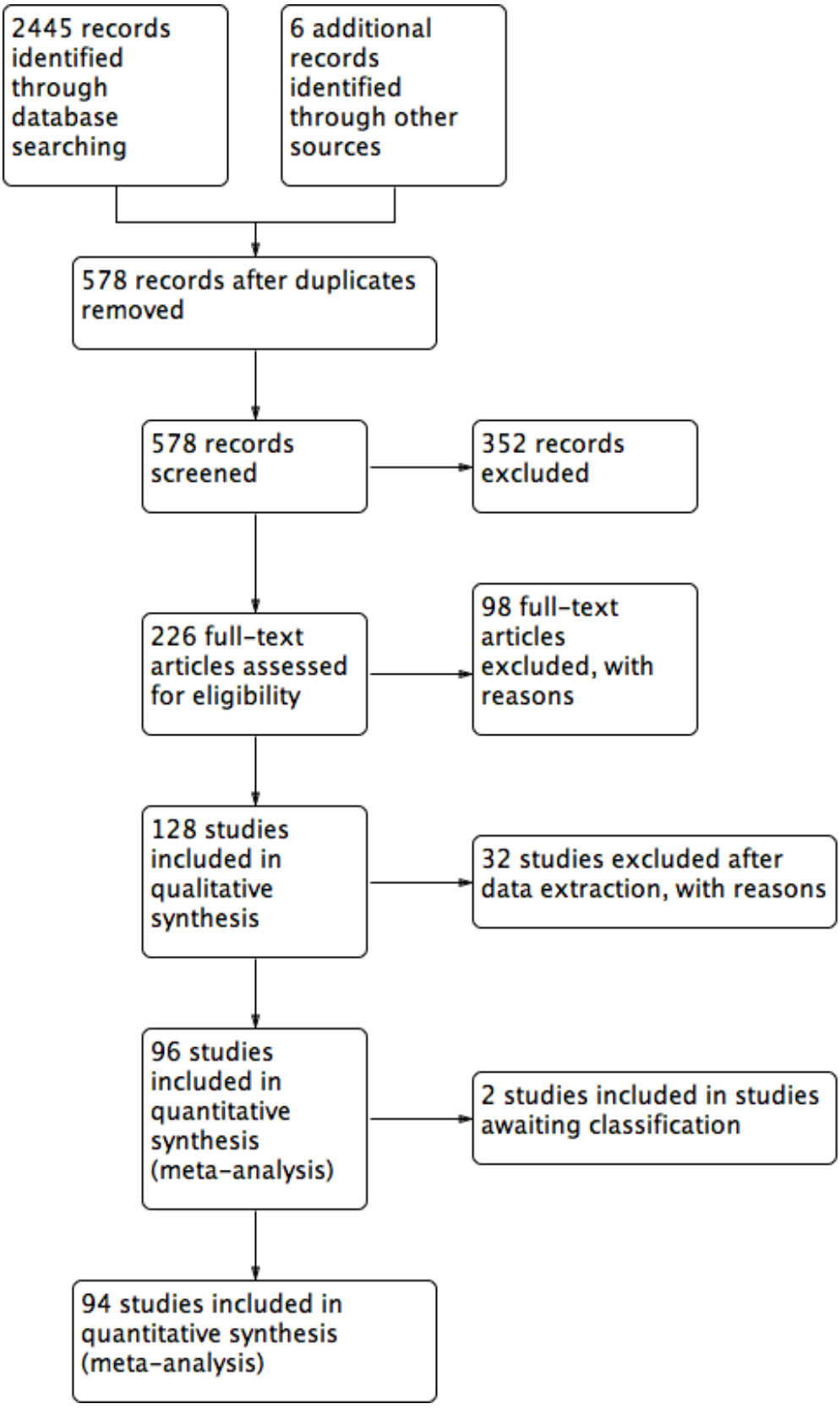
On the website ClinicalTrials.gov in November 2014, we found 10 ongoing studies after using the keywords "luteal phase support". One study did not provide sufficient contact details. Five study authors did not reply (NCT01178931, NCT00828191, NCT00656201, NCT00708539, NCT01850030). One study author replied, and this study turned out to be already published (NCT00827983 as Baker 2014). Three studies were already published (NCT01147770 as Kyrou 2011, NCT01367912 as Tonguc 2011 and NCT01177904 as Kohls 2012). The World Health Organization International Trials Registry Platform (ICTRP), when searched with the keywords "luteal phase support", brought up eight new studies. Three studies did not provide sufficient contact details. Three studies were already published (ISRCTN88722916 as Aboulghar 2008, ICTR2013050713265N1 as Salehpour 2013, and ICTR138807192568N1 as Aghsa 2012). One study author did reply but had no data ready (EUCTR2013-001105-81-HU). One study author did not reply (NCT01237535). From both these sites there were 11 ongoing studies.

Further database searches on 4 August 2015 identified two new studies eligible for inclusion and we have incorporated their data in the abstract, results and discussion sections of the review. Two studies requiring additional information before we could assess eligibility await classification for inclusion or exclusion at the next update of this review.

A further search of the ICTRP and clinicaltrials.gov (Appendix 8) sites on 4 August 2015 found another 17 ongoing studies. After de-duplication a total of 22 ongoing studies remained. For full details of all ongoing studies see Characteristics of ongoing studies.

After duplicates were removed, 578 studies were left for screening. We excluded 352 clearly irrelevant studies. We obtained and fully reviewed the full-text articles for the other 226 studies. We excluded all quasi-randomised trials, together with articles that did not meet our inclusion criteria. We excluded another 31 articles from the review and included in the meta-analysis a total of 94 studies (see Figure 1 for a study flow diagram). Three trials are awaiting assessment (Pirard 2015; Tomic 2015; Zafardoust 2015) .

Figure 1. Study flow diagram.



Included studies

Study design

We included 94 studies, all of which were randomised controlled trials. We found no cross-over trials for inclusion. In total, included studies consisted of 25,471 women with a mean age of 32.4 years. Inclusion and exclusion criteria varied among studies. Some studies included women with polycystic ovarian syndrome (PCOS), but this was an exclusion criterion in other studies. A few studies included women undergoing their first cycle, but most studies included women who had already undergone ART. Overall a mean of 2.43 embryos per woman were transferred, most with a maximum of three or four embryos.

For 24 studies, only the abstract was published (Albert 1991; Ata 2010; Beltsos 2011; Brigante 2013; Caligara 2007; Colakoglu 2011; Dunstone 1999; Erdem 2013; Geber 2007; Geusa 2001; Kably Ambe 2005; Loh 1996; Macrolin 1993; Miller 2010; Nallapeta 2013; Porcu 2003; Rodriguez-Pezino 2004; Salehpour 2013; Saucedo 2000; Saucedo 2003; Serour 2012; Strehler 1999; Sumita 2003; Ugur 2001); the other studies were full-text journal publications. Only 13 were multi-centre studies (Baker 2014; Belaisch-Allart 1990; Beltsos 2011; Bergh 2012; Doody 2009; Elgindy 2010; Kleinstein 2005; Lockwood 2014; Miller 2010; Nyboe Andersen 2002; Pouly 1996; Stadtmauer 2013; Zegers-Hochschild 2000).

Thirteen of our included studies were carried out in the United States of America (Albert 1991; Baker 2014; Beltsos 2011; Doody 2009; Engmann 2008; Goudge 2010; Hurd 1996; Licciardi 1999; Miller 2010; Propst 2001; Stadtmauer 2013; Williams 2001; Yanushpolsky 2010). Ten studies were reported from Turkey (Ata 2008; Ata 2010; Ceyhan 2008; Colakoglu 2011; Erdem 2013; Gorkemli 2004; Isik 2009; Isikoglu 2007; Tonguc 2011; Ugur 2001; Yildiz 2014) and eight from Italy (Abate 1999; Abate 1999a; Artini 1995; Brigante 2013; Dal Prato 2008; Geusa 2001; Perino 1997; Porcu 2003). Twenty-seven studies were conducted in other European countries: Austria (Feichtinger 2011), Belgium (Fatemi 2006), Denmark (Humaidan 2006; Nyboe Andersen 2002), Finland (Vimpeli 2001), France (Belaisch-Allart 1987; Belaisch-Allart 1990; Macrolin 1993; Pouly 1996), Germany (Kleinstein 2005; Ludwig 2001; Ludwig 2002; Strehler 1999), Greece (Drakakis 2007; Kyrou 2011), the Netherlands (Beckers 2000; Mochtar 2006), Spain (Caligara 2007; Kably Ambe 2005; Kohls 2012; Martinez 2000; Serna 2008; Tesarik 2006) and the UK (Dunstone 1999; Nallapeta 2013; Tay 2005). Thirteen were carried out in Asia: China (Lam 2008; Lin 2013; Ng 2003; Ng 2007; Wong 1990), India (Chakravarty 2005; Ganesh 2011; Inamdar 2012; Patki 2007; Sumita 2003), Japan (Fujimoto 2002; Iwase 2008) and Singapore (Loh 1996). We also found studies from Australia (Torode 1987), Brasil (Geber 2007; Geber 2007a), Canada (Colwell 1991), Egypt (Aboulghar 2008; Elgindy 2010; Serour 2012; Aboulghar 2015), Israel (Friedler 1999; Golan 1993; Kupferminc 1990; Lewin 1994), Iran (Aghahosseini 2011; Aghsa 2012; Moini 2011; Salehpour 2013), Jordan (Qublan 2008) and Mexico (Rodriguez-Pezino 2004; Saucedo 2000; Saucedo 2003), and we found three multi-centre, multi-national studies: one from Chile, Colombia and Brazil (Zegers-Hochschild 2000), one from Denmark and Sweden (Bergh 2012) and one from Hungary, Germany, Italy, Switzerland and the UK (Lockwood 2014).

Participants

Participants were women undergoing ART for a large variety of indications, including (low-grade) endometriosis, polycystic ovarian syndrome or an unknown or unspecified cause of infertility.

Interventions

Thirteen studies investigated down-regulation using GnRH antagonists (Baker 2014; Ceyhan 2008; Engmann 2008; Fatemi 2006; Geber 2007; Humaidan 2006; Isik 2009; Kohls 2012; Kyrou 2011; Nyboe Andersen 2002; Rodriguez-Pezino 2004; Serna 2008; Tesarik 2006), and six studies did not use down-regulation with GnRH analogues (Colwell 1991; Hurd 1996; Kupferminc 1990; Lewin 1994; Torode 1987; Wong 1990); clomiphene citrate, human menopausal gonadotropin (hMG) or both were used in most of those studies. Fifty-three studies investigated GnRH agonists, and two studies investigated both GnRH agonists and antagonists (Kably Ambe 2005; Lockwood 2014). The other studies did not define the down-regulation protocol used.

Outcomes

Live birth was reported in only 28 studies (Abate 1999; Abate 1999a; Ata 2010; Baker 2014; Beckers 2000; Bergh 2012; Chakravarty 2005; Dal Prato 2008; Doody 2009; Golan 1993; Goudge 2010; Isik 2009; Isikoglu 2007; Iwase 2008; Lewin 1994; Lin 2013; Lockwood 2014; Ludwig 2001; Mochtar 2006; Nyboe Andersen 2002; Pouly 1996; Propst 2001; Qublan 2008; Stadtmauer 2013; Tay 2005; Tesarik 2006; Yanushpolsky 2010; Zegers-Hochschild 2000).

Fifty-five studies reported ongoing pregnancy (Abate 1999a; Aghahosseini 2011; Aghsa 2012; Ata 2010; Aboulghar 2015 Baker 2014; Beckers 2000; Belaisch-Allart 1987; Belaisch-Allart 1990; Beltsos 2011; Bergh 2012; Brigante 2013; Ceyhan 2008; Chakravarty 2005; Colwell 1991; Dal Prato 2008; Doody 2009; Engmann 2008; Fatemi 2006; Feichtinger 2011; Friedler 1999; Ganesh 2011; Golan 1993; Gorkemli 2004; Goudge 2010; Hurd 1996; Inamdar 2012; Isik 2009; Isikoglu 2007; Iwase 2008; Kleinstein 2005; Kohls 2012; Kupferminc 1990; Kyrou 2011; Lewin 1994; Lin 2013; Lockwood 2014; Ludwig 2001; Ludwig 2002; Macrolin 1993; Miller 2010; Mochtar 2006; Ng 2007; Nyboe Andersen 2002; Perino 1997; Pouly 1996; Propst 2001; Qublan 2008; Salehpour 2013; Serna 2008; Stadtmauer 2013; Tay 2005; Tesarik 2006; Tonguc 2011; Yanushpolsky 2010; Yildiz 2014 Zegers-Hochschild 2000).

All studies reported (clinical) pregnancy, except for seven studies, which used miscarriage rate (Nallapeta 2013) or ongoing pregnancy as the main outcome (Beltsos 2011; Colwell 1991; Fatemi 2006; Feichtinger 2011; Serna 2008; Tay 2005).

Miscarriage is reported in 45 studies (Aghahosseini 2011; Aghsa 2012; Ata 2008; Baker 2014; Beckers 2000; Belaisch-Allart 1987; Bergh 2012; Chakravarty 2005; Colwell 1991; Dal Prato 2008; Drakakis 2007; Elgindy 2010; Engmann 2008; Fatemi 2006; Friedler 1999; Ganesh 2011; Geber 2007a; Golan 1993; Iwase 2008; Kably Ambe 2005; Kleinstein 2005; Kohls 2012; Kupferminc 1990; Kyrou 2011; Lam 2008; Licciardi 1999; Lin 2013; Lockwood 2014; Ludwig 2001; Ludwig 2002; Martinez 2000; Miller 2010; Nallapeta 2013; Ng 2007; Nyboe Andersen 2002; Perino 1997; Pouly 1996; Qublan 2008; Rodriguez-Pezino 2004; Salehpour 2013; Saucedo 2000; Serna 2008; Strehler 1999; Tonguc 2011; Yanushpolsky 2010), OHSS in 10 studies (Albert 1991; Belaisch-Allart 1990; Ceyhan 2008; Doody 2009; Iwase 2008; Lin 2013; Ludwig 2001; Macrolin 1993; Martinez 2000; Ugur

2001) and multiple pregnancy in 20 studies (Aghsa 2012; Ata 2008; Bergh 2012; Colwell 1991; Geber 2007a; Goudge 2010; Inamdar 2012; Isik 2009; Iwase 2008; Kleinstein 2005; Kohls 2012; Kyrou 2011; Licciardi 1999; Ludwig 2001; Ng 2007; Nyboe Andersen 2002; Pouly 1996; Strehler 1999; Tonguc 2011; Zegers-Hochschild 2000).

Excluded studies

We excluded from the review 129 studies that did not meet our inclusion criteria. In accordance with the guidelines of the MDSG, we excluded all quasi-randomised trials (Anserini 2001; Anthony 1993; Buvat 1988; Buvat 1990; Herman 1990; Herman 1996; Leeton 1985; Mahadevan 1985; McBain 1987; Polson 1992; Smith 1989; Smitz 1993; Yovich 1984; Yovich 1985; Yovich 1991), which had been included in an older version of this review (Daya 2004). We excluded all studies that included GIFT or ZIFT in more than 20% of cycles, or that did not mention the percentage of GIFT or ZIFT cycles used (Allen 2004; Araujo 1994; Araujo Filho 1996; Smitz 1988; Smitz 1992; van Steirteghem 1988).

Risk of bias in included studies

See the 'Summary of findings' tables for an overall assessment of the quality of evidence for each comparison. We prepared a table for each comparison (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7). See also the risk of bias graph (see Figure 2) and the risk of bias summary (see Figure 3) for an overview.

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

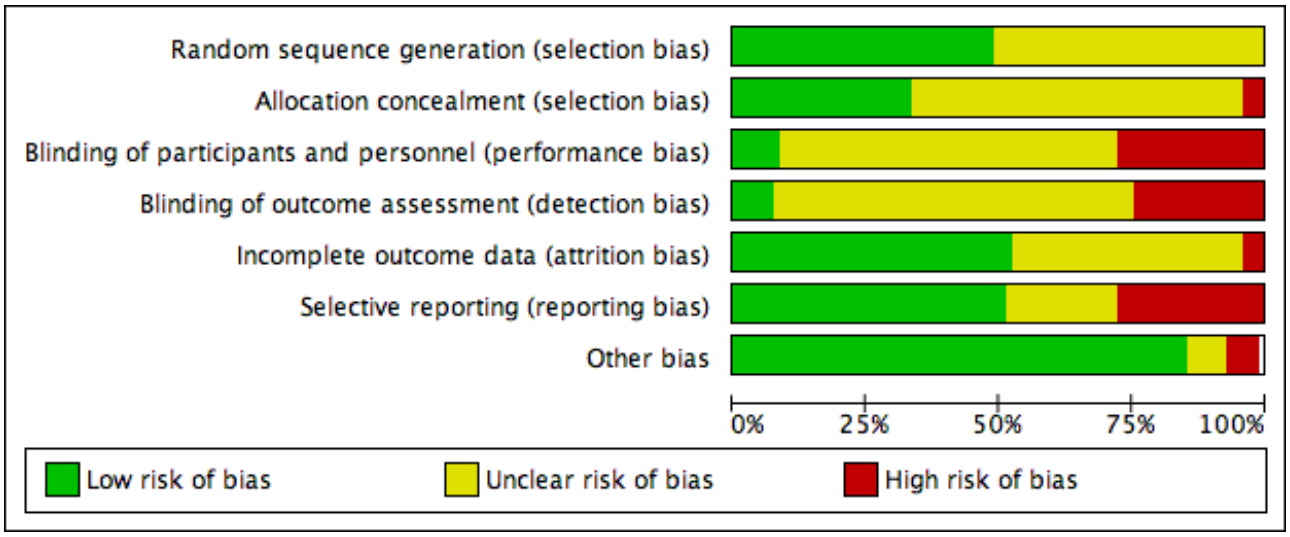


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

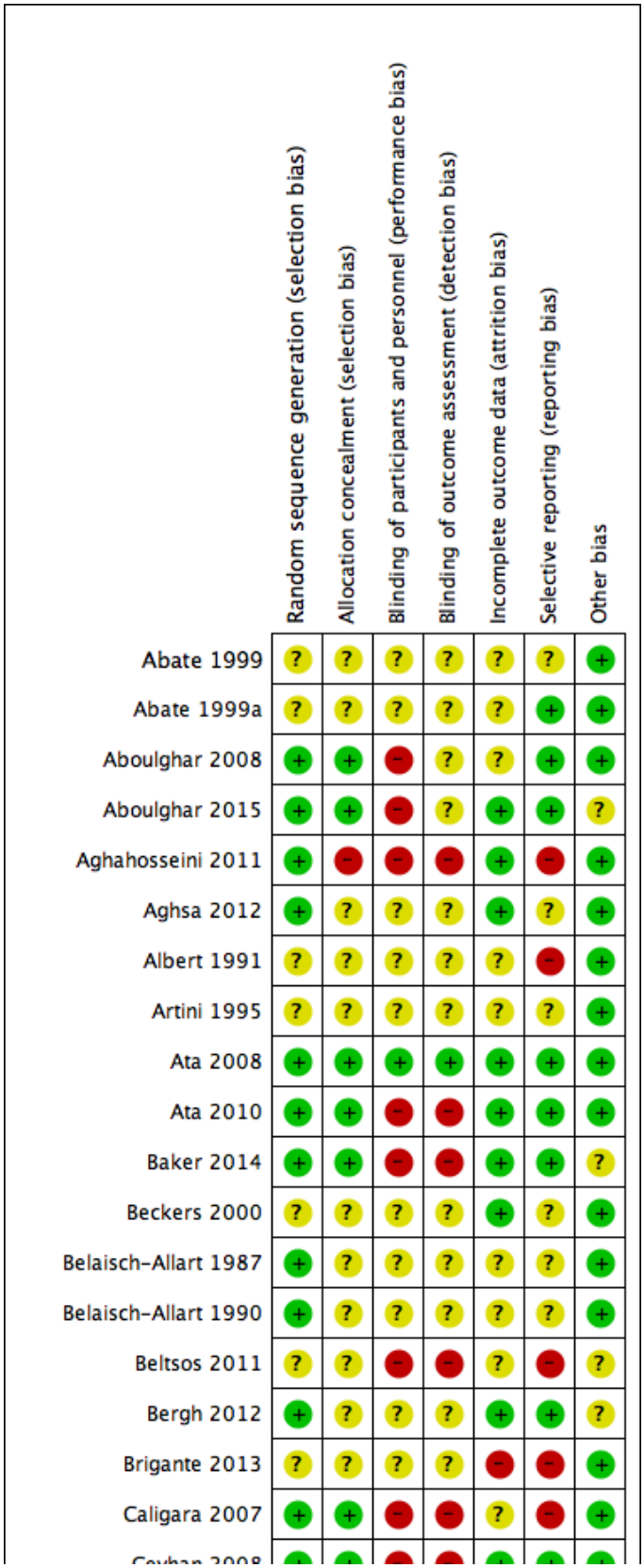


Figure 3. (Continued)

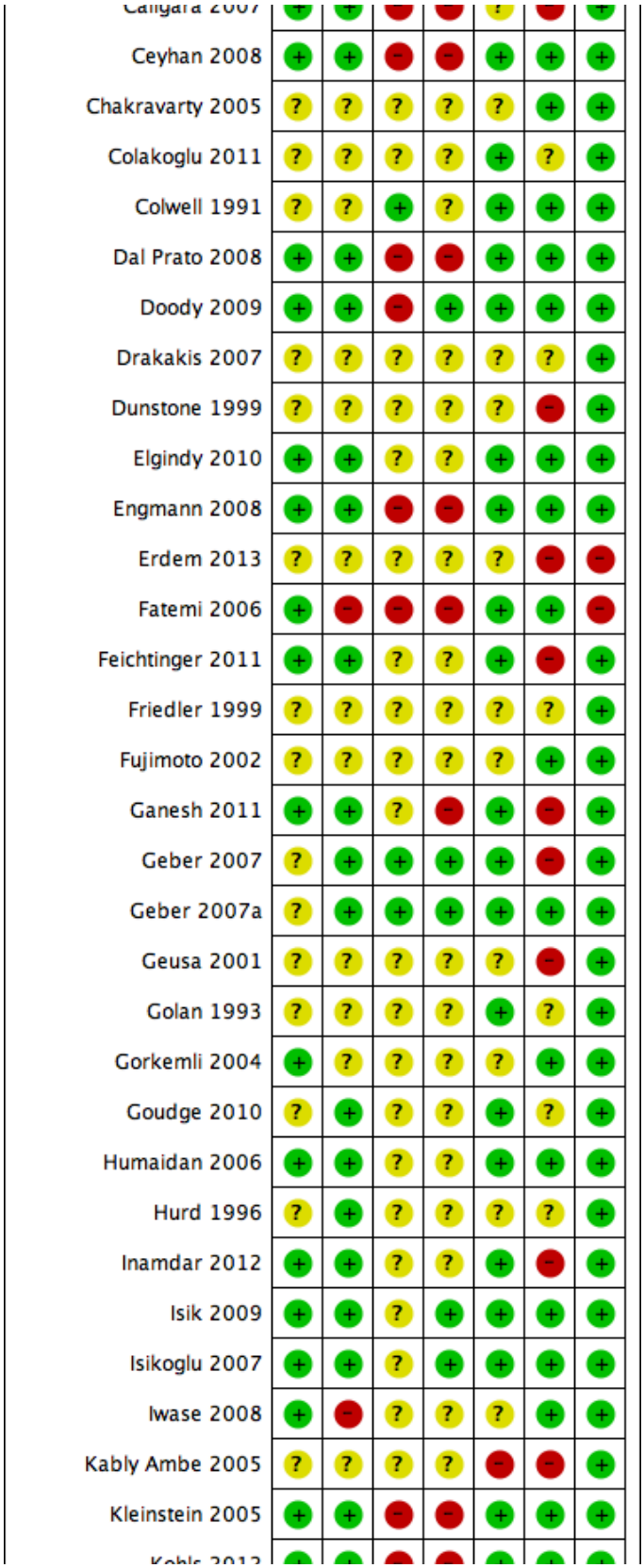


Figure 3. (Continued)

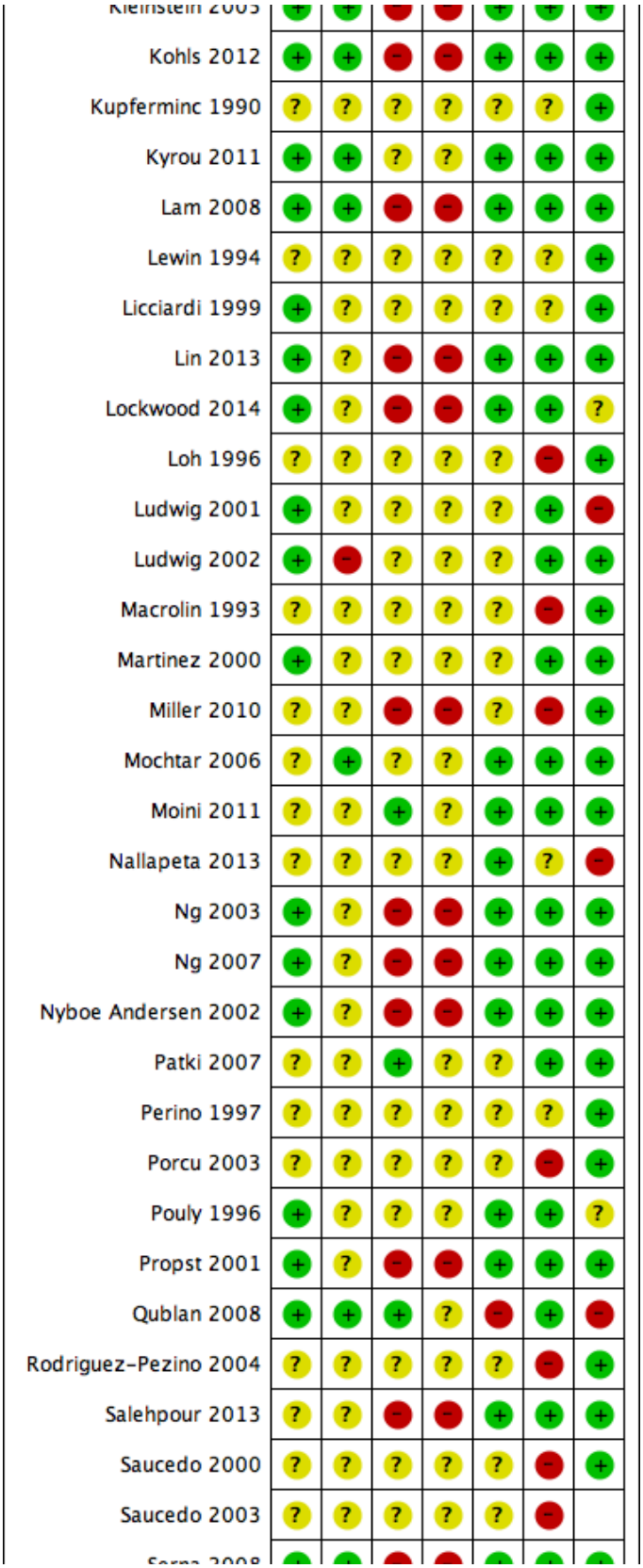
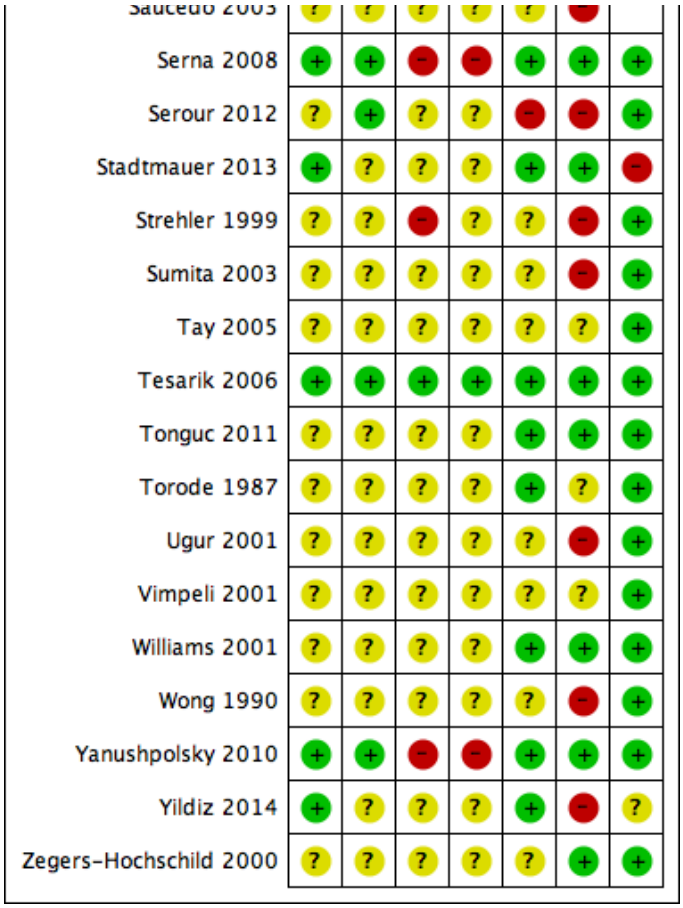


Figure 3. (Continued)



Allocation

Forty eight studies did not report the method of randomisation used. Most of those that did report the randomisation method used computerised randomisation (Aghahosseini 2011; Aghsa 2012; Ata 2008; Ata 2010; Aboulghar 2015; Baker 2014; Bergh 2012; Caligara 2007; Ceyhan 2008; Engmann 2008; Fatemi 2006; Feichtinger 2011; Gorkemli 2004; Humaidan 2006; Inamdar 2012; Isik 2009; Isikoglu 2007; Iwase 2008; Kleinstein 2005; Kohls 2012; Kyrou 2011; Lam 2008; Lin 2013; Lockwood 2014; Ludwig 2002; Martinez 2000; Ng 2003; Ng 2007; Pouly 1996; Serna 2008; Tesarik 2006; Yanushpolsky 2010; Yildiz 2014; Zegers-Hochschild 2000). Randomisation lists or tables were often used (Belaisch-Allart 1987; Belaisch-Allart 1990; Ludwig 2001; Qublan 2008), as was a third party or study investigator (Aboulghar 2008; Dal Prato 2008; Ganesh 2011; Stadtmauer 2013). Doody 2009 used a telephone-based electronic interactive voice response system, and Elgindy 2010 and Propst 2001 used permuted block randomisation.

Fifty studies did not report the method of allocation concealment used. Numbered, sealed envelopes were used most of the time (Aboulghar 2008; Ata 2008; Baker 2014; Beckers 2000; Dal Prato 2008; Elgindy 2010; Engmann 2008; Ganesh 2011; Geber 2007; Geber 2007a; Goudge 2010; Humaidan 2006; Hurd 1996; Kleinstein 2005; Kohls 2012; Kyrou 2011; Lam 2008; Lockwood 2014; Mochtar 2006; Ng 2003; Ng 2007; Nyboe Andersen 2002; Propst 2001; Qublan 2008; Salehpour 2013; Serna 2008; Serour 2012; Tesarik 2006; Tonguc 2011; Williams 2001). Caligara 2007 used a phone call to an unrelated department, Ceyhan 2008 central consultation, Doody 2009 a telephone-based electronic interactive voice response system and Feichtinger 2011; Inamdar 2012 and Isik 2009 a third party nurse. Ata 2010, Isikoglu 2007, Lam 2008 and Yanushpolsky 2010 concealed allocation via an onsite computer system by utilising locked files.

Fatemi 2006 and Ludwig 2002 were the only studies that reported using a non-concealed randomisation list.

Blinding

Fourteen studies mentioned that they used blinding (Aghsa 2012; Ata 2008; Belaisch-Allart 1990; Bergh 2012; Colwell 1991; Doody 2009; Ganesh 2011; Geber 2007; Geber 2007a; Inamdar 2012; Isik 2009; Isikoglu 2007; Tesarik 2006; Tonguc 2011). The other studies did not blind personnel, researchers or participants (Aboulghar 2008; Aghahosseini 2011; Ata 2010; Caligara 2007; Ceyhan 2008; Dal Prato 2008; Doody 2009; Engmann 2008; Fatemi 2006; Ganesh 2011; Kleinstein 2005; Kohls 2012; Lam 2008; Lin 2013; Lockwood 2014; Miller 2010; Ng 2003; Ng 2007; Nyboe Andersen 2002; Propst 2001; Salehpour 2013; Serna 2008; Yanushpolsky 2010) or did not mention blinding. The studies of Moini 2011, Patki 2007 and Qublan 2008 were placebo controlled but did not specify the use of blinding. The main reason reported (in the paper or after contact with the original authors) for not blinding was that the study authors believed blinding would be difficult because of the

different routes of administration used. We believe it is possible to use proper blinding with a double-dummy design.

Incomplete outcome data

Fifty-two studies reported the numbers of and reasons for withdrawal, or reported no drop-outs. Qublan 2008 reported that more participants were recruited than analysed but did not report the reasons, and Brigante 2013 reported more outcomes than included patients.

Selective reporting

As stated before, only an abstract was available for 14 studies, which suggested high risk of selective reporting. Most studies reported planned outcomes, except for 18 (Abate 1999; Artini 1995; Beckers 2000; Belaisch-Allart 1987; Belaisch-Allart 1990; Drakakis 2007; Feichtinger 2011; Friedler 1999; Golan 1993; Goudge 2010; Hurd 1996; Kupferminc 1990; Lewin 1994; Licciardi 1999; Perino 1997; Tay 2005; Torode 1987; Vimpeli 2001). Aghahosseini 2011, Aghsa 2012, Ganesh 2011 and Wong 1990 reported outcomes in the Results section that were different from those reported in the Methods section.

Other potential sources of bias

Eight studies were supported by the pharmaceutical companies that had supplied the investigated interventions (Baker 2014; Beltsos 2011; Bergh 2012; Doody 2009; Lockwood 2014; Miller 2010; Propst 2001; Stadtmauer 2013). Two were supported by a grant from a pharmaceutical company (Ludwig 2002; Vimpeli 2001), and Kleinstein 2005 was supported by a pharmaceutical company, but this company does not supply the investigated products. One study (Ludwig 2001) reported a relatively large number of miscarriages, which were not consistent with reported rates of live birth, clinical pregnancy and ongoing pregnancy. This study was rated as having high risk of bias in this domain.

Assessment for publication bias

We looked at the following comparisons: 3.2 Progesterone versus hCG regimens, outcome clinical pregnancy rate (CPR); 4.2 Progesterone versus progesterone + oestrogen (CPR); 6.2.2 Progesterone regimens, outcome CPR: IM progesterone versus vaginal or rectal progesterone; and 6.2.4 Progesterone regimens, outcome CPR: low-dose vaginal progesterone versus high-dose vaginal progesterone for publication bias, as these four comparisons involved more than 10 included studies. We did this by making three funnel plots, combining comparisons 6.2.2 Progesterone regimens, outcome CPR: IM progesterone versus vaginal or rectal progesterone; and 6.2.4 Progesterone regimens, outcome CPR: low-dose vaginal progesterone versus high-dose vaginal progesterone (see Figure 4; Figure 5; Figure 6). Figure 4 shows most of the studies around the pooled estimate, suggesting that different sizes of studies were included. Although one study (Golan 1993) seemed to be out of the expected pattern, we did not see asymmetry; therefore this funnel plot indicated a small risk of publication bias. Figure 5 shows most of the studies around the pooled estimate with the studies reasonably equally divided on both sides. A large space at the lower side of the graph means that small studies may not be published. Overall the funnel plot revealed a small risk of publication bias. Figure 6 shows most of the studies around the pooled estimate with all studies reasonably equally divided on both sides. This funnel plot also showed that small studies may not be published. Overall it indicated a small risk of publication bias.

Figure 4. Funnel plot of comparison: 2 Progesterone vs hCG, outcome: 2.2 Clinical pregnancy rate.

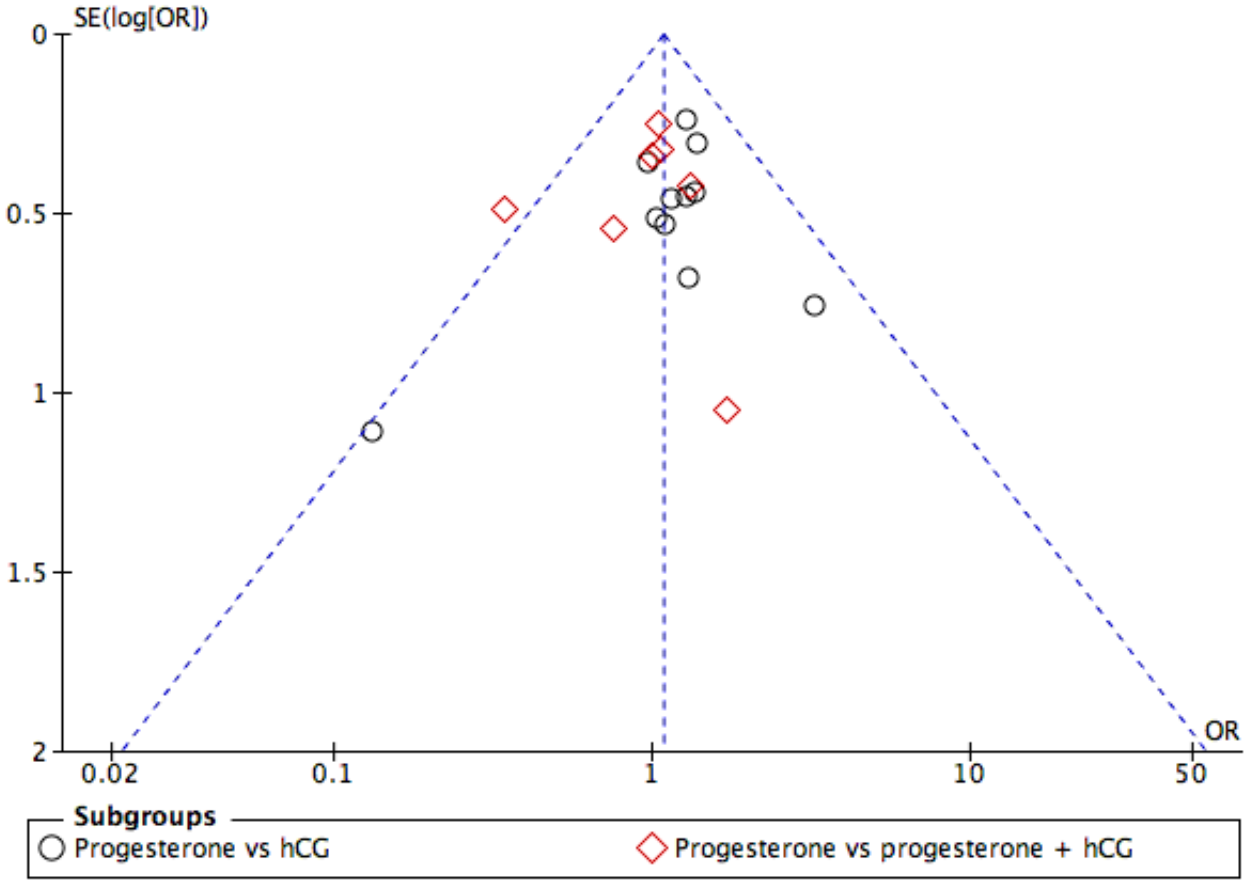


Figure 5. Funnel plot of comparison: 4 [NEW] Progesterone vs progesterone + oestrogen, outcome: 4.2 Clinical pregnancy rate.

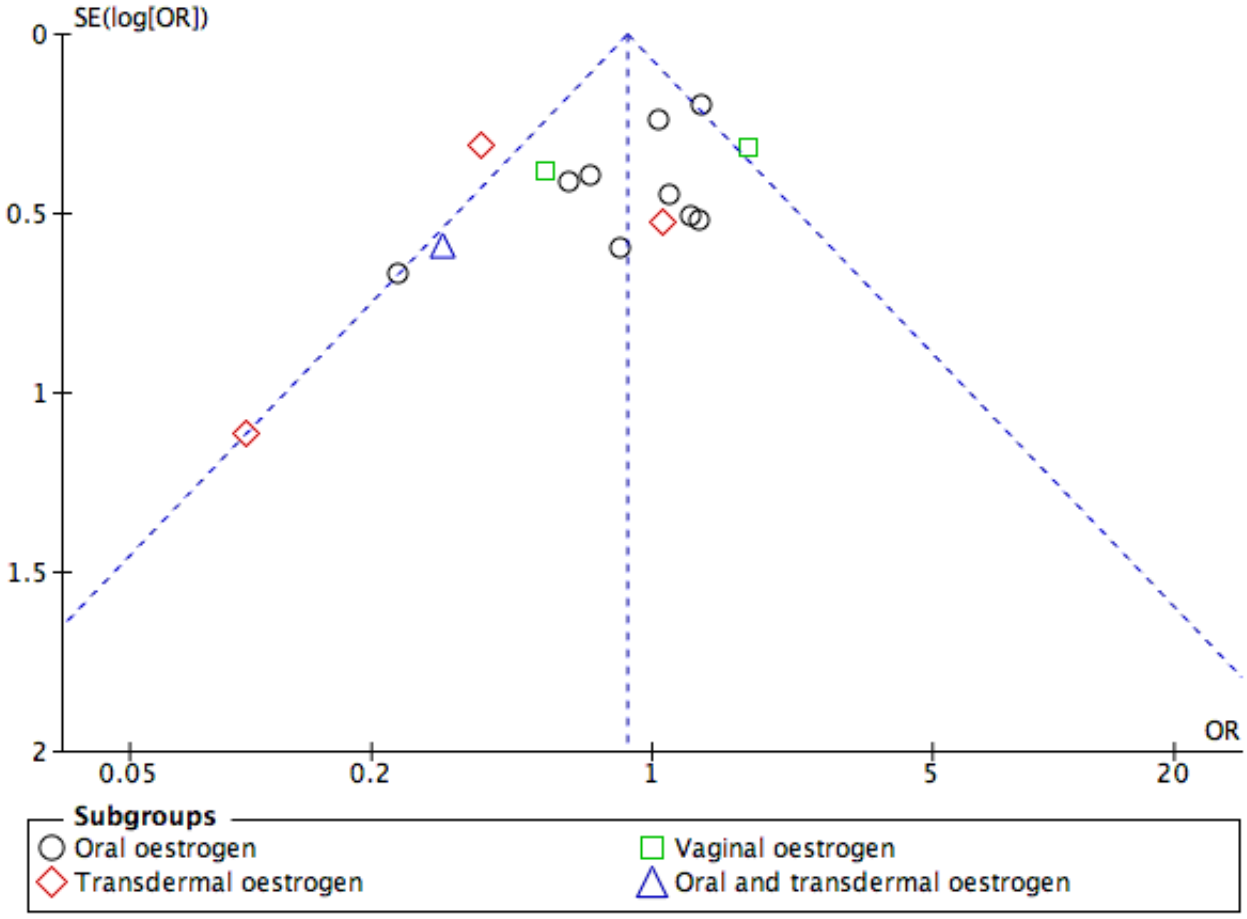
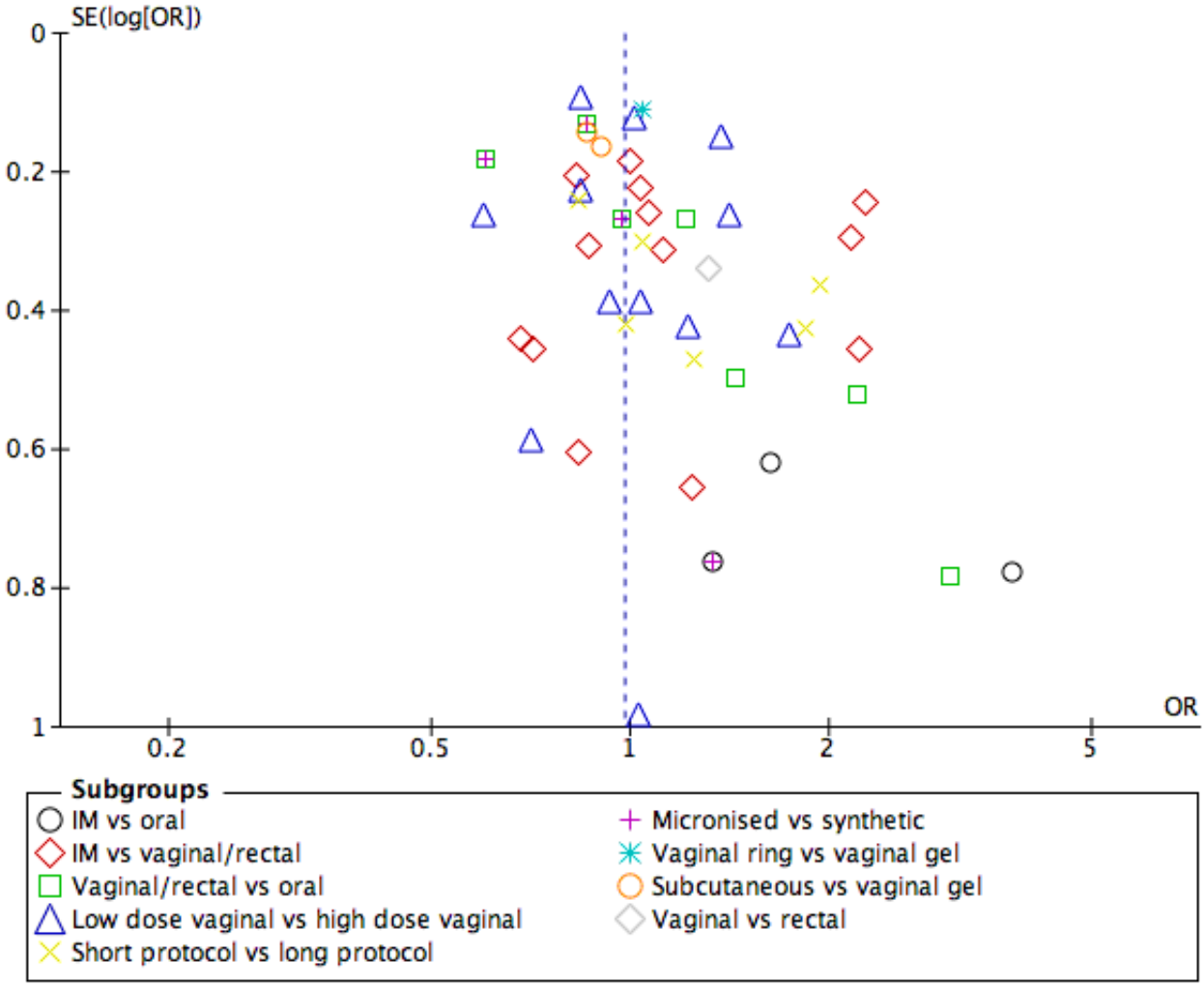


Figure 6. Funnel plot of comparison: 6 [NEW] Progesterone regimens, outcome: 6.2 Clinical pregnancy rate.



Effects of interventions

See: **Summary of findings for the main comparison** hCG compared with placebo/no treatment for assisted reproduction cycles; **Summary of findings 2** Progesterone compared with placebo/no treatment for assisted reproduction cycles; **Summary of findings 3** Progesterone compared with hCG regimens for assisted reproduction cycles; **Summary of findings 4** Progesterone compared with progesterone + oestrogen for assisted reproduction cycles; **Summary of findings 5** Progesterone compared with progesterone + GnRH agonist for assisted reproduction cycles; **Summary of findings 6** Progesterone regimens for assisted reproduction cycles; **Summary of findings 7** Progesterone + oestrogen regimens for assisted reproduction cycles

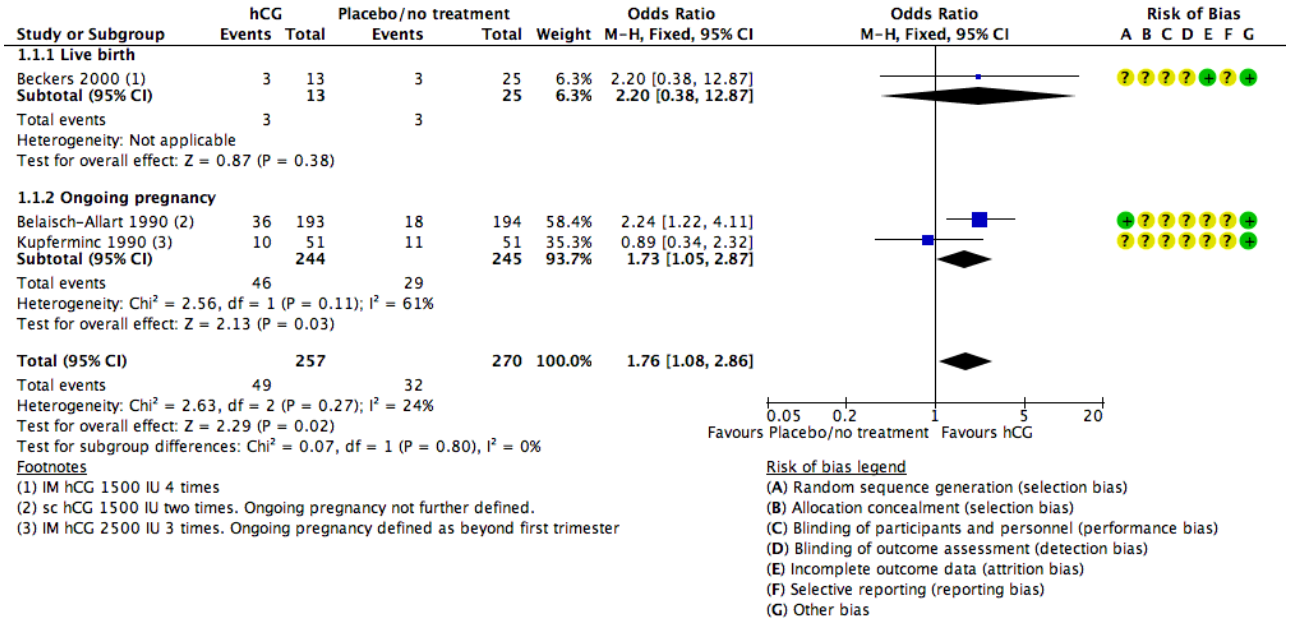
1. hCG versus placebo or no treatment

Primary outcome

1.1 Live birth/ongoing pregnancy rate

Three studies reported live birth (Beckers 2000) or ongoing pregnancy (Belaisch-Allart 1990; Kupferminc 1990). See Figure 7 for details of this comparison.

Figure 7. Forest plot of comparison: 1 Human chorionic gonadotropin (hCG) vs placebo or no treatment, outcome: 1.1 Live birth/ongoing pregnancy rate.



Live birth and pregnancy rates were higher in the hCG group (OR 1.76, 95% CI 1.08 to 2.86, three RCTs, 527 women, I^2 = 24%, very low-quality evidence).

However this findings was sensitive to choice of statistical model, and when a random-effects model was used there was no longer evidence of a difference between the groups (OR 1.67, 95% CI 0.90 to 3.12).

When the analysis was restricted to live birth, only 38 women were included and again there was no evidence of a difference between the groups (OR 2.20, 95% CI 0.38 to 12.87).

Secondary outcomes

1.2 Clinical pregnancy rate (CPR)

Five studies (Artini 1995; Beckers 2000; Belaisch-Allart 1990; Kupferminc 1990; Torode 1987) reported this outcome.
Evidence suggested no differences between groups (OR 1.30, 95% CI 0.90 to 1.88, five RCTs, 746 women, I^2 = 0%, very low quality evidence). See Analysis 1.2 for details of this comparison.

Subgroup analyses*for clinical pregnancy rate*

1.2.1 Ovarian stimulation protocol

Five studies were included in subgroups. Researchers utilised hCG with clomiphene citrate without GnRH agonists (Torode 1987), hCG with or without GnRH agonists (Artini 1995; Beckers 2000; Belaisch-Allart 1990) or hCG with or without GnRH agonists (Kupferminc 1990). Evidence suggested no substantial differences from the main analysis in any of the subgroups. See Analysis 1.3 for details.

1.2.2 Women with previously failed cycles

No data were available for this subgroup analysis.

1.2.3 Duration of treatment

Not applicable.

1.2.4*Number of embryos transferred*

No data were available for this subgroup analysis.

1.3 Miscarriage rate

Two studies (Beckers 2000; Kupferminc 1990) reported this outcome.
Evidence suggested no differences between groups (OR 1.51, 95% CI 0.37 to 6.21, two RCTs, 140 women, I^2 = 0%). See Analysis 1.4 for details of this comparison.

1.4 Ovarian hyperstimulation syndrome (OHSS)

One study (Belaisch-Allart 1990) reported this outcome.

This result showed benefit for the placebo group (OR 4.28, 95% CI 1.91 to 9.60, one RCT, 387 women, low quality evidence). As this result was based on a single study, it should be interpreted with caution. See Analysis 1.5 for details of this comparison.

1.5 Multiple pregnancy

No studies reported this outcome.

2. Progesterone versus placebo or no treatment

Primary outcome

2.1 Live birth/ongoing pregnancy rate

Five studies reported live birth (Abate 1999a) or ongoing pregnancy (Belaisch-Allart 1987; Colwell 1991; Hurd 1996; Kupferminc 1990).

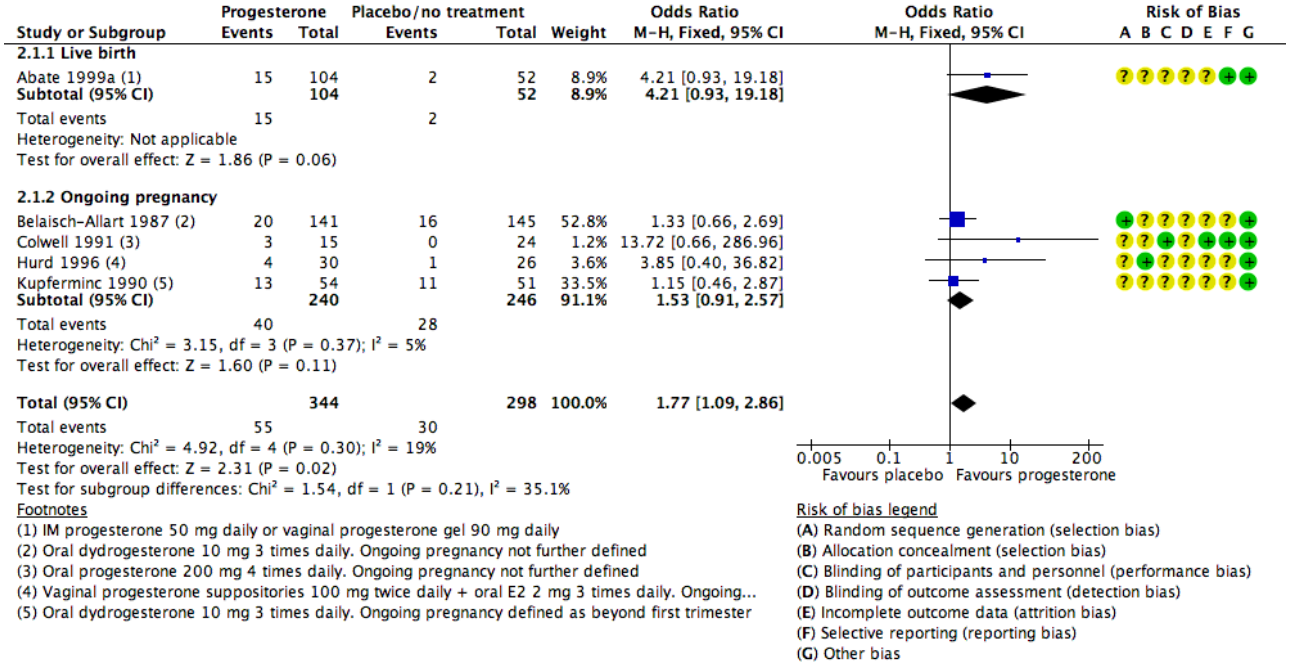
Rates of live birth or ongoing pregnancy were higher in the progesterone group (OR 1.77, 95% CI 1.09 to 2.86, five RCTs, 642 women, I^2 = 19%, very low quality evidence).

Findings require cautious interpretation, as when the analysis was restricted to live birth, evidence suggested no differences between groups (OR 4.21, 95% CI 0.93 to 19.18, one RCT, 156 women).

Heterogeneity was high in the studies of ongoing pregnancy (I^2 = 68%).

See Figure 8 for details of this comparison.

Figure 8. Forest plot of comparison: 2 Progesterone vs placebo or no treatment, outcome: 2.1 Live birth/ongoing pregnancy rate.



Sensitivity analyses

Pooled findings for live birth/ongoing pregnancy were no longer statistically significant when a random-effects model was used (OR 1.77, 95% CI 0.96 to 3.26); this underlines the need for caution in interpreting these findings. Other sensitivity analyses did not materially affect the findings.

Secondary outcomes

2.2 Clinical pregnancy rate

Seven studies (Abate 1999; Abate 1999a; Artini 1995; Belaisch-Allart 1987; Hurd 1996; Kupferminc 1990; Wong 1990) reported this outcome.

Pregnancy rates were higher in the progesterone group (OR 1.89, 95% CI 1.30 to 2.75, seven RCTs, 841 women, I^2 = 0%, low quality evidence). See Analysis 2.2 for details of this comparison.

Subgroup analyses*for clinical pregnancy rate*

***2.2.1* Ovarian stimulation protocol**

Findings of the subgroup of four studies (Abate 1999; Abate 1999a; Artini 1995; Kupferminc 1990) that administered human gonadotropins with or without GnRH agonists were consistent with the main findings, showing benefit for the progesterone group. Benefit was stronger when the study without GnRH agonists was excluded. Studies that administered clomiphene citrate alone without GnRH agonists (Hurd 1996) or human gonadotropins with clomiphene citrate without GnRH agonists (Belaisch-Allart 1987; Wong 1990) did not clearly show benefit for the progesterone group. However results of the test for subgroup differences were not statistically significant.

See Analysis 2.3 for details.

2.2.2 Women with previously failed cycles

No data were available for this subgroup analysis.

2.2.3 Duration of progesterone

Findings of the subgroup of four studies (Abate 1999; Abate 1999a; Belaisch-Allart 1987; Hurd 1996) that administered progesterone for up to 12 weeks were consistent with the main findings, showing benefit for the progesterone group. The subgroup of three studies (Artini 1995; Kupferminc 1990; Wong 1990) that stopped progesterone at the time of the pregnancy test did not clearly show benefit for the progesterone group. However results of the test for subgroup differences were not statistically significant.

See Analysis 2.4 for details.

2.2.4 Number of embryos transferred

No data were available for this subgroup analysis.

2.3 Miscarriage rate

Three studies (Belaisch-Allart 1987; Colwell 1991; Kupferminc 1990) reported this outcome.

No evidence suggested differences between groups (OR 1.22, 95% CI 0.49 to 3.03, three RCTs, 425 women, I^2 = 0%). See Analysis 2.5 for details of this comparison.

2.4 Ovarian hyperstimulation syndrome (OHSS)

No studies reported this outcome.

2.5 Multiple pregnancy

One study (Colwell 1991) reported this outcome.

Evidence suggested no differences between groups (OR 5.87, 95% CI 0.22 to 155.76, one RCT, 34 women). See Analysis 2.6 for details of this comparison.

3. Progesterone versus hCG regimens

Primary outcome

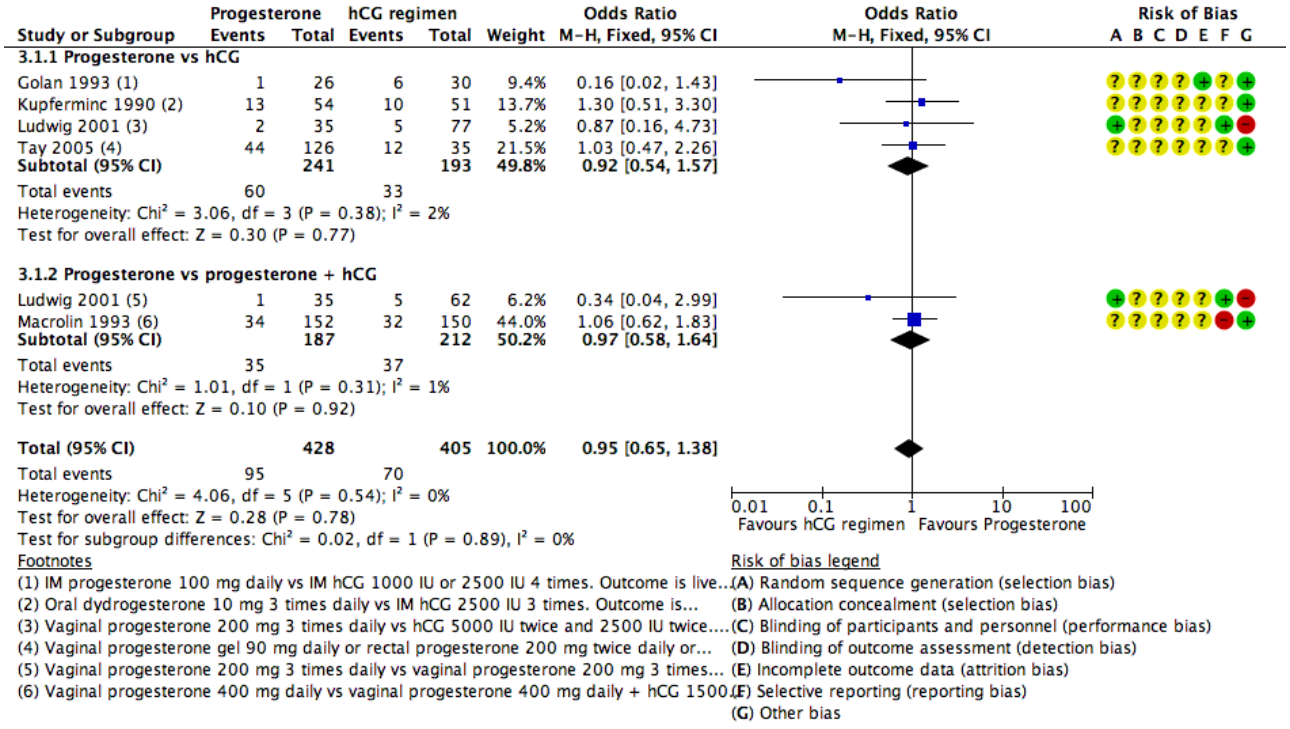
3.1 Live birth/ongoing pregnancy rate

Five studies reported live birth (Golan 1993; Ludwig 2001) or ongoing pregnancy (Kupferminc 1990; Macrolin 1993; Tay 2005). Researchers compared progesterone versus hCG (four RCTs, 434 women) or versus progesterone plus hCG (two RCTs, 399 women).

Evidence suggested no differences between groups in rates of live birth or ongoing pregnancy (OR 0.95, 95% CI 0.65 to 1.38, five RCTs, 833 women, I^2 = 0%, low quality evidence).

Findings were similar, regardless of whether the comparison group received hCG only or hCG plus progesterone. See Figure 9 for details of this comparison.

Figure 9. Forest plot of comparison: 3 Progesterone vs hCG regimens, outcome: 3.1 Live birth or ongoing pregnancy rate.



Restriction of the analysis to studies reporting live birth also showed no evidence of differences between groups.

Secondary outcomes

3.2 Clinical pregnancy rate

Eighteen studies reported this outcome. Researchers compared progesterone versus hCG (11 RCTs, 1378 women) or versus progesterone plus hCG (seven RCTs, 977 women).

Evidence suggested no differences between groups in rates of clinical pregnancy (OR 1.08, 95% CI 0.90 to 1.30, 16 RCTs, 2355 women, I^2 = 0%, moderate quality evidence).

Findings did not differ substantially, regardless of whether the comparison group received hCG only or hCG plus progesterone. See Analysis 3.2 for details.

Because this comparison included more than 10 studies, we prepared a funnel plot to determine the risk of publication bias (see Figure 4), which is assessed in the section Selective reporting (reporting bias). We concluded that this study showed a small risk of publication bias.

Subgroup analyses for clinical pregnancy rate

3.2.1 Ovarian stimulation method

Four studies of progesterone versus progesterone plus hCG were subgrouped by method of ovarian stimulation. One (Wong 1990)

utilised hCG with clomiphene citrate without GnRH agonists, and three utilised hCG with or without GnRH agonists (Fujimoto 2002; Ludwig 2001; Macrolin 1993). Findings did not differ substantially from those of the main analysis in either subgroup (see Analysis 3.3). No studies of progesterone versus hCG alone were available for this subgroup analysis.

3.2.2 Women with previously failed cycles

No data were available for this subgroup analysis.

3.2.3 Duration of progesterone

Seven studies of progesterone versus progesterone plus hCG were subgrouped by duration of progesterone treatment. Six stopped treatment at the pregnancy test (Artini 1995; Golan 1993; Humaidan 2006; Kupferminc 1990; Ludwig 2001; Martinez 2000), and one administered progesterone for up to 12 weeks when pregnant (Vimpeli 2001). Findings did not differ substantially from those of the main analysis in either subgroup. No studies of progesterone versus hCG alone were available for this subgroup analysis. See Analysis 3.4 for details of this comparison.

3.2.4 Number of embryos transferred

No data were available for this subgroup analysis.

3.3 Miscarriage rate

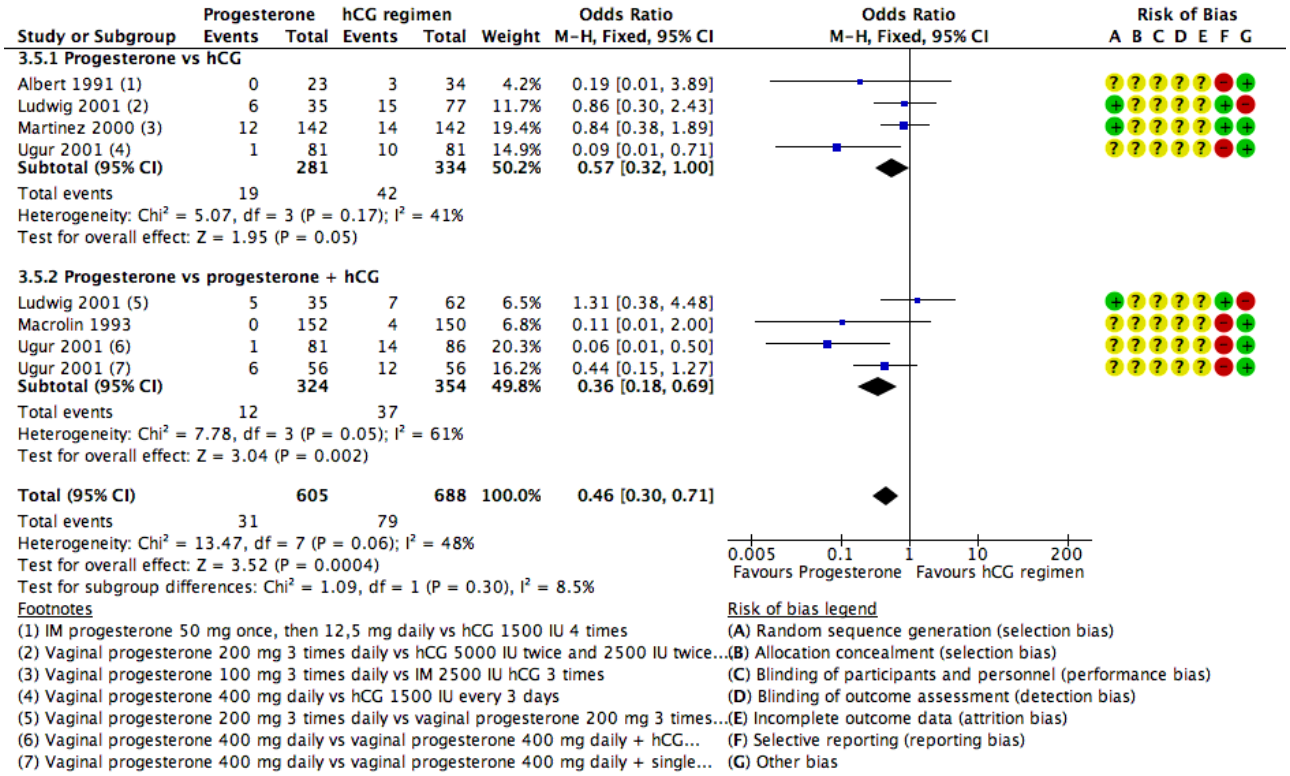
Five studies reported this outcome. Researchers compared progesterone versus hCG (five RCTs, 735 women) or versus progesterone plus hCG (one RCT, 97 women).

Evidence suggested no differences between groups in rates of miscarriage (OR 1.24, 95% CI 0.66 to 12.31, five RCTs, 832 women, $I^2 = 0\%$). Findings did not differ substantially, regardless of whether the hCG group received progesterone as well. See Analysis 3.6 for details.

3.4 Ovarian hyperstimulation syndrome (OHSS)

Five studies reported this outcome. They compared progesterone versus hCG (four RCTs, 671 women) or versus progesterone plus hCG (three RCTs, 678 women). Figure 10

Figure 10. Forest plot of comparison: 3 Progesterone vs hCG regimens, outcome: 3.5 OHSS.



Progesterone was associated with lower rates of OHSS rates than hCG with or without progesterone (OR 0.46, 95% CI 0.30 to 0.71, 5 RCTs, 1293 women , I^2=48%) .

Findings differed according to whether the hCG group received progesterone as well, though the statistical test for subgroup differences suggested no significant difference between the groups (p=0.30). When progesterone was compared with hCG alone, there was no clear evidence of a difference between the groups (OR 0.57, 95% CI 0.32 to 1.00, 4 studies I^2=41%). When progesterone alone was compared with hCG plus progesterone, rates were lower in the progesterone alone group, though with substantial statistical heterogeneity (OR 0.36, 95% CI 0.18 to 0.69, 3 RCTs, 678 women ,I^2=61%).

3.5 Multiple pregnancy

One study reported this outcome. Researchers compared progesterone versus hCG (112 women) or versus progesterone plus hCG (97 women).

Evidence suggested no differences between groups for this outcome (OR 0.44, 95% CI 0.07 to 2.65, one RCT, 209 women). See Analysis 3.7 for details of this comparison.

4. Progesterone versus progesterone + oestrogen

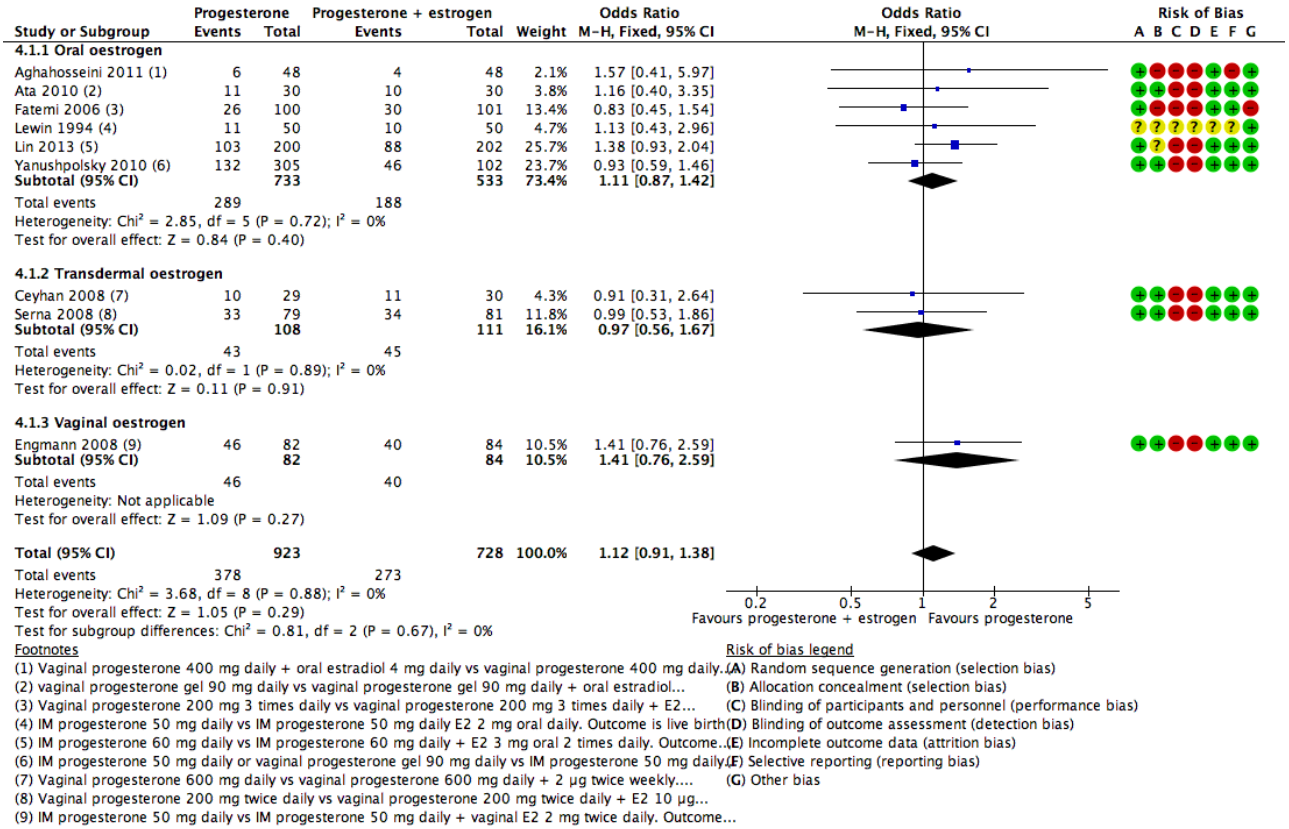
After data extraction, we found that different routes of oestrogen administration were used as well as different dosages of oestrogen. Therefore we decided to stratify the analysis on the basis of route of administration.

Primary outcome

4.1 Live birth/ongoing pregnancy rate

Nine studies reported live birth (Ata 2010; Lewin 1994; Lin 2013) or ongoing pregnancy (Aghahosseini 2011; Ceyhan 2008; Engmann 2008; Fatemi 2006; Serna 2008; Yanushpolsky 2010). Routes of oestrogen administration were oral (six RCTs, 1266 women), transdermal (two RCTs, 219 women) and vaginal (one RCT, 166 women). See Figure 11 for details of this comparison.

Figure 11. Forest plot of comparison: 4 Progesterone vs progesterone + oestrogen, outcome: 4.1 Live birth/ongoing pregnancy rate.



Footnotes
(1) Vaginal progesterone 400 mg daily + oral estradiol 4 mg daily vs vaginal progesterone 400 mg daily...
(2) vaginal progesterone gel 90 mg daily vs vaginal progesterone gel 90 mg daily + oral estradiol...
(3) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + E2...
(4) IM progesterone 50 mg daily vs IM progesterone 50 mg daily E2 2 mg oral daily. Outcome is live birth
(5) IM progesterone 60 mg daily vs IM progesterone 60 mg daily + E2 3 mg oral 2 times daily. Outcome...
(6) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily vs IM progesterone 50 mg daily...
(7) Vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + 2 µg twice weekly....
(8) Vaginal progesterone 200 mg twice daily vs vaginal progesterone 200 mg twice daily + E2 10 µg...
(9) IM progesterone 50 mg daily vs IM progesterone 50 mg daily + vaginal E2 2 mg twice daily. Outcome...

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Evidence suggested no differences between groups in rates of live birth or ongoing pregnancy (OR 1.12, 95% CI 0.91 to 1.38, nine RCTs, 1651 women, I^2 = 0%, low quality evidence).

Findings were similar when the analysis was restricted to studies reporting live birth (OR 1.32, 95% CI 0.93 to 1.86, three RCTs, 562 women, I^2 = 0%).

When data were considered by route of oestrogen administration, findings did not differ substantially from those of the main analysis.

Secondary outcomes

4.2 Clinical pregnancy rate

Fourteen studies reported this outcome (Aghahosseini 2011; Ata 2010; Ceyhan 2008; Colakoglu 2011; Drakakis 2007; Elgindy 2010; Engmann 2008; Erdem 2013; Gorkemli 2004; Kably Ambe 2005; Lewin 1994; Lin 2013; Moini 2011; Yanushpolsky 2010).

Routes of oestrogen administration were oral (nine RCTs, 1427 women), transdermal (three RCTs, 364 women), vaginal (two RCTs, 301 women) and oral/transdermal (one RCT, 77 women). Elgindy 2010 was a three-arm study comparing progesterone, progesterone + oral oestrogen and progesterone + vaginal oestrogen. To make sure we did not duplicate data, we divided data from the progesterone-only arm by two, so half of the progesterone-only events and participants were reported under the subgroup 'oral', and the other half of the progesterone-only events and participants were reported under the subgroup 'vaginal'.

When studies were pooled, no evidence suggested differences between groups (OR 0.86, 95% CI 0.72 to 1.04, 14 RCTs, 4169 women, I^2 = 56%, low quality evidence). However substantial heterogeneity was noted for this analysis (56%), and results of the test for subgroup differences were statistically significant (P value = 0.004).

When the data were considered by route of oestrogen administration, heterogeneity in the comparison using oral

oestrogen was relatively low (I^2 = 16%), and evidence suggested no differences between groups. However heterogeneity in comparisons using other routes of administration was high (I^2 = 56% to 82%), and in studies using transdermal oestrogen, a higher pregnancy rate was reported in the progesterone + oestrogen groups. These findings should be regarded with caution because of the inconsistency observed between studies and the small quantity of data provided.

Because this comparison included more than 10 studies, we prepared a funnel plot to determine the risk of publication bias (see Figure 5), which is discussed in the section Selective reporting (reporting bias). We concluded that the study showed a small risk of publication bias.

Subgroup analyses*for clinical pregnancy rate*

4.2.1 Ovarian stimulation protocol

Eight studies were subgrouped by method of ovarian stimulation. Seven utilised hCG with or without GnRH agonists (Aghahosseini 2011; Drakakis 2007; Elgindy 2010; Engmann 2008; Lewin 1994; Moini 2011; Yanushpolsky 2010), and two utilised hCG with or without GnRH antagonists (Ceyhan 2008; Engmann 2008). Findings did not differ substantially from those of the main analysis in either subgroup. See Analysis 4.3.

4.2.2 Women with previously failed cycles

No data were available for this subgroup analysis.

4.2.3 Duration of progesterone

Ten studies were subgrouped by duration of progesterone. Two stopped treatment at the pregnancy test (Drakakis 2007; Lewin 1994), and eight administered progesterone for up to 12 weeks when pregnant (Aghahosseini 2011; Ceyhan 2008; Elgindy 2010; Engmann 2008; Gorkemli 2004; Lin 2013; Moini 2011; Yanushpolsky 2010). Studies in the subgroups were not pooled because of marked heterogeneity (I^2 = 63% to 67%), possibly related to the differing methods of oestrogen administration described within each subgroup. See Analysis 4.4.

4.2.4 Number of embryos transferred

No data were available for this subgroup analysis.

4.3 Miscarriage rate

Ten studies reported this outcome (Aghahosseini 2011; Ata 2008; Drakakis 2007; Elgindy 2010; Engmann 2008; Fatemi 2006; Kably Ambe 2005; Lin 2013; Serna 2008; Yanushpolsky 2010). Routes of oestrogen administration were oral (seven RCTs, 1370 women), transdermal (one RCT, 160 women), vaginal (two RCTs, 301 women) and oral/transdermal (one RCT, 77 women).

When studies were pooled, no evidence suggested differences between groups (OR 0.98, 95% CI 0.72 to 1.35, 10 RCTs, 1908 women, I^2 = 15%).

When data were considered by route of oestrogen administration, findings did not differ substantially from those of the main analysis. However heterogeneity was high in the comparison using vaginal oestrogen (I^2 = 59%).

4.4 Ovarian hyperstimulation syndrome (OHSS)

Two studies reported this outcome (Ceyhan 2008; Lin 2013). Routes of oestrogen administration were oral (one RCT, 461 women) and transdermal (one RCT, 59 women).

When these studies were pooled, evidence suggested no differences between groups (OR 0.58, 95% CI 0.20 to 1.68, two RCTs, 461 women, I^2 = 0%, low quality evidence).

When the data were considered by route of oestrogen administration, findings did not differ substantially. See Analysis 4.6 for details of this comparison.

4.5 Multiple pregnancy

No studies reported this outcome.

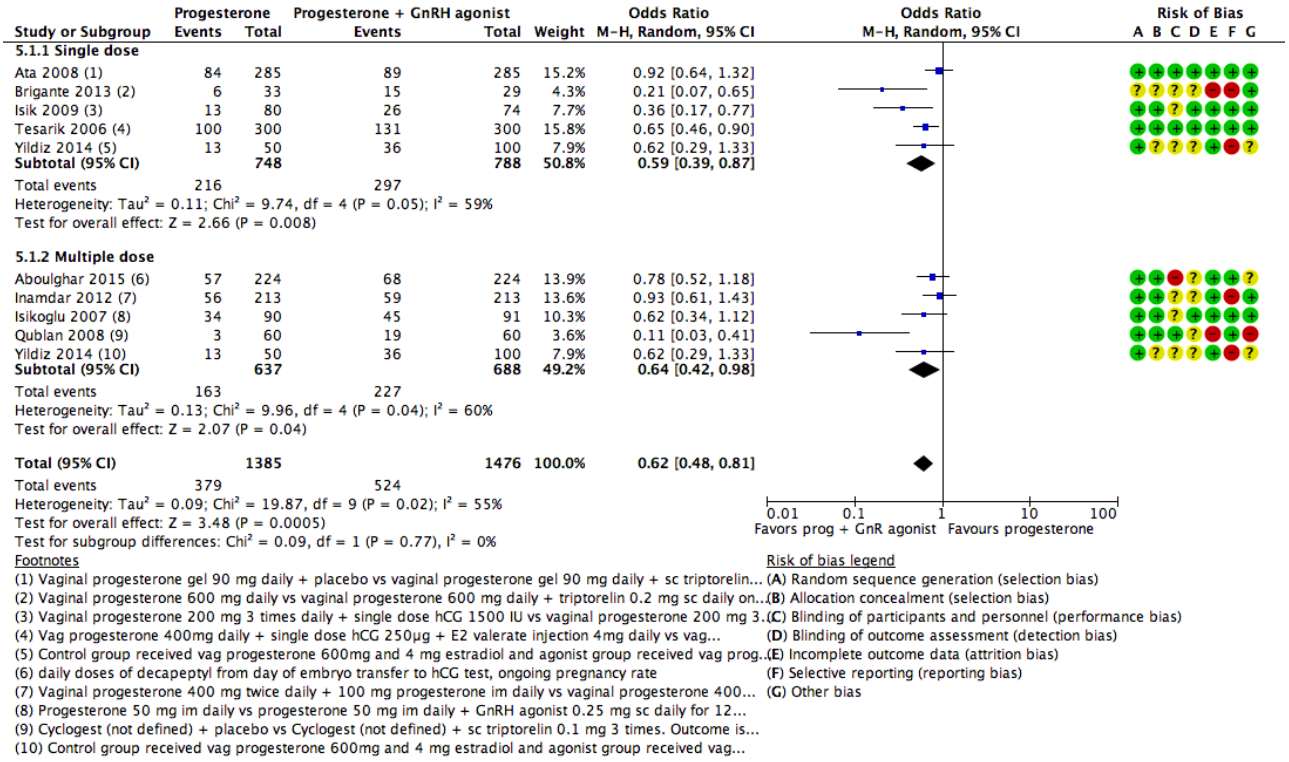
5. Progesterone versus progesterone + GnRH agonist

Primary outcome

5.1 Live birth/ongoing pregnancy rate

Nine studies reported live birth (Isik 2009; Isikoglu 2007; Qublan 2008) or ongoing pregnancy (Aboulghar 2015; Ata 2008; Brigante 2013; Inamdar 2012; Tesarik 2006; Yildiz 2014). Researchers administered the GnRH agonist as a single dose (five RCTs, 1536 women) or in multiple doses (five RCTs, 1325 women). See Figure 12 for details of this comparison.

Figure 12. Forest plot of comparison: 5 Progesterone vs progesterone + GnRH agonist, outcome: 5.1 Live birth or ongoing pregnancy rate.



The live birth/ongoing pregnancy rate was lower in the progesterone-only group than the progesterone + GnRHa group (OR 0.62, 95% CI 0.48 to 0.81, nine RCTs, 2861 women, I^2 = 55%, random effects, low quality evidence). The high statistical heterogeneity in this analysis was due to wide variation between studies in size of the effect, although the direction of the effect was consistent.

Findings were similar when the analysis was restricted to studies reporting live birth only (OR 0.34, 95% CI 0.15 to 0.59, three RCTs, 455 women, I^2 = 66%).

When the data were considered by number of doses of GnRH agonist, findings did not differ substantially. See Analysis 5.1 for details of this comparison.

Secondary outcomes

5.2 Clinical pregnancy rate

Eight studies reported this outcome (Ata 2008; Aboulghar 2015; Brigante 2013; Isik 2009; Isikoglu 2007; Qublan 2008; Tesarik 2006; Yildiz 2014). Researchers administered the GnRH agonist as a single dose (five RCTs, 1536 women) or in multiple doses (four RCTs, 899 women); One trial had two intervention arms of single and multiple doses (Yildiz 2014).

Pregnancy rates were lower in the progesterone-only group (OR 0.66, 95% CI 0.51 to 0.85, eight RCTs, 2435 women, I^2 = 47%, random effects, low quality evidence). High statistical heterogeneity in this analysis appeared to be largely due to wide variation between studies in the size of the effect. See Analysis 5.2 for details.

When data were considered by number of doses of GnRH agonist, findings were consistent with those of the analysis of live birth/ongoing pregnancy in the single-dose progesterone group but were not statistically significant in the multiple-dose group. Results of the statistical test for subgroup differences were not significant. See Analysis 5.1 for details.

Subgroup analyses for clinical pregnancy rate

5.2.1 Ovarian stimulation protocol

In subgroup analyses, findings were consistent with those of the main analysis in the subgroup that received hCG with or without GnRH antagonists (Isik 2009; Porcu 2003; Tesarik 2006;Yildiz 2014) and the subgroup that received hCG with or without GnRH agonists (Aboulghar 2015 Ata 2008; Isikoglu 2007; Qublan 2008; Tesarik 2006). Results of the statistical test for subgroup differences were not significant. See Analysis 5.3 for details.

5.2.2 Women with previously failed cycles

No data were available for this subgroup analysis.

5.2.3 Duration of progesterone (clinical pregnancy rate)

In subgroup analyses, findings were consistent with those of the main analysis in the subgroup that stopped treatment at the time of the pregnancy test (Aboulghar 2015; Isik 2009; Isikoglu 2007; Tesarik 2006; Yildiz 2014). Random effects model. Evidence suggested no differences between groups in the subgroup of women who were treated for up to 12 weeks when pregnant (Ata 2008). However results of the statistical test for subgroup differences were not significant. See Analysis 5.4 for details of this comparison.

5.2.4 Number of embryos transferred (clinical pregnancy rate)

No data were available for this subgroup analysis.

5.3 Miscarriage rate

Two studies reported this outcome (Qublan 2008;Yildiz 2014). The GnRH agonist was mostly administered in multiple doses. Evidence suggested no differences between groups (OR 1.37, 95% CI 0.53 to 3.52, 2 RCTs, 420 women). See Analysis 5.5 for details.

5.4 Multiple pregnancy

Four studies reported this outcome (Ata 2008; Inamdar 2012; Isik 2009;Yildiz 2014). Researchers administered the GnRH agonist as a single dose (two RCTs, 724 women) or in multiple doses (one RCT, 426 women) and one study both single and multiple doses.

Evidence suggested no differences between groups. When the data were considered by number of doses of GnRH agonist, findings did not differ substantially. See Analysis 5.6 for details.

5.5 Ovarian hyperstimulation syndrome (OHSS)

One study reported OHSS and showed no evidence of a difference between the groups (OR 1.00, 95% CI 0.33 to 3.01, 1 RCT, 300 women, very low quality evidence). See Analysis 5.7 for details.

6. Progesterone regimens

Primary outcome

6.1 Live birth/ongoing pregnancy rate

Twenty-five studies compared progesterone regimens and reported live birth (Abate 1999a; Baker 2014; Bergh 2012; Chakravarty 2005; Dal Prato 2008; Doody 2009; Goudge 2010; Iwase 2008; Lockwood 2014; Mochtar 2006; Nyboe Andersen 2002; Pouly 1996; Propst 2001; Stadtmauer 2013; Zegers-Hochschild 2000) or ongoing pregnancy (Aghsa 2012; Beltsos 2011; Friedler 1999; Kohls 2012; Kyrou 2011; Ludwig 2002; Perino 1997; Salehpour 2013; Tay 2005; Yanushpolsky 2010).

See Figure 13 for details of this comparison.

Figure 13. Forest plot of comparison: 6 Progesterone regimens, outcome: 6.1 Live birth or ongoing pregnancy rate.

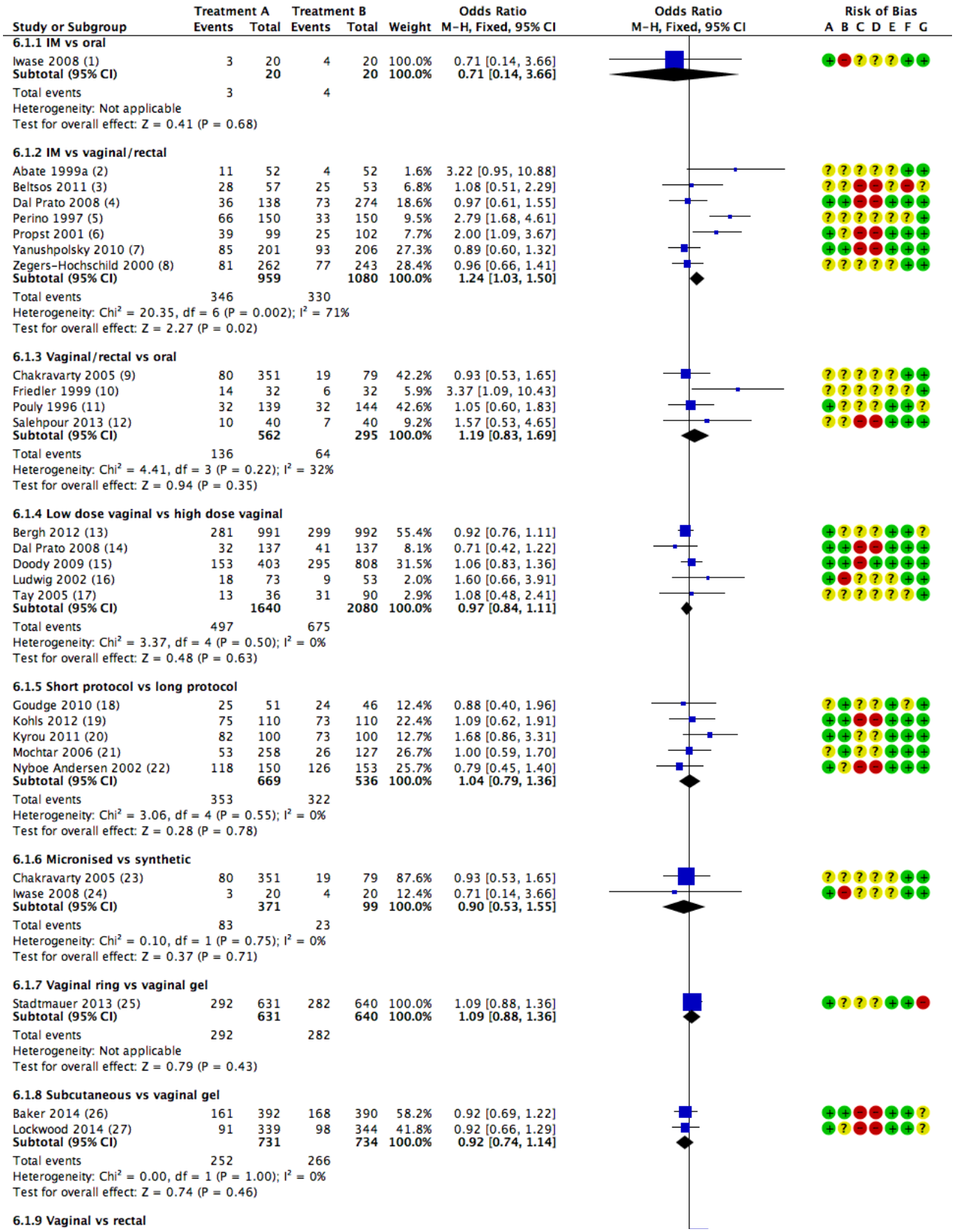
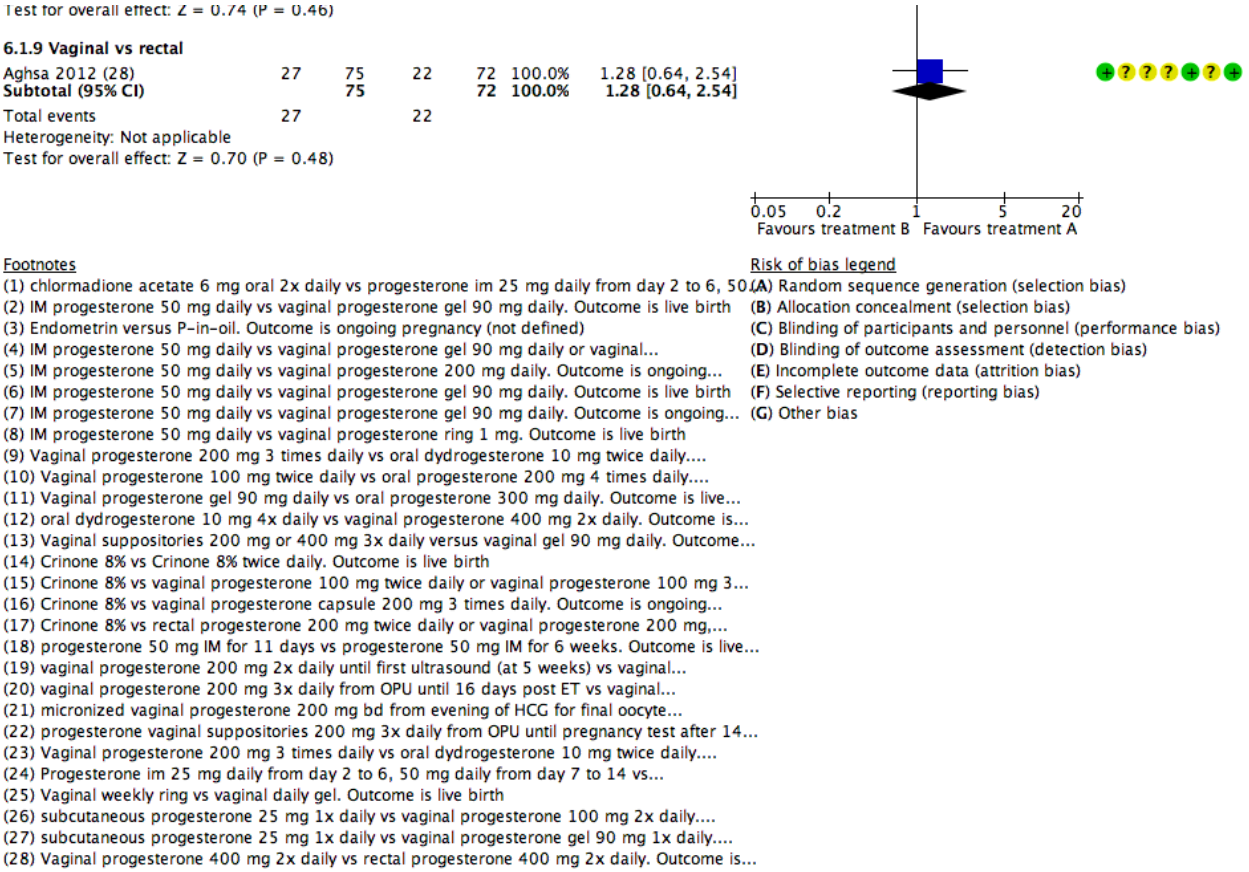


Figure 13. (Continued)



6.1.1 Intramuscular (IM) vs oral

One study made this comparison and reported live birth (Iwase 2008). No evidence suggested differences between groups (OR 0.71, 95% CI 0.14 to 3.66, one RCT, 40 women, very low quality evidence).

6.1.2 IM vs vaginal or rectal

Seven studies made this comparison and reported live birth (Abate 1999a; Dal Prato 2008; Propst 2001; Zegers-Hochschild 2000) or ongoing pregnancy (Beltsos 2011; Perino 1997; Yanushpolsky 2010;). Dal Prato 2008 was a three-arm study investigating IM progesterone versus vaginal gel 90 mg daily versus vaginal gel 90 mg twice daily. We combined both vaginal arms and compared them with the IM arm.

Live birth and ongoing pregnancy rates were higher in the vaginal/rectal group (OR 1.24, 95% CI 1.03 to 1.50, seven RCTs, 2039 women, I^2 = 71%, very low quality evidence). However, statistical heterogeneity was high, and when a random-effects model was used, no evidence suggested differences between groups (OR 1.37, 95% CI 0.94 to 1.99).

When analysis was restricted to studies reporting live birth, no evidence suggested differences between groups (OR 1.31, 95% CI 0.84 to 2.05, four RCTs, 1222 women, I^2 = 59%, random-effects model).

6.1.3 Vaginal or rectal vs oral

Four studies made this comparison and reported live birth (Chakravarty 2005; Pouly 1996) or ongoing pregnancy (Friedler 1999; Salehpour 2013).
Evidence suggested no differences between groups (OR 1.19, 95% CI 0.83 to 1.69, four RCTs, 857 women, I^2 = 32%, low quality evidence).

Findings did not differ substantially when analysis was restricted to studies reporting live birth.

6.1.4 Low dose vaginal (≤ 100 mg) vs high dose vaginal (> 100 mg)

Five studies made this comparison and reported live birth (Bergh 2012; Dal Prato 2008; Doody 2009) or ongoing pregnancy (Ludwig 2002; Tay 2005). Doody 2009 was a three-arm study comparing micronised progesterone vaginal gel 90 mg versus vaginal progesterone 100 mg twice daily versus vaginal progesterone 100 mg three times daily. We combined the two high-dose arms in this comparison.

Evidence suggested no differences between groups (OR 0.97, 95% CI 0.84 to 1.11, five RCTs, 3720 women, I^2 = 0%, moderate quality evidence).

Findings did not differ substantially when analysis was restricted to studies reporting live birth.

6.1.5 Short protocol vs long protocol

FIve studies made this comparison and reported live birth (Goudge 2010; Mochtar 2006; Nyboe Andersen 2002) or ongoing pregnancy (Kohls 2012; Kyrou 2011). Mochtar 2006 was a three-arm study comparing micronised vaginal progesterone 200 mg twice daily starting at the evening of hCG administration for final oocyte maturation versus starting at the evening after oocyte retrieval versus starting at the evening after ET. We combined the first two arms.

No evidence suggested differences between groups (OR 1.04, 95% CI 0.79 to 1.36, five RCTs, 1205 women, I^2 = 0%, low quality evidence).

Findings did not differ substantially when analysis was restricted to studies reporting live birth.

6.1.6 Micronised progesterone vs synthetic progesterone

Two studies made this comparison (Chakravarty 2005; Iwase 2008). Both reported live birth.
Evidence suggested no differences between groups (OR 0.90, 95% CI 0.53 to 1.55, two RCTs, 470 women, I^2 = 0%, low quality evidence).

6.1.7 Vaginal ring vs vaginal gel

One study made this comparison (Stadtmauer 2013) and reported live birth.

Evidence suggested no differences between groups (OR 1.09, 95% CI 0.88 to 1.36, one RCT, 1271 women, low quality evidence).

6.1.8 Subcutaneous vs vaginal gel

Two studies made this comparison (Baker 2014; Lockwood 2014). Both reported live births.

Evidence suggested no differences between groups (OR 0.92, 95% CI 0.74 to 1.14, two RCTs, 1465 women, I^2 = 0%, low quality evidence).

6.1.9 Vaginal vs rectal

One study made this comparison (Aghsa 2012) and reported ongoing pregnancy.

Evidence suggested no differences between groups (OR 1.28, 95% CI 0.64 to 2.54, one RCT, 147 women, very low quality evidence).

Secondary outcomes

6.2 Clinical pregnancy rate

Forty-one studies compared progesterone regimens and reported clinical pregnancy. See Analysis 6.2 for details of this comparison.

6.2.1 IM vs oral

Three studies made this comparison (Iwase 2008; Licciardi 1999; Saucedo 2000).
Evidence suggested no differences between groups (OR 1.96, 95% CI 0.89 to 4.32, three RCTs, 123 women, I^2 = 0%).

Subgroup analyses for clinical pregnancy rate

No data were available for subgroup analyses.

6.2.2 IM vs vaginal*or* rectal

Thirteen studies made this comparison (Abate 1999a; Artini 1995; Dal Prato 2008; Geusa 2001; Miller 2010; Perino 1997; Porcu 2003; Propst 2001; Saucedo 2000; Saucedo 2003; Sumita 2003; Yanushpolsky 2010; Zegers-Hochschild 2000). Dal Prato 2008 was a three-arm study investigating IM progesterone versus vaginal gel 90 mg daily versus vaginal gel 90 mg twice daily. We combined both vaginal arms and compared them with the IM arm.
Evidence suggested no differences between groups (OR 1.14, 95% CI 0.97 to 1.33, 13 RCTs, 2932 women, I^2 = 43%).

Because this comparison included more than 10 studies, we prepared a funnel plot to determine the risk of publication bias (see Figure 5). This was discussed in the section Selective reporting (reporting bias). We concluded that the study showed a small risk of publication bias.

Subgroup analyses for clinical pregnancy rate

6.2.2.1 Ovarian stimulation protocol

Eleven studies were subgrouped by method of ovarian stimulation. Ten utilised hCG with or without GnRH agonists (Abate 1999a; Artini 1995; Dal Prato 2008; Geusa 2001; Perino 1997; Porcu 2003; Saucedo 2003; Sumita 2003; Yanushpolsky 2010; Zegers-Hochschild 2000). Studies in this subgroup were not pooled because of marked heterogeneity (I^2 = 65%). A single study utilised hCG with or without GnRH agonists (Miller 2010) and reported findings similar to those of the main analysis. See Analysis 6.6 for details.

6.2.2.2 Women with previously failed cycles

No data were available for this subgroup analysis.

6.2.2.3 Duration of progesterone

Seven studies were subgrouped by duration of progesterone. Two stopped treatment at the pregnancy test (Artini 1995; Perino 1997), and five administered progesterone for up to 12 weeks when pregnant (Abate 1999a; Dal Prato 2008; Propst 2001; Sumita 2003; Yanushpolsky 2010). Studies in these subgroups were not pooled because of statistical heterogeneity (I^2 = 68%), and inconsistency was noted in the directions of effect. See Analysis 6.7 for details of this comparison.

6.2.2.4 Number of embryos transferred

No data were available for this subgroup analysis.

6.2.3 Vaginal or rectal vs oral

Seven studies made this comparison (Chakravarty 2005; Friedler 1999; Ganesh 2011; Patki 2007; Pouly 1996; Salehpour 2013; Saucedo 2000).

Evidence suggested no differences between groups (OR 0.89, 95% CI 0.75 to 1.05, seven RCTs, 2815 women, I^2 = 52%).

Heterogeneity was substantial, in part because of the findings of Patki 2007. This study compared vaginal progesterone versus vaginal progesterone + oral progesterone, and the two different routes may have played a role in creating heterogeneity. When this study was omitted from the analysis, the I^2 value was reduced to 25%.

Subgroup analyses for clinical pregnancy rate

6.2.3.1 Ovarian stimulation protocol

No data were available for this subgroup analysis.

6.2.3.2 Women with previously failed cycles

No data were available for this subgroup analysis.

6.2.3.3 Duration of progesterone

Five studies were subgrouped by duration of progesterone treatment. Two studies stopped treatment at the pregnancy test (Friedler 1999; Patki 2007), and four administered progesterone for up to 12 weeks when pregnant (Chakravarty 2005; Ganesh 2011; Pouly 1996; Salehpour 2013). Findings in the subgroup that stopped at the pregnancy test suggested benefit for the oral group, but inconsistency and very high heterogeneity were noted for the subgroup (I^2 = 82%), which indicates that this finding should be regarded very cautiously. Findings in the group that administered progesterone for up to 12 weeks did not differ substantially from those of the main analysis. Results of the test for subgroup differences were not statistically significant. See Analysis 6.8 for details of this comparison.

6.2.3.4 Number of embryos transferred

No data were available for this subgroup analysis.

6.2.4 Low dose vaginal (≤ 100 mg) vs high dose vaginal (> 100 mg)

Twelve studies made this comparison (Bergh 2012; Dal Prato 2008; Doody 2009; Dunstone 1999; Ganesh 2011; Geber 2007a; Kleinstein 2005; Ludwig 2002; Ng 2003; Ng 2007; Rodriguez-Pezino 2004; Strehler 1999). Doody 2009 was a three-arm study comparing micronised progesterone vaginal gel 90 mg versus vaginal progesterone 100 mg twice daily versus vaginal progesterone 100 mg three times daily. We combined the two high-dose arms in this comparison.

Evidence suggested no differences between groups (OR 0.98, 95% CI 0.87 to 1.09, 12 RCTs, 5659 women, I^2 = 30%).

Because this comparison included more than 10 studies, we prepared a funnel plot to determine the risk of publication bias (see Figure 5). This was discussed in the section Selective reporting (reporting bias); we concluded that the study showed a small risk of publication bias.

Subgroup analyses for clinical pregnancy rate

6.2.4.1 Ovarian stimulation protocol

Nine studies were subgrouped by method of ovarian stimulation. Eight utilised hCG with or without GnRH agonists (Dal Prato 2008; Doody 2009; Ganesh 2011; Geber 2007a; Kleinstein 2005; Ng 2003; Ng 2007; Strehler 1999), and one utilised hCG with or without GnRH agonists (Rodriguez-Pezino 2004). For both subgroups, findings were similar to those of the main analysis. See Analysis 6.9 for details.

6.2.4.2 Women with previously failed cycles

No data were available for this subgroup analysis.

6.2.4.3 Duration of progesterone

Nine studies were subgrouped by duration of progesterone. Three stopped treatment at the pregnancy test (Ludwig 2002; Ng 2003; Ng 2007), and six administered progesterone for up to 12 weeks when pregnant ((Dal Prato 2008; Doody 2009; Ganesh 2011; Geber 2007a; Kleinstein 2005; Strehler 1999). In both subgroups, findings were similar to those of the main analysis. See Analysis 6.10 for details.

6.2.4.4 Number of embryos transferred

No data were available for this subgroup analysis.

6.2.5 Short protocol vs long protocol

Six studies made this comparison (Goudge 2010; Kohls 2012; Kyrou 2011; Mochtar 2006; Serour 2012; Williams 2001). Mochtar 2006 was a three-arm study comparing micronised vaginal progesterone 200 mg twice daily starting at the evening of hCG administration for final oocyte maturation versus starting at the evening after oocyte retrieval versus starting at the evening after embryo transfer (ET). We combined the first two arms.
Evidence suggested no differences between groups (OR 1.14, 95% CI 0.87 to 1.50, six RCTs, 1128 women, I^2 = 5%).

Subgroup analyses for clinical pregnancy rate

6.2.5.1 Ovarian stimulation protocol

Four studies were subgrouped by method of ovarian stimulation. Two utilised hCG with or without GnRH agonists (Goudge 2010; Mochtar 2006), and two utilised hCG with or without GnRH antagonists (Kohls 2012; Kyrou 2011). In both subgroups, findings were similar to those of the main analysis. See Analysis 6.11 for details.

6.2.5.2 Women with previously failed cycles

No data were available for this subgroup analysis.

6.2.5.3 Duration of progesterone

No data were available for this subgroup analysis.

6.2.5.4 Number of embryos transferred

No data were available for this subgroup analysis.

6.2.6 Micronised progesterone vs synthetic progesterone

Four studies made this comparison (Chakravarty 2005; Ganesh 2011; Iwase 2008; Patki 2007).

Clinical pregnancy rates were lower in the micronised progesterone group (OR 0.79, 95% CI 0.66 to 0.96, four RCTs, 2388 women, I^2 = 19%), suggesting benefit for the synthetic progesterone group.

Subgroup analyses for clinical pregnancy rate

No data were available for subgroup analyses.

6.2.7 Vaginal ring vs vaginal gel

One study made this comparison (Stadtmauer 2013).

Evidence suggested no differences between groups (OR 1.05, 95% CI 0.84 to 1.31, one RCT, 1271 women).

6.2.8 Subcutaneous vs vaginal gel

Two studies made this comparison (Baker 2014; Lockwood 2014).

Evidence suggested no differences between groups (OR 0.88, 95% CI 0.71 to 1.08, two RCTs, 1465 women, I^2 = 0%).

Subgroup analyses for clinical pregnancy rate

No data were available for subgroup analyses.

6.2.9 Vaginal vs rectal

One study made this comparison (Aghsa 2012).

Evidence suggested no differences between groups (OR 1.32, 95% CI 0.68 to 2.56, one RCT, 147 women).

6.3 Miscarriage rate

Twenty-six studies compared progesterone regimens and reported miscarriage. See Analysis 6.3 for details of this comparison.

6.3.1 IM vs oral

Three studies made this comparison (Iwase 2008; Licciardi 1999; Saucedo 2000).
Evidence suggested no differences between groups (OR 1.43, 95% CI 0.34 to 6.11, three RCTs, 123 women, I^2 = 13%).

6.3.2 IM vs vaginal or rectal

Six studies made this comparison (Dal Prato 2008; Miller 2010; Nallapeta 2013; Perino 1997; Saucedo 2000; Yanushpolsky 2010).
Evidence suggested no differences between groups (OR 0.79, 95% CI 0.56 to 1.13, six RCTs, 1468 women, I^2 = 0%).

6.3.3 Vaginal*or* rectal vs oral

Five studies made this comparison (Chakravarty 2005; Friedler 1999; Ganesh 2011; Pouly 1996; Salehpour 2013). Dal Prato 2008 was a three-arm study investigating IM progesterone versus vaginal gel 90 mg daily versus vaginal gel 90 mg twice daily. We combined both vaginal arms and compared them with the IM arm.
Evidence suggested no differences between groups (OR 1.18, 95% CI 0.76 to 1.82, five RCTs, 2220 women, I^2 = 0%).

6.3.4 Low dose vaginal (≤ 100 mg) vs high dose vaginal (> 100 mg)

Nine studies made this comparison (Bergh 2012; Dal Prato 2008; Ganesh 2011; Geber 2007a; Kleinstein 2005; Ludwig 2002; Ng 2007; Rodriguez-Pezino 2004; Strehler 1999).

Miscarriage rates were lower in the low-dose group (OR 0.73, 95% CI 0.55 to 0.98, nine RCTs, 4333 women, I^2 = 0%), suggesting benefit for this group.

6.3.5 Short protocol vs long protocol

Three studies made this comparison (Kohls 2012; Kyrou 2011; Nyboe Andersen 2002).
Evidence suggested no differences between groups (OR 0.96, 95% CI 0.61 to 1.50, three RCTs, 662 women, I^2 = 0%).

6.3.6 Micronised progesterone vs synthetic progesterone

Two studies made this comparison (Chakravarty 2005; Ganesh 2011).
Evidence suggested no differences between groups (OR 1.16, 95% CI 0.69 to 1.95, two RCTs, 1793 women, I^2 = 0%).

6.3.7 Vaginal ring vs vaginal gel

No studies reported this outcome.

6.3.8 Subcutaneous vs vaginal gel

Two studies made this comparison (Baker 2014; Lockwood 2014).
Evidence suggested no differences between groups (OR 0.82, 95% CI 0.44 to 1.54, two RCTs, 1465 women, I^2 = 0%).

6.3.9 Vaginal vs rectal

One study made this comparison (Aghsa 2012).

Evidence suggested no differences between groups (OR 1.21, 95% CI 0.31 to 4.71, one RCT, 147 women).

6.4 Ovarian hyperstimulation syndrome (OHSS)

Two studies compared progesterone regimens and reported OHSS. See Analysis 6.4 for details of this comparison.

6.4.1 IM vs oral

One study made this comparison (Iwase 2008).

Evidence suggested no differences between groups (OR 1.00, 95% CI 0.06 to 17.18, one RCT, 40 women, very low quality evidence).

6.4.2 IM vs vaginal or rectal

No studies made this comparison.

6.4.3 Vaginal or rectal vs oral

No studies made this comparison.

6.4.4 Low dose vaginal (≤ 100 mg) vs high dose vaginal (> 100 mg)

Two studies made this comparison (Doody 2009; Iwase 2008). Doody 2009 was a three-arm study comparing micronised progesterone vaginal gel 90 mg versus vaginal progesterone 100 mg twice daily versus vaginal progesterone 100 mg three times daily. We combined the two high-dose arms in this comparison.
Evidence suggested no differences between groups (OR 0.91, 95% CI 0.57 to 1.46, two RCTs, 1251 women, I^2 = 0%, low quality evidence).

6.4.5 Short protocol vs long protocol

No studies made this comparison.

6.4.6 Micronised progesterone vs synthetic progesterone

No studies made this comparison.

6.4.7 Vaginal ring vs vaginal gel

No studies made this comparison.

6.4.8 Subcutaneous vs vaginal gel

No studies made this comparison.

6.4.9 Vaginal vs rectal

No studies made this comparison.

6.5 Multiple pregnancy

Fourteen studies compared progesterone regimens and reported multiple pregnancy. See Analysis 6.5 for details of this comparison.

6.5.1 IM vs oral

Two studies made this comparison (Iwase 2008; Licciardi 1999).

More multiple pregnancies were reported in the IM arm (OR 4.23, 95% CI 1.16 to 15.40, two RCTs, 83 women, I^2 = 0%), suggesting benefit for the oral arm. This analysis included only 14 events and 80 women, so this finding should be interpreted with caution.

6.5.2 IM vs vaginal*or* rectal

One study made this comparison (Zegers-Hochschild 2000).

Evidence suggested no differences between groups (OR 0.97, 95% CI 0.60 to 1.59, one RCT, 505 women).

6.5.3 Vaginal*or* rectal vs oral

One study made this comparison (Pouly 1996).

Evidence suggested no differences between groups (OR 1.13, 95% CI 0.50 to 2.58, one RCT, 283 women).

6.5.4 Low *d*ose vaginal (≤ 100 mg) vs high dose vaginal (> 100 mg)

Five studies made this comparison (Bergh 2012; Geber 2007a; Kleinstein 2005; Ng 2007; Strehler 1999).
Evidence suggested no differences between groups (OR 1.24, 95% CI 0.85 to 1.80, five RCTs, 2888 women, I^2 = 0%).

6.5.5 Short protocol vs long protocol

Four studies made this comparison (Goudge 2010; Kohls 2012; Kyrou 2011; Nyboe Andersen 2002).
Evidence suggested no differences between groups (OR 1.13, 95% CI 0.80 to 1.60, four RCTs, 820 women, I^2 = 15%).

6.5.6 Micronised progesterone vs synthetic progesterone

No studies reported this outcome.

6.5.7 Vaginal ring vs vaginal gel

No studies reported this outcome.

6.5.8 Subcutaneous vs vaginal gel

No studies reported this outcome.

6.5.9 Vaginal vs rectal

One study made this comparison (Aghsa 2012).

Evidence suggested no differences between groups (OR 0.96, 95% CI 0.19 to 4.91, one RCT, 147 women).

7. Progesterone + oestrogen regimens

Primary outcome

7.1 Live birth/ongoing pregnancy rate

Two studies comparing progesterone and oestrogen regimens reported ongoing pregnancy. One compared short versus long protocol (Feichtinger 2011), and one compared low versus high dosage (Tonguc 2011).

Tonguc 2011 was a three-arm study comparing 2 mg oestradiol versus 4 mg oestradiol versus 6 mg oestradiol. We combined the arms with 4 mg and 6 mg oestradiol supplementation.

7.1.1 Short protocol vs long protocol

No studies making this comparison reported live birth.

Evidence suggested no differences between groups (OR 1.08, 95 CI 0.81 to 1.43, one RCT, 910 women, low quality evidence).

7.1.2 Low dosage vs high dosage

Evidence suggested no differences between groups (OR 0.65, 95% CI 0.37 to 1.13, one RCT, 285 women, very low quality evidence).

Secondary outcomes

7.2 Clinical pregnancy rate

7.2.1 Short protocol vs long protocol

No reported studies made this comparison.

7.2.2 Low dosage vs high dosage

One study (Tonguc 2011) made this comparison.

Evidence suggested no differences between groups (OR 0.81, 95% CI 0.48 to 1.37, one RCT, 285 women). See Analysis 7.2 for details.

7.3 Miscarriage rate

7.3.1 Short protocol vs long protocol

No studies reported this outcome.

7.3.2 Low dosage vs high dosage

One study made this comparison (Tonguc 2011) .

Evidence suggested no differences between groups (OR 3.13, 95% CI 0.86 to 11.39, one RCT, 285 women).

See Analysis 7.3 for details of this comparison.

7.4 OHSS

No studies reported this outcome.

7.5 Multiple pregnancy rates

7.5.1 Short protocol vs long protocol

No studies reported this outcome.

7.5.2 Low dosage vs high dosage

One study made this comparison (Tonguc 2011).

Evidence suggested no differences between groups (OR 0.25, 95% CI 0.06 to 1.12, one RCT, 285 women). See Analysis 7.4 for details,

8. Funnel plots

For comparisons with more than 10 included studies, we constructed a funnel plot. None of the funnel plots (Figure 4; Figure 5; Figure 6) suggested publication bias.

DISCUSSION

Summary of main results

This systematic review of all randomised controlled trials (RCTs) of luteal phase support from 1987 to 2015 had a broad range of subjects. We had seven comparisons to ensure we included as many studies as possible. Because we did not include quasi-RCTs, we

had to exclude quite a few older studies; therefore we have sparse evidence regarding current standard luteal phase protocols. For an overview of the main findings, see the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7).

We can summarise the following results based on our review.

Human chorionic gonadotropin (hCG) for luteal phase support

hCG given during the luteal phase may be associated with higher rates of live birth or ongoing pregnancy than placebo or no treatment, but the evidence is not conclusive. hCG increased the risk of ovarian hyperstimulation syndrome (OHSS) (1 RCT only).

Progesterone for luteal phase support

Progesterone given during the luteal phase may be associated with higher rates of live birth or ongoing pregnancy than placebo or no treatment, but the evidence is not conclusive. Progesterone was associated with lower rates of OHSS rates than hCG with or without progesterone.

Progesterone and oestrogen for luteal phase support

We found no conclusive evidence of differences between groups for any outcome. Supplementation of progesterone with oral oestrogen did not appear to influence live birth and ongoing pregnancy rates, but benefit from transdermal or oral + transdermal oestrogen supplementation is suggested. Findings for supplementation of progesterone with vaginal oestrogen were inconsistent.

Progesterone and GnRH agonists for luteal phase support

A relatively new method of luteal phase support involves use of GnRH agonists, which appeared to increase rates of live birth/ongoing pregnancy and clinical pregnancy compared with progesterone alone. There was no evidence of a difference between the groups for other outcomes, though OHSS was reported in only one study.

Different progesterone regimens

When we compared routes of progesterone administration, we gathered no conclusive findings. Vaginal progesterone is the most commonly used formulation in Europe according to a survey of 21 European centres (Aboulghar 2008). Sixteen centres used vaginal progesterone, three used IM progesterone, one used oral progesterone and one hCG.

We found several studies investigating Crinone 8% vaginal micronised progesterone gel. Therefore we conducted a comparison to investigate low-dose (≤ 100 mg) versus high-dose (> 100 mg) vaginal progesterone. The analysis for the miscarriage rate suggested benefit derived from low-dose vaginal progesterone. No evidence revealed differences between low-dose and high-dose groups for the other outcomes. A new method consists of a weekly progesterone ring, for which we also conducted a comparison. No evidence favoured the vaginal ring or gel.

Comparisons of long versus short duration of progesterone administration showed no evidence of differences between groups in live birth and ongoing pregnancy rates. Findings for clinical pregnancy were inconsistent.

Comparisons of synthetic versus micronised progesterone yielded no evidence of differences between groups in live birth and ongoing pregnancy rates. However, evidence suggested that synthetic progesterone was associated with a higher clinical pregnancy rate than micronised progesterone. The only synthetic progesterone used was oral dydrogesterone.

With regard to multiple pregnancy, the only evidence of differences between groups was seen for the comparison of IM progesterone with oral progesterone, which suggested that IM progesterone is associated with multiple pregnancies to a greater extent than oral progesterone.

Overall completeness and applicability of evidence

Most studies provided 'implantation rate' as an outcome. For clinicians, this outcome is not useful, as they would rather know the pregnancy rate or the live birth rate.

For women the most important outcome is live birth, which was reported in only 31 studies. For the 2015 update of this review, we pooled live birth and ongoing pregnancy rates to increase the power of the analysis. Sensitivity analyses limited to studies reporting live birth yielded findings very similar to those obtained for the combined outcome, suggesting that ongoing pregnancy was a reasonable surrogate for live birth in this review. The outcome clinical pregnancy was reported in most studies and did provide a few significant results. To investigate the safety of luteal phase support, we also looked at the negative side effects, OHSS and multiple pregnancy. These outcomes were not reported in all studies; therefore this review might not give an accurate representation of these important factors in luteal phase support.

Adverse effects were reported poorly in most of the included studies.

Some of the studies that we found investigated procedures or interventions influencing the luteal phase but did not investigate an intervention used as luteal phase support. All of these studies are reported in the Characteristics of excluded studies.

We included only first cycle data, and four studies reported more cycles than included women (Erman Akar 2005; Lukaszuk 2005; Unfer 2004; Unfer 2004a). We contacted the authors but have not received a reply.

In our protocol, we stated that we would include two other comparisons: urinary hCG versus recombinant hCG and single-dose GnRH agonist versus placebo. We found no studies that were conducted to investigate these comparisons. It is unlikely that these comparisons will be made in the future, as hCG is an older method of luteal phase support and is known for its high risk of OHSS. We do not expect new trials to investigate the differences between urinary and recombinant hCG. Nowadays, progesterone is an accepted method for luteal phase support, and it is considered unethical to not provide any form of luteal phase support. Therefore we do not expect any new trials to investigate the effects of GnRH agonists for luteal phase support versus placebo. For these reasons, we chose to remove these comparisons.

To make sure we were as thorough as possible, we came up with some additional comparisons: low-dose vaginal progesterone versus high-dose vaginal progesterone, short protocol progesterone versus long protocol progesterone, vaginal

ring versus vaginal gel, subcutaneous versus vaginal gel, vaginal versus rectal progesterone and progesterone versus progesterone + multiple-dose GnRH agonist.

The included studies used differing inclusion and exclusion criteria, but this was not a limitation for inclusion in our review.

In conclusion, we included all first cycles of randomised trials of luteal phase support. We changed our comparisons after we completed our search to ensure that we covered as much as possible on this topic.

Quality of the evidence

This review has a huge number of included studies - 94 studies - that investigated many different interventions for luteal phase support. The total number of included participants was 25,471, but because of the variety of included studies per comparison, the total sample size per comparison ranged from 30 to well over 5000 participants.

Only 25 studies (27%) reported methods of randomisation and allocation concealment in sufficient detail, and only half (48/93) were rated as having low risk of attrition bias. More than half were rated as having high risk of bias in one or more domains. Although sensitivity analyses limited to studies with clear description of allocation concealment did not substantially affect any of our findings, we rated down the quality of evidence for all comparisons in our 'Summary of findings' tables because of the high proportions of "unclear" and "high" risk of bias ratings in most studies (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7).

Heterogeneity was low for most comparisons. For most cases in which substantial heterogeneity was detected, we were not able to find a clear reason, and for these analyses, our findings should be interpreted with caution.

The overall quality of the evidence ranged from very low to moderate. The main limitations were poor reporting of study methods and imprecision.

Potential biases in the review process

Two review authors extracted all data. MvdL extracted data from all studies, and MM and KB divided all studies between them; thus each extracted data from half of the studies. MvdL, who wrote the review, compared all results. In cases of disagreement, CF acted as a third review author and determined the final verdict. This usually happened after consultation with MvdL. This means that MvdL had a big influence on these decisions, and this might have introduced bias.

As a result of the large number of topics within the review, we might not have discussed all topics in depth.

We are quite sure that we found all relevant studies, but some studies might not have been published at the time of our search and are published now, at the time of publication. As discussed above, four studies did meet our inclusion criteria but reported more cycles than included women (Erman Akar 2005; Lukaszuk 2005; Unfer 2004; Unfer 2004a). We contacted these study authors but received no reply, so we did not include these studies.

In the 2015 update, we have made several changes and additions to the original protocol (see Differences between protocol and review). We believe that these changes are likely to have reduced rather than increased the potential for bias in the review, by ensuring that we consider all relevant comparisons and use the latest recommended Cochrane standards.

Agreements and disagreements with other studies or reviews

Upon comparing this review with a previous version (Daya 2004), we found a lot of similarities regarding the quality of included studies. Although this previous review included quasi-randomised trials, the overall quality of the present review is still poor. As stated in the implications for research section of the previous versions of this review (Daya 2004, van der Linden 2011), improvement of the quality of studies, especially in terms of blinding, is important for further research. Among the more recent (after 2004) studies that we have included, the quality of studies does indeed seem to be better, although most of these researchers did not use blinding. In Daya 2004, it was discussed that live birth was not often reported as an outcome. This seems to be improved but in most cases, it still is not the main outcome.

We have noted some agreements and some disagreements between the findings of Daya 2004 and the results of this review. As no new studies have investigated hCG versus placebo, we found no new results. In all comparisons investigating hCG, we found that hCG involves higher risk of OHSS. This was significant for hCG versus placebo and progesterone versus progesterone + hCG.

In the previous versions of this review (Daya 2004 and van der Linden 2011), no evidence favoured a particular route of administration. Both versions of the review reported no differences in effect between different doses of vaginal progesterone.

Both reviews found higher pregnancy rates for progesterone in GnRH agonist-stimulated cycles.

AUTHORS' CONCLUSIONS

Implications for practice

hCG or progesterone given during the luteal phase may be associated with higher rates of live birth or ongoing pregnancy than placebo or no treatment, but the evidence is not conclusive. The addition of GnRHa to progesterone appears to improve outcomes. hCG may increase the risk of OHSS compared to placebo. Moreover hCG, with or without progesterone, is associated with higher rates of OHSS than progesterone alone. Neither the addition of oestrogen nor the route of progesterone administration appears to be associated with an improvement in outcomes.

Implications for research

Of the 94 included studies, only 10 used blinding. The method of blinding used and specification of who was blinded were poorly reported. If high-quality evidence is to be gained, studies should be properly blinded and should use a double-dummy design.

Only 31 studies reported live birth as an outcome. We believe this outcome is more valuable than short-term outcomes such as clinical pregnancy rate. Therefore researchers should use live birth as the main outcome of their study.

Early studies were placebo controlled. As research has shown that luteal phase support has a positive effect on pregnancy outcomes, it is unethical to not use luteal phase support. Therefore we support the trend in more recent studies to compare different kinds of support, doses or routes of administration. GnRH agonist is relatively new as a method of providing luteal phase support, but it shows promising results. Therefore, high-quality randomised double-blind controlled trials should be conducted to compare GnRH agonist support versus progesterone.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abate 1999

Methods	Randomised placebo-controlled trial
Participants	Women undergoing first-time IVF/ET for tubal factor infertility, age < 38 (n = 86)
Interventions	Pituitary desensitisation (PD) and controlled ovarian hyperstimulation (COH): GnRH agonist, 400 µg SC twice daily, and FSH ET: day +2, max 4 embryos transferred

Abate 1999 *(Continued)*

	LPS: 17 alpha-hydroxyprogesterone 341 mg IM every 3 days vs saline IM every 3 days. From day before ET until pregnancy test (day +14)
Outcomes	Pregnancy (not defined)
Notes	No reply from author in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients [...] were randomly allocated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Abate 1999a

Methods	Randomised placebo-controlled trial
Participants	Women undergoing IVF/ET for tubal occlusion, age 25 to 35 years (n = 156)
Interventions	PD/COH: GnRH agonist IM and FSH ET: day +2, max 4 embryos transferred LPS: progesterone 50 mg IM daily vs progesterone 90 mg vaginal gel daily vs saline solution every 3 days. All from day before ET (+1) until hCG test (+16)
Outcomes	Biochemical pregnancy (small transitory increase in β-hCG levels, followed by a decrease within a week), clinical pregnancy (gestational sac or serum hCG ≥1400 mIU), ongoing pregnancy (20 weeks' gestation), live birth
Notes	No reply from study author in 2004

Risk of bias

Abate 1999a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly treated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Aboulghar 2008

Methods	Randomised controlled trial
Participants	Women who have a clinical pregnancy after ICSI with IM progesterone or vaginal progesterone as luteal phase support, mean age 30 (n = 257)
Interventions	PD/COH: GnRH agonist LPS: vaginal progesterone 600 mg or progesterone 50 mg IM until first US vs vaginal progesterone 600 mg or progesterone 50 mg IM until 3 weeks after first US
Outcomes	Miscarriage (up to 20 weeks' gestation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Dark, sealed envelopes contained the intervention (continuation or stoppage of LPS) were created by a third party not involved in the allocation process. Randomization was performed by picking one envelope for each patients from sequentially numbered envelopes"
Allocation concealment (selection bias)	Low risk	Dark, sealed envelopes created by third party

Aboulghar 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"Patient was informed about the allocated arm"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Aboulghar 2015

Methods	Randomsed controlled trial
Participants	Women who were having IVF-ICSI were randomised on the day of embryo transfer, "all received standard long GnRHa protocol)
Interventions	LPS both groups: vaginal progesterone suppositories daily (total dose prontogest 600mg) Gp 1 (224 women): vaginal progesterone daily vaginal progesterone suppositories plus daily sub cutaneous 0.1 decapeptyl (agonist) until day of beta-hCG detection Gp 2 (222 women): vaginal progesterone daily vaginal progesterone suppositories, GnRHa stopped on day of hCG injection
Outcomes	clinical and ongoing pregnancy rate
Notes	ISRCTN13123887

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomisation table 1:1"
Allocation concealment (selection bias)	Low risk	"a nurse not involved in the study picked one envelope for each patient from sequentially numbered envelopes on the day of embryo transfer and informed patient about their allocated arm. Allocation concealment was ensured by the use of dark, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were "informed about their allocation" on the day of randomisation.
Blinding of outcome assessment (detection bias)	Unclear risk	no stated

Aboulghar 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed. see Figure 1 in paper
Selective reporting (reporting bias)	Low risk	ongoing pregnancy reported
Other bias	Unclear risk	nil

Aghahosseini 2011

Methods	Randomised controlled trial
Participants	Women undergoing IVF, mean age 35 (n = 108)
Interventions	PD/COH: GnRH agonist 500 mg/d SC from day 21 to 3 ET: mean 2 embryos transferred LPS: vaginal progesterone 400 mg daily + oral estradiol 4 mg daily vs vaginal progesterone 400 mg daily. Both until 12th week of gestation
Outcomes	Clinical pregnancy (heartbeat on ultrasound at 12 weeks), ongoing pregnancy (not defined), miscarriage rate (not defined), multiple pregnancy rate (not defined)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	High risk	None used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	High risk	Planned outcomes reported but not analysed (MPR not analysed)
Other bias	Low risk	No specific source of other potential bias identified

Aghsa 2012

Methods	Randomised controlled trial
Participants	Women undergoing ICSI, mean age 31 (n = 145)
Interventions	PD/COH: GnRH antagonist 0.25 mg SC daily from day 8 until trigger + FSH ET: mean 2 embryos transferred, max 3 LPS: vaginal progesterone 400 mg 2× daily vs rectal progesterone 400 mg 2× daily. Both from ET until 8th week of gestation
Outcomes	Clinical pregnancy (foetal heart rate on ultrasound at 8 weeks' gestation), ongoing pregnancy (being pregnant after 12th week of gestation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	Unclear risk	More outcomes reported than stated in protocol
Other bias	Low risk	No specific source of other potential bias identified

Albert 1991

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET (n = 57)
Interventions	PD/COH: GnRH agonist and hMG LPS: hCG 2500 IU 4× vs progesterone 50 mg IM at day of ET, then 12.5 mg IM daily

Albert 1991 *(Continued)*

Outcomes	Clinical pregnancy (not defined), OHSS
Notes	Only abstract available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were treated in a prospective, randomized fashion" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Artini 1995

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET for tubal factor, oligospermia or unexplained infertility, mean age 33 (n = 176)
Interventions	COH: GnRH agonist IM and FSH ET: day +2 LPS: progesterone 50 mg IM daily vs progesterone 100 mg daily in vaginal cream vs hCG 2000 IU IM every 3 days vs no supplementation
Outcomes	Viable pregnancy (not defined)
Notes	No reply from study author in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement

Artini 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Patients were randomly divided" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Ata 2008

Methods	Randomised controlled trial
Participants	Women undergoing ART with at least 1 embryo available for transfer, mean age 31 (n = 570)
Interventions	COH: GnRH agonist 0.1 mg SC from 21st day of preceding cycle + rFSH ET: day +3, max 3 embryos transferred LPS: progesterone 90 mg vaginal gel daily + 0.1 mg GnRH agonist (triptorelin) SC at day +9 vs progesterone 90 mg vaginal gel daily + saline SC at day +9
Outcomes	Clinical pregnancy (foetus with heartbeat at 6 weeks' gestation), ongoing pregnancy (beyond 20th week of gestation), multiple pregnancy (gestation with more than 1 foetus)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Women were randomized according to a computer generated randomization list prepared by the chief investigator. Study subjects were randomized in blocks of 10. Opaque envelopes, which were numbered and sealed, containing the allocation information were given to the hospital pharmacy"
Allocation concealment (selection bias)	Low risk	Numbered, sealed, opaque envelopes were given to hospital pharmacy "The allocation code was broken upon completion of the 20th gestational week of the last pregnant subject"

Ata 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both the nurse injecting the study medication and the women receiving injections were blinded for allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Outcome assessors who performed the pregnancy tests and ultrasonographic examinations to determine if the patient was pregnant were also blinded for allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Ata 2010

Methods	Randomised controlled trial
Participants	Women undergoing ICSI after long GnRH agonist protocol, mean age 32.3 (n = 60)
Interventions	PD: GnRH agonist LPS: vaginal progesterone gel 90 mg daily vs vaginal progesterone gel 90 mg daily + oral oestradiol valerate 3 mg 2× daily. Both until 10th week of gestation
Outcomes	Live birth rate, clinical pregnancy rate, miscarriage rate
Notes	Abstract only Study author contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Computerised allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias)	Low risk	Withdrawal reported with reasons

Ata 2010 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Study author contacted
Other bias	Low risk	No specific source of other potential bias identified

Baker 2014

Methods	Multi-centre, randomised, open-label trial
Participants	Women undergoing IVF/ICSI, mean age 34.3 (n = 800)
Interventions	PD/COH: local protocol, including GnRH agonists, GnRH antagonist or both ET: days 2 to 7, mean 2.2 embryos transferred LPS: subcutaneous progesterone 25 mg 1× daily vs vaginal progesterone 100 mg 2× daily. Both from OPU until 12th week of gestation
Outcomes	Clinical pregnancy (not defined), ongoing pregnancy (12 weeks' gestation), live birth rate
Notes	Study author contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Sealed, opaque, sequentially numbered, identical envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Unclear risk	Supported by developer of subcutaneous progesterone

Beckers 2000

Methods	Randomised controlled trial, 3 different pituitary desensitisation protocols whether combined with LPS
Participants	Women undergoing IVF for tubal or male factor, age < 39, mean age 32 (n = 38). Women with ovarian hyperresponse (oestradiol > 8000 pmol/L) were excluded from analysis
Interventions	PD/COH: GnRH agonist 0.1 mg SC from cycle day 1 until trigger vs GnRH agonist 0.1 mg SC from cycle day 1 until 3rd day of hMG stimulation vs GnRH agonist 0.1 mg SC from cycle day 1 until hCG trigger. Followed by hMG for COH ET: day 4, max 2 embryos transferred LPS: hCG 1500 IU IM on day of oocyte retrieval, +2, +4, +6 vs no treatment vs no treatment
Outcomes	Pregnancy (positive urine test), ongoing pregnancy, live birth and miscarriage. Multiple pregnancy rate is mentioned but is not defined per group
Notes	Study author contacted in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized on the same day (i.e. day 1 of the treatment cycle) by means of sealed envelopes for one of the three treatment groups A, B or C (20 patients each)" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Belaisch-Allart 1987

Methods	Randomised placebo-controlled trial
Participants	Women undergoing IVF (87% for tubal factor), mean age 33 (n = 286)
Interventions	PD/COH: clomiphene + hMG or pure FSH or FSH + hMG or oral contraceptive pill + clomiphene-hMG

Belaisch-Allart 1987 *(Continued)*

	ET: mean 2.2 embryos transferred LPS: oral dydrogesterone 10 mg 3× daily vs oral placebo 3× daily. Both from oocyte retrieval for 21 days
Outcomes	Pregnancy (not defined), ongoing pregnancy, miscarriage
Notes	Study author contacted in 2004, unable to provide information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The treatment was allocated according to a double-blind randomized list"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind randomized list" Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind randomized list" Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Belaisch-Allart 1990

Methods	Multi-centre (12) randomised placebo-controlled trial
Participants	Women undergoing IVF for tubal sterility (50%), serum oestradiol on day of ET < 2500 pg/mL, mean age 33 (n = 387)
Interventions	PD/COH: GnRH agonist in long (67%) or short protocol + hMG ET: mean 3 embryos transferred, up to > 4 LPS: hCG 1500 IU vs placebo. Both on day of ET and 4 days after ET
Outcomes	Pregnancy (not defined), ongoing pregnancy rate, OHSS
Notes	2 study authors employed by Organon Study author contacted in 2004, unable to provide information

Risk of bias

Belaisch-Allart 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A double-blind, randomized list in each centre"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Beltsos 2011

Methods	Multi-centre randomised controlled trial
Participants	PCOS patients undergoing IVF, mean age 31 (n = 110)
Interventions	LPS: vaginal progesterone vs progesterone IM
Outcomes	Ongoing pregnancy (not defined)
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study

Beltsos 2011 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawal reported
Selective reporting (reporting bias)	High risk	Abstract only
Other bias	Unclear risk	Supported by Ferring Pharmaceuticals Inc

Bergh 2012

Methods	Multi-centre randomised controlled trial
Participants	Women undergoing IVF (n = 1983)
Interventions	PD/COH: GnRH agonist 400 to 600 mg daily nasally + FSH ET: 1 embryo transferred LPS: progesterone vaginal gel 90 mg daily vs vaginal progesterone suppositories 200 mg or 400 mg 3× daily. Both for 19 days
Outcomes	Ongoing pregnancy (sonographically verified intrauterine pregnancy, positive heartbeat 5 weeks after ET), clinical pregnancy (not defined), miscarriage rate (not defined), multiple pregnancy rate (not defined)
Notes	As the result of data entry errors in the date of birth of 2 participants, the distribution of participants by age was very unbalanced. Both participants were in the vaginal progesterone gel arm of the study. Therefore, subsequent participants tended to be allocated to that arm if they were younger than average, and to the vaginal micronised progesterone tablet arm if they were older. Study authors contacted 2 well-recognised and independent statisticians. Both statisticians came to the same conclusion: The results would be correct provided that a stratified analysis with regard to age as a continuous variable was performed. Investigators followed this advice, and results are presented accordingly in the article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Web-based randomisation programme
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Clinicians blinded, participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Researchers blinded, method not reported
Incomplete outcome data (attrition bias)	Low risk	Withdrawal reported with reasons

Bergh 2012 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Unclear risk	Statistical errors reported and handled appropriately Financial support provided by Merck Serono

Brigante 2013

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI (n = 61)
Interventions	LPS: vaginal progesterone 600 mg daily from OPU vs vaginal progesterone 600 mg daily from OPU + triptorelin 0.2 mg SC daily on day 6 after OPU
Outcomes	Clinical pregnancy (not defined), ongoing pregnancy (not defined)
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcomes of 62 women reported; 61 were randomly assigned
Selective reporting (reporting bias)	High risk	Abstract only
Other bias	Low risk	No specific source of other potential bias identified

Caligara 2007

Methods	Randomised controlled trial

Caligara 2007 *(Continued)*

Participants	Women undergoing IVF with 10 or fewer oocytes retrieved and a max oestradiol level of 2500 pg/mL at hCG trigger
Interventions	LPS: vaginal progesterone 200 mg 2× daily vs vaginal progesterone 200 mg 2× daily plus hCG 1000 IU SC on days +4, +7 and +10. Progesterone from day after oocyte retrieval
Outcomes	Pregnancy rate (not defined)
Notes	Only abstract available Study author contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	By phone call to unrelated department
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Ceyhan 2008

Methods	Randomised controlled trial
Participants	Women undergoing IVF, excluding endometriosis, polycystic ovarian syndrome and severe male factor, age < 36, mean 31 (n = 60)
Interventions	PD/COH: GnRH antagonist 0.25 mg daily from day 6 until day of trigger + rFSH ET: day 3 or 5, mean 2 embryos transferred LPS: vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + oestrogen transdermal 100 µg/d estradiol release, twice weekly. Both from day of oocyte retrieval until 8 weeks' gestation when pregnant
Outcomes	Pregnancy rate (serum β-hCG > 10 mIU/mL), clinical pregnancy (intrauterine gestational sac), ongoing pregnancy (intrauterine gestational sac and foetal heartbeat after 13th week amenorrhoea), OHSS

Ceyhan 2008 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Sample randomization performed by a computer"
Allocation concealment (selection bias)	Low risk	"Central consultation was used for allocation of patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"No blinding was used during follow-up"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"No blinding was used during follow-up"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Chakravarty 2005

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI-ET, excluding women with PCOS, advanced endometriosis, dense pelvic adhesions, genital tuberculosis or previous failed IVF/ICSI cycles, age 25 to 42 (n = 430)
Interventions	PD/COH: GnRH agonist 1 mg SC + rFSH 150 to 200 IU SC ET: day 2, average of 3 embryos transferred LPS: micronised vaginal progesterone 200 mg 3× daily vs oral dydrogesterone 10 mg twice daily. Both from day of ET until β-hCG test or up to 12 weeks when pregnant
Outcomes	Clinical pregnancy (not defined), miscarriage and viable delivery rate
Notes	No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly selected" Method of randomisation not reported

Chakravarty 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Colakoglu 2011

Methods	Randomised controlled trial
Participants	Women with PCOS undergoing IVF (n = 39)
Interventions	LPS: progesterone 50 mg daily IM vs progesterone 50 mg daily IM + transdermal E2 100 µg every 2 days
Outcomes	Clinical pregnancy rate (not defined)
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"These patients were divided randomly into 2 groups." Methods not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported

Colakoglu 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Abstract only Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Colwell 1991

Methods	Randomised controlled trial
Participants	Women undergoing IVF, excluding women with luteal phase < 12 days in previous cycles, mean age 33 (n = 39)
Interventions	PD/COH: clomiphene citrate 100 mg oral from day 5 until 9+ hMG ET: day +2, mean 2.6 embryos transferred, ET in only 55% of women LPS: progesterone 200 mg oral 4× daily vs no supplementation
Outcomes	Ongoing pregnancy (not defined), multiple pregnancy
Notes	No reply from study author in 2004

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomly assigned" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All RIAs were performed by personnel blinded to the group assignment of each subject"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Dal Prato 2008

Methods	Randomised controlled trial
Participants	Women undergoing IVF for idiopathic, tubal or male factor, grade I to II endometriosis and no more than 3 previous cycles, mean age 33 (n = 412)
Interventions	PD/COH: long protocol GnRH agonist + FSH IVF/ET: age < 35: 2 embryos transferred; age > 35: 3 embryos transferred LPS: progesterone 50 mg IM daily vs vaginal progesterone gel 90 mg once daily vs vaginal progesterone gel 90 mg twice daily. All from oocyte retrieval for 15 days or until first US when pregnant
Outcomes	Live birth (1 or more live babies), clinical pregnancy (1 or more gestational sacs), ongoing pregnancy, miscarriage (pregnancy loss after US confirmation of embryo implantation and before 12 weeks).
Notes	Study author contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization list was provided by an external statistician and the treatment sequence given to the investigator using sealed envelopes containing the name of one of the three medications"
Allocation concealment (selection bias)	Low risk	"Dark envelopes were used, so their content could not be seen against bright light. Each envelope and allocation was sequentially numbered to prevent patients from being randomized out of sequence. Envelopes were not allowed to be opened in advance and were opened only by a nurse not involved in the trial"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"No blinding procedure was planned for this study due to the complex management of the blinding procedures with two different routes of administration"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"No blinding procedure was planned for this study due to the complex management of the blinding procedures with two different routes of administration"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Doody 2009

Methods	Multi-centre (25) randomised controlled trial
Participants	Women undergoing IVF, excluding women who had a history of recurrent (≥ 3 spontaneous abortions) pregnancy loss, abnormal uterine bleeding of undetermined origin or a history of poor response to gonadotropin or 2 previously cancelled cycles, mean age 33 (n = 1211)

Doody 2009 *(Continued)*

Interventions	PD/COH: long protocol GnRH agonist + hMG (Menopur) + FSH (Bravelle) ET: max 3, mean 2.4 embryos transferred LPS: progesterone vaginal capsules 100 mg 2× daily vs progesterone vaginal capsules 100 mg 3× daily vs progesterone vaginal gel.
Outcomes	Ongoing pregnancy (foetal heart movement at 6 weeks), clinical pregnancy (gestational sac), live birth
Notes	2 study authors are employees of Ferring Pharmaceuticals; 1 author receives grant support from Ferring Pharmaceuticals; acts as a consultant for Ferring Pharmaceuticals, Ethicon Endo Surgery, Ethicon Women's Health and Urology, Smith & Nephew, Galil Medical and Boston Scientific; and serves on speakers bureaus for Boston Scientific, Ferring Pharmaceuticals, Ethicon Endo Surgery and Ethicon Women's Health and Urology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation to treatment group was performed by a telephone-based electronic interactive voice response system, which ensured an equal number of patients per treatment group across the study centers and stratification factors"
Allocation concealment (selection bias)	Low risk	Telephone-based electronic interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Study drug was administered on an open-label basis"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The study was assessor-blinded; the person who performed the transvaginal ultrasound examinations to confirm clinical and ongoing pregnancy was blinded to the patient's treatment group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Drakakis 2007

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI for tubal factor, male infertility, anovulation, endometriosis and unexplained infertility, mean age 35 (n = 76)
Interventions	PD/COH: GnRH agonist 100 µg intranasal 5× daily from day 21 preceding cycle for 15 to 24 days + rFSH LPS: progesterone 100 µg oral 3× daily + vaginal progesterone capsules 200 mg 3× daily until pregnancy test + oestradiol valerate oral 2 mg + 0.5 mg norgestrel 3× daily for 15 days + oestradiol hemihydrate 50 µg transdermal patch every 4 days vs progesterone 100 µg oral 3× daily + vaginal progesterone capsules 200 mg 3× daily until pregnancy test

Drakakis 2007 *(Continued)*

Outcomes	Clinical pregnancy, miscarriage
Notes	No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were divided randomly into two groups according to the protocol used" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Dunstone 1999

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET (n = 38)
Interventions	LPS: progesterone 400 mg vaginal pessaries twice daily vs progesterone 90 mg vaginal gel daily. Both from night before oocyte retrieval until pregnancy test
Outcomes	Clinical pregnancy (foetal heartbeat at ultrasound)
Notes	No reply from study author in 2004 Only abstract available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Women undergoing IVF-ET treatment were randomly assigned" Method of randomisation not reported

Dunstone 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Preliminary results are available for 38 women of a planned total of 100" Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Elgindy 2010

Methods	Randomised controlled trial
Participants	Women undergoing their first ICSI cycle for male factor infertility, mean age 29 (n = 270)
Interventions	PD/COH: GnRH agonist 0.1 mg SC from midluteal phase of pretreatment cycle + rFSH + hMG ET: day 2, mean 3 embryos transferred LPS: progesterone 100 mg IM daily vs progesterone 100 mg IM daily + E2 valerate 2 mg orally 3× daily vs progesterone 100 mg IM daily + E2 valerate 2 mg vaginally 3× daily
Outcomes	Clinical pregnancy (not defined)
Notes	No reply from study author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Study participants were randomized into three groups, 90 women each, using the block randomization technique"
Allocation concealment (selection bias)	Low risk	"Two hundred seventy identical sealed envelopes were prepared by one of the investigators (M.I.M.) and kept in the unit pharmacy. When the woman was eligible and agreed to participate, she was instructed to select only one envelope only once to determine the group to which she was assigned. The randomization key was kept with the pharmacy director and was not opened until after statistical analysis"
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Elgindy 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcome reported
Other bias	Low risk	No specific source of other potential bias identified

Engmann 2008

Methods	Randomised controlled trial
Participants	Women undergoing first cycle of IVF, excluding women with high risk of OHSS, mean age 35 (n = 166)
Interventions	PD/COH: GnRH agonist or antagonist or microdose GnRH agonist and rFSH or FSH + u-hMG ET: day 3, mean 2.5 embryos transferred LPS: progesterone 50 mg IM daily vs progesterone 50 mg IM daily + oestradiol 2 mg vaginally 2× daily. Both from oocyte retrieval until pregnancy test or foetal heartbeat when pregnant
Outcomes	Clinical pregnancy (gestational sac and positive heartbeat), ongoing pregnancy (beyond 12 weeks), miscarriage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"They were randomly assigned to either group in a ratio of 1:1 by means of computer-generated random numbers on the day of ET. To ensure similar distribution of patients with low peak serum E2 concentration in the two groups, separate randomization schedules were drawn up for women with peak E2 levels on the day of hCG administration of %1200 pg/mL and for those with levels > 1200 pg/mL by the use of stratified randomized blocks"
Allocation concealment (selection bias)	Low risk	"Selection into the groups was performed by a research nurse using a series of consecutively numbered sealed opaque envelopes (one for each category of peak serum E2 level), so the sequence of allocation was concealed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The study was not blinded because the patients as well as the clinicians were aware of the treatment group"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The study was not blinded because the patients as well as the clinicians were aware of the treatment group"

Engmann 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Erdem 2013

Methods	Randomised controlled trial
Participants	Women with poor ovarian response undergoing IVF (n = 95)
Interventions	LPS: intravaginal progesterone gel daily vs intravaginal progesterone gel + oral oestradiol hemihydrate 2 mg daily vs intravaginal progesterone gel + oral oestradiol hemihydrate 6 mg daily
Outcomes	Clinical pregnancy rate (not defined)
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawal reported
Selective reporting (reporting bias)	High risk	Only outcomes of groups 1 and 2 are reported
Other bias	High risk	Abstract only

Fatemi 2006

Methods	Randomised controlled trial

Fatemi 2006 *(Continued)*

Participants	Women undergoing IVF or ICSI/ET, excluding women with PCO, endometriosis > grade 2, TESE and need for pre-implantation genetic diagnosis; mean age 32 (n = 201)
Interventions	PD/COH: GnRH antagonist 0.25 mg daily from day 6+ rFSH ICSI or IVF/ET: day 3, 1 or 2 embryos transferred LPS: natural micronised progesterone vaginal capsules 200 mg 3× daily vs natural micronised progesterone vaginal capsules 200 mg 3× daily + oral E2 valerate 2 mg twice daily. From day after oocyte retrieval until 7 weeks' gestation
Outcomes	Ongoing pregnancy (beyond 12 weeks), early pregnancy loss (initially positive hCG test, failed to develop beyond 12 weeks)
Notes	Study author contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"According to a computer-generated not concealed randomization list prior to initiation of stimulation"
Allocation concealment (selection bias)	High risk	No concealed randomisation list
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	High risk	Only abstract available

Feichtinger 2011

Methods	Randomised controlled trial
Participants	Women undergoing IVF (n = 1053)
Interventions	ET: mean 1.9 embryos transferred LPS: oral micronised progesterone 200 mg 3× daily + oral dydrogesterone 20 mg daily + oestradiol valerate 2 mg daily from day 1 after OPU vs oral micronised progesterone 200 mg 3× daily + oral dydrogesterone 20 mg daily + oestradiol valerate 2 mg daily from day 4 after OPU

Feichtinger 2011 *(Continued)*

Outcomes	Ongoing pregnancy rate (not defined)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Third party
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Clinician and researcher blinded, method unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	High risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Friedler 1999

Methods	Randomised controlled trial
Participants	Women undergoing ICSI/ET for male factor infertility with > 1 embryo available and serum oestradiol > 2500 pg/mL on day of hCG, mean age 31 (n = 64)
Interventions	PD/COH: GnRH agonist + hMG ICSI/ET: day 2, max 3 embryos transferred except in older women (> 38 years) or in cases of recurrent failure of implantation LPS: micronised progesterone 200 mg oral 4× daily vs micronised progesterone 100 mg vaginal 2× daily. Both from day +1 after ET until serum test (+14)
Outcomes	Pregnancy (not defined), ongoing pregnancy, miscarriage
Notes	No reply from study author in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement

Friedler 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"The patients included in this study were prospectively randomized by order of embryo transfer" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Fujimoto 2002

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET, including only women with low midluteal serum oestradiol in a previous cycle, mean age 35 (n = 114)
Interventions	PD/COH: long protocol GnRH agonist 300 µg intranasal 3× daily + hMG ET: day 2 or 3, max 3 embryos transferred LPS: progesterone 25 mg injection once daily from day after oocyte retrieval vs progesterone 25 mg injection once daily from day after oocyte retrieval + hCG 3000 IU IM on days 1, 4, 7 after ET
Outcomes	Pregnancy (gestational sac)
Notes	Study investigates progesterone as luteal phase support in 436 women. Women who fail to conceive (n = 114) are included in a second cycle, in which they are randomly assigned to receive progesterone or progesterone + hCG. Only women undergoing the second cycle are included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"They were randomly treated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Fujimoto 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcome reported
Other bias	Low risk	No specific source of other potential bias identified

Ganesh 2011

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI, excluding women with baseline FSH > 12 IU and adenomyosis, mean age 32 (n = 1363)
Interventions	PD/COH: GnRH agonist 500 µg SC daily + rFSH ET: day 2, average of 3 embryos transferred LPS: dydrogesterone 10 mg oral daily vs micronised progesterone vaginal gel 90 mg daily vs micronized progesterone vaginal capsules 200 mg 3× daily. All from ET until 12 weeks' gestation
Outcomes	Clinical pregnancy (viable foetus on US), ongoing pregnancy (viable foetus at 12 weeks' gestation), miscarriage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Sequentially numbered sealed envelopes were prepared and provided by the study coordinator, according to random-number tables"
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Single-blinding was achieved by keeping the person enrolling participants, study investigators, ultrasound technicians, and clinicians unaware of the type of protocol used" Method of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Only the statisticians had access to the unblinded data. A double-blind study protocol was not possible because the drug delivery method in the three groups was different"

Ganesh 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	High risk	Ongoing pregnancy results not reported, but they are reported in the protocol
Other bias	Low risk	No specific source of other potential bias identified

Geber 2007

Methods	Randomised controlled trial
Participants	Women undergoing ART (n = 150)
Interventions	PD/COH: GnRH agonist or antagonist + rFSH ET: mean 3 embryos transferred LPS: vaginal progesterone daily (dose not reported) + rLH on day 5, 8, 11 and 14 vs vaginal progesterone daily (dose not reported)
Outcomes	Clinical pregnancy (not defined)
Notes	Only abstract available Study author contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated on the day of embryo transfer" By sealed envelopes
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicians blinded, a non-participant (nurse) gave the medicine
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported Dose of progesterone not reported

Geber 2007 *(Continued)*

Other bias	Low risk	No specific source of other potential bias identified

Geber 2007a

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI-ET with serum FSH concentrations < 15 IU/L on day 3 of menstrual cycle, mean age 35 (n = 122)
Interventions	PD/COH: GnRH agonist 3.6 mg SC + rFSH SC IVF/ICSI-ET: day 3 or 5, 1 to 4, mean 3.4 embryos transferred LPS: micronised progesterone vaginal capsules 200 mg 3× daily vs micronised progesterone vaginal gel 90 mg daily. Both from day after oocyte retrieval for 13 days or 12 weeks when pregnant
Outcomes	Pregnancy (foetal heartbeat), miscarriage, multiple pregnancy
Notes	Study author contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated (sealed envelopes) into two groups"
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicians blinded, a non-participant (nurse) gave the medicine
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"A total of 122 patients were allocated to each group and all completed the study"
Selective reporting (reporting bias)	Low risk	Planned outcome data reported
Other bias	Low risk	No specific source of other potential bias identified

Geusa 2001

Methods	Randomised controlled trial

Geusa 2001 *(Continued)*

Participants	Women undergoing IVF/ET, excluding women with systemic or endocrine pathologies, age < 42 years (n = 300)
Interventions	PD/COH: GnRH agonist + rFSH LPS: progesterone 90 mg vaginal gel daily vs progesterone 50 mg IM daily. Both starting at oocyte retrieval
Outcomes	Clinical pregnancy (not defined)
Notes	Only abstract available No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"All 318 patients were randomized" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Golan 1993

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET for male factor infertility, mechanical or unexplained infertility, mean age 33 (n = 56)
Interventions	PD/COH: GnRH agonist + hMG IVF/ET: max 4 embryos transferred LPS: hCG 1000 or 2500 IU IM every 3 days, 4× vs progesterone 100 mg IM daily. Both from day of ET

Golan 1993 *(Continued)*

Outcomes	Clinical pregnancy (gestational sac), miscarriage, OHSS
Notes	Study author contacted in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were prospectively randomized" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Gorkemli 2004

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI (n = 266)
Interventions	PD/COH: GnRH agonist 1 mg/mL SC from day 21 from menstruation + rFSH or rFSH/hMG ET: day 2 or 3, mean 3.5 embryos transferred LPS: progesterone vaginal capsules 200 mg 3× daily vs progesterone vaginal capsules 200 mg 3× daily + oestradiol transdermal 100 µg daily. Both from oocyte retrieval for 14/15 days, when pregnant progesterone until 10 weeks' gestation
Outcomes	Clinical pregnancy (foetal heart), ongoing pregnancy, miscarriage
Notes	First cycle data obtained from study author (only clinical pregnancy)

Risk of bias

Bias	Authors' judgement	Support for judgement

Gorkemli 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Computer-generated randomization"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcome reported
Other bias	Low risk	No specific source of other potential bias identified

Goudge 2010

Methods	Randomised controlled trial
Participants	Women undergoing their first IVF/ET cycle for any indication, mean age 32 (n = 97)
Interventions	PD/COH: GnRH agonist 0.5 mg SC daily + oral contraceptive IVF/ET: mean 2 embryos transferred LPS: progesterone-in-oil 50 mg IM daily from oocyte retrieval until US at 5 or 6 weeks vs progesterone-in-oil 50 mg IM daily from oocyte retrieval until 11 days after ET
Outcomes	Live birth, clinical pregnancy, ongoing pregnancy, multiple pregnancy (all not defined)
Notes	No reply from study author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization was accomplished using sequentially numbered, opaque, sealed envelopes" Method of randomisation not reported
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Goudge 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Humaidan 2006

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI-ET with baseline FSH and LH < 12 IU/L, menstrual cycles between 25 and 34 days, body mass index (BMI) > 18 and < 30, both ovaries present and absence of uterine abnormalities, aged 25 to 40 (n = 45)
Interventions	PD/COH: single bolus of 10.000 hCG SC or GnRH antagonist 0.25 mg SC + rFSH 150 to 200 IU SC ET: day 2 or 3, 2 embryos transferred LPS: micronised vaginal progesterone gel 90 mg daily vs micronised vaginal progesterone gel 90 mg daily + single bolus hCG 1500 IU IM 12 hours after trigger vs micronised vaginal progesterone gel 90 mg daily + single bolus hCG 1500 IU IM 35 hours after trigger. Progesterone from day after OPU until β-hCG test
Outcomes	Clinical pregnancy (intrauterine gestational sac with a heartbeat 3 weeks after a positive hCG test)
Notes	Participants were randomly assigned for ovulation induction protocol (hCG vs GnRH antagonist). Participants randomly assigned for GnrH antagonist were randomly assigned again for time of single-bolus hCG during LPS. All participants received vaginal progesterone for LPS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Third party, sealed and unlabelled envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Humaidan 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Hurd 1996

Methods	Randomised cross-over study
Participants	Women undergoing IVF-ET, excluding women with a history of anovulation, unresponsive to CC or with ovaries not accessible for vaginal retrieval of oocytes, mean age 34 (n = 56)
Interventions	PD/COH: CC 100 mg oral ET: day 2, mean 2.2 embryos transferred LPS: none vs vaginal progesterone suppositories 100 mg 2× daily from embryo transfer + E2 2 mg oral 3× daily from oocyte retrieval. Both until pregnancy test or until 8th week when pregnant
Outcomes	Clinical pregnancy (gestational sac), multiple pregnancy, miscarriage, ongoing pregnancy, OHSS
Notes	Contacted in 2004, only first cycle data used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"..., she was randomized" Method of randomisation not reported
Allocation concealment (selection bias)	Low risk	"using a sealed opaque envelope technique with blocked allocation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Inamdar 2012

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI, mean age 31 (n = 426)
Interventions	PD/COH: GnRH agonist from 21st day until rhCG trigger 0.5 mg daily, from start menses 0.25 mg + rFSH ET: day 2, max 3 embryos transferred LPS: vaginal progesterone 400 mg twice daily + 100 mg progesterone IM daily vs vaginal progesterone 400 mg twice daily + 100 mg progesterone IM daily + lupiride 1 mg SC on days 6, 7 and 8 after oocyte retrieval
Outcomes	CPR (pregnancy diagnosed by ultrasonographic visualisation of 1 or more gestational sacs or definitive clinical signs of pregnancy), OPR (pregnancy proceeding beyond the 20th gestational week)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table
Allocation concealment (selection bias)	Low risk	Third party
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	High risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Isik 2009

Methods	Randomised controlled trial
Participants	Women undergoing ICSI/ET, excluding donor, freeze/thaw and/or TESA cycles, mean age 35 (n = 154)
Interventions	PD/COH: GnRH antagonist + FSH

Isik 2009 *(Continued)*

	LPS: micronised progesterone 600 mg 3× daily vaginal capsules from oocyte retrieval for 17 days + single-dose hCG 1500 IU SC on day +8 + single dose GnRH agonist 0.5 mg SC on day +6 vs micronised progesterone 600 mg 3× daily vaginal capsules from oocyte retrieval for 17 days + single-dose hCG 1500 IU SC on day +8
Outcomes	Live birth, clinical pregnancy (foetal heartbeat), multiple pregnancy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated random table was used for randomization and performed on the day of embryo transfer by a nurse to assign participants to their groups"
Allocation concealment (selection bias)	Low risk	By a nurse
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The clinicians and the laboratory staff were blinded to groups" Participant blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The clinicians and the laboratory staff were blinded to groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Isikoglu 2007

Methods	Randomised controlled trial
Participants	Women undergoing ICSI, mean age 30 (n = 181)
Interventions	PD/COH: GnRH agonist 0.5 mg SC daily from 21st day of preceding cycle + FSH ET: max 4, mean 2.8 embryos transferred LPS: progesterone 50 mg IM daily vs progesterone 50 mg IM daily + GnRH agonist 0.25 mg SC daily for 12 days
Outcomes	Live birth, clinical pregnancy (foetal cardiac activity)
Notes	Study author contacted

Risk of bias

Isikoglu 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized at initiation of stimulation by a computer-generated list"
Allocation concealment (selection bias)	Low risk	Via onsite computer system utilising locked files
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The embryologists were blind to this randomization process"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Iwase 2008

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI for tubal factor, male factor or unexplained infertility, mean age 33 (n = 40)
Interventions	PD/COH: long or short protocol GnRH agonist + hMG ET: day 2, max 3 embryos transferred LPS: chlormadione acetate 6 mg oral 2× daily vs progesterone IM 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14. Both until pregnancy test, when pregnant 125 mg hydroxyprogesterone caproate weekly until 6 or 7 weeks' gestation
Outcomes	Live birth, clinical pregnancy (foetal heart activity) and OHSS
Notes	No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"According to a randomization table generated using computer software into two groups of 20 patients each"
Allocation concealment (selection bias)	High risk	"The random allocation sequence was concealed until the interventions were assigned"

Iwase 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Kably Ambe 2005

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI (n = 69).
Interventions	PD/COH: GnRH analogues + rFSH LPS: progesterone 100 mg IM daily vs progesterone 100 mg IM daily + estradiol valerate 2 mg
Outcomes	Clinical pregnancy rate (not defined), miscarriage (not defined)
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal not reported

Kably Ambe 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Abstract only
Other bias	Low risk	No specific source of other potential bias identified

Kleinstein 2005

Methods	Multi-centre (17) randomised controlled trial
Participants	Women undergoing first IVF/ICSI cycle, successful transfer of 2 or 3 embryos, normal smear in past 12 months, age ≥ 18 and ≤ 35, mean age 30 (n = 430)
Interventions	PD/COH: long GnRH agonist protocol + hMG or FSH ET: 2 (74.4%) or 3 embryos transferred LPS: progesterone vaginal capsules 200 mg 3× daily vs progesterone vaginal gel 90 mg daily. Both from ET until pregnancy or 12 weeks' gestation when pregnant
Outcomes	Clinical pregnancy (amniotic sac), ongoing pregnancy (12 weeks' gestation, with foetal heart activity)
Notes	Supported by Dr Kade, Besins Pharma GmbH

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were randomly assigned to one of the treatments with the aid of a randomization code. The randomization code (Blocking-Factor 10) was generated by a computer program"
Allocation concealment (selection bias)	Low risk	"The trial investigators received consecutively numbered envelopes corresponding to the envisaged number to be recruited. An envelope was allowed to be opened in chronological sequence to assign treatment group only after successful transfer"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open, phase 3 RCT
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open, phase 3 RCT
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Kohls 2012

Methods	Randomised controlled trial
Participants	Women with gestational sac at first ultrasound, mean age 35 (n = 220)
Interventions	PD/COH: GnRH antagonist 0.25 µg SC daily from day 5 or 6 + rFSH 200 to 225 IU ET: mean 2 embryos transferred LPS: vaginal progesterone 200 mg 2× daily until first ultrasound (at 5 weeks) vs vaginal progesterone 200 mg 2× daily until 3 weeks after ultrasound
Outcomes	Clinical pregnancy (gestational sac and heartbeat at 6 weeks), ongoing pregnancy (gestation > 12 weeks), miscarriage rate (in singleton pregnancies only) and multiple pregnancy rate
Notes	Study author contacted in 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Opaque consecutively numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	Results directly obtained from study author in 2010, complemented study published in 2012

Kupferminc 1990

Methods	Randomised placebo-controlled trial, allocation computer generated, using sealed envelopes, partially blinded, power calculation done
Participants	Women undergoing IVF/ET for mechanical, male factor or unexplained infertility, mean age 33 (n = 156)
Interventions	PD/COH: hMG from day 3 of menses ET: day 2, mean 2.8 embryos transferred

Kupferminc 1990 *(Continued)*

	LPS: dydrogesterone 10 mg oral 3× daily from ET for 14 days vs oral placebo vs hCG 2500 IU IM on days 3, 6 and 10
Outcomes	Clinical pregnancy (gestational sac), ongoing pregnancy (beyond first trimester) and miscarriage
Notes	Study author contacted in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomized into one of three treatment groups" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The current prospective blind study..." Method of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The current prospective blind study..." Method of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Kyrou 2011

Methods	Randomised controlled trial
Participants	Women with a positive b-hCG test after a fixed recombinant FSH/GnRH antagonist protocol for IVF/ICSI and a day 3 fresh embryo transfer, mean age 31 (n = 200)
Interventions	PD/COH: GnRH antagonist 0.25 mg SC daily from day 6 + rFSH 150 to 200 IU ET: day 3, mean 1.5 embryos transferred LPS: vaginal progesterone 200 mg 3× daily from OPU until 16 days post ET vs vaginal progesterone 200 mg 3× daily from OPU until 7th week of gestation
Outcomes	Pregnancies (> 7 weeks' gestation), ongoing pregnancies (> 12 weeks' gestation), miscarriage rate (not defined), multiple pregnancy rates
Notes	

Risk of bias

Kyrou 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated by third party
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Lam 2008

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET with a normal uterine cavity, excluding women using vaginal progesterone for LPS, age < 40, mean age 34 (n = 197)
Interventions	PD/COH: long GnRH agonist protocol 600 µg intranasal for at least 14 days + hMG or rFSH IVF/ET: day 3, mean 2.2 embryos transferred LPS: micronised progesterone 200 mg 3× daily vaginal capsules from oocyte retrieval until ET + hCG 2000 IU on day of oocyte retrieval, +3, +6 and +9 vs hCG 2000 IU IM on day of oocyte retrieval, +3, +6 and +9
Outcomes	Pregnancy (positive urine pregnancy test), miscarriage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was performed by a computer-generated program"
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes were used for allocation"

Lam 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"Both investigators and the participants were not blinded of the intervention groups"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Both investigators and the participants were not blinded of the intervention groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Lewin 1994

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET for mechanical infertility, mean age 33 (n = 100)
Interventions	PD/COH: 3 ampoules hMG a day and GnRH agonist 0.5 mg/d SC ET: max 4 embryos transferred LPS: progesterone 50 mg IM from ET vs progesterone 50 mg IM + oestradiol valerate 2 mg oral daily
Outcomes	Clinical pregnancy (not defined), live birth
Notes	No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" Method of allocation not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Withdrawal not reported

Lewin 1994 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Licciardi 1999

Methods	Randomised controlled trial, allocation by randomisation table
Participants	Women undergoing IVF/ET, age < 40 years, mean 35 years (n = 43)
Interventions	PD/COH: GnRH agonist and FSH IM or hCG or a combination of both ET: day 3, mean 3.4 embryos transferred LPS: progesterone 50 mg IM daily vs micronised progesterone 200 mg 3× daily. Both from day after oocyte retrieval
Outcomes	Clinical pregnancy (gestational sac), multiple pregnancy, miscarriage
Notes	No reply from study author in 2004 Study terminated early for ethical reasons: differences in implantation rates highly statistically significant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were assigned to receive either IM or oral progesterone supplementation according to a randomization table"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Lin 2013

Methods	Randomised controlled trial
Participants	Women undergoing GnRG agonist long protocol IVF/ICSI cycles, mean age 31 (n = 402)
Interventions	PD/COH: GnRH agonist ET: day 2 or 3, mean 2.2 embryos transferred LPS: progesterone 60 mg IM 1× daily + oral oestradiol valerate 3 mg 2× daily from OPU for 17 days vs progesterone 60 mg IM 1× daily from OPU for 17 days
Outcomes	Live birth rate, clinical pregnancy rate (positive b-hCG test and gestational sac with heartbeat on ultrasound), miscarriage rate (clinical pregnancy failed to develop > 12 weeks' gestation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Lockwood 2014

Methods	Open-label, multi-centre randomised controlled trial
Participants	Women undergoing ART, mean age 34 (n = 683)
Interventions	PD/COH: any kind of LH suppression and any gonadotropin stimulation regimen LPS: subcutaneous progesterone 25 mg 1× daily vs vaginal progesterone gel 90 mg 1× daily. Both from OPU until 8th week of pregnancy

Lockwood 2014 *(Continued)*

Outcomes	Live birth (delivery of 1 or more live babies), clinical pregnancy (presence of 1 or more gestational sacs detected on ultrasound scan performed 4 weeks after embryo transfer), ongoing pregnancy (pregnancy after 10 weeks' treatment), miscarriage (pregnancy loss after ultrasound confirmation of embryo implantation and before 12 weeks)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Unclear risk	Supported by developer of subcutaneous progesterone

Loh 1996

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET (n = 156); 8% of randomised cycles did not result in ET (numbers by group not provided)
Interventions	PD/COH: "standard GnRH agonist" protocol LPS: IM progesterone vs hCG
Outcomes	Pregnancy (not defined)
Notes	Only abstract available No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement

Loh 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Randomized at recruitment" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Ludwig 2001

Methods	Randomised controlled trial
Participants	Women undergoing IVF or ICSI, excluding women with abdominal discomfort on day of ET and oestradiol levels > 5000 pg/mL, mean age 32 (n = 413)
Interventions	PD/COH: long protocol GnRH agonist + rFSH or hMG ET: mean 2.7 embryos transferred LPS: low risk category (< 12 oocytes retrieved and oestradiol on day of ovulation induction < 2.500 pg/mL); hCG 5000 IU on day of ET and day +3, 2500 IU on day +6 vs hCG 5000 IU on day of ET + progesterone vaginal capsules 200 mg 3× daily vs progesterone vaginal capsules 200 mg 3× daily High risk category (≥ 12 oocytes retrieved and oestradiol on day of ovulation induction ≥ 2.500 pg/mL); hCG 5000 IU on day of ET + progesterone vaginal capsules 200 mg 3× daily vs progesterone vaginal capsules 200 mg 3× daily
Outcomes	Clinical pregnancy (positive foetal heartbeat), ongoing pregnancy (delivery of live born or stillborn baby > 500 g or delivery of live born baby < 500 g), miscarriage
Notes	Because the high risk category is quasi-randomised, data for these arms are not included in the meta-analysis Study author contacted in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement

Ludwig 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Subsequently randomized according to a randomization list"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	High risk	This study had a relatively high rate of miscarriage, which was not consistent with reported rates of live birth, clinical pregnancy and ongoing pregnancy

Ludwig 2002

Methods	Randomised controlled trial, allocation by computer-generated open list
Participants	Women undergoing IVF or ICSI/ET, age < 40, mean age 31 (n = 126). Patients with oestradiol levels < 2000 pg/mL on day of hCG trigger were not selected
Interventions	PD/COH: long protocol GnRH agonist or multiple dose antagonist + FSH or hMG ET: mean 2.8 embryos transferred LPS: progesterone in capsules 200 mg 3× daily vaginally vs progesterone in gel 90 mg daily. Both from evening before ET until menses or pregnancy test
Outcomes	Clinical pregnancy (positive foetal heartbeat on US), ongoing pregnancy (> 12 weeks), miscarriage
Notes	Additional information obtained in 2004 from handout provided at poster presentation Funded by an unconditional grant from Wyeth Pharma GmbH

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomized on an individual basis by use of an open computerized randomization list"
Allocation concealment (selection bias)	High risk	Open randomisation list

Ludwig 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Macrolin 1993

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET, excluding women with OHSS, repeated implantation failure or oestradiol > 2700 pg/mL, age < 38 years (n = 302)
Interventions	PD/COH: GnRHa in long or short protocol + hMG ET: max 3 (41%) or 2 embryos transferred LPS: vaginal micronised progesterone 400 mg daily from the day after oocyte retrieval vs vaginal micronised progesterone 400 mg daily from the day after oocyte retrieval + hCG 1500 IU every other day 3× from ET
Outcomes	Clinical pregnancy, OHSS, ongoing pregnancy (13 weeks)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomisée' Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Macrolin 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available
Other bias	Low risk	No specific source of other potential bias identified

Martinez 2000

Methods	Randomised controlled trial, sample size calculation based on OHSS rates
Participants	Women undergoing IVF/ICSI with normal ovarian response, mean age 33, BMI between 21 and 27, no history of OHSS (n = 310)
Interventions	PD/COH: GnRH agonist 0.2 mL SC and FSH or hMG ET: day 2, when possible at least 3 embryos transferred LPS: progesterone 100 mg 3× daily vaginally for 10 days from ET vs hCG 2500 IU IM on days +2, +4 and +6 after oocyte retrieval
Outcomes	Clinical pregnancy (gestational sac), miscarriage, multiple pregnancy, OHSS
Notes	Study author contacted in 2004

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomly allocated (according to a computer-generated random assignment table)"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Miller 2010

Methods	Multi-centre randomised controlled trial, number of centres not reported
Participants	Women undergoing IVF with GnRH antagonist down-regulation, mean age 33 (n = 165)
Interventions	PD/COH: GnRH antagonist + Menopur or rFSH ET: mean 2.3 embryos transferred LPS: progesterone vaginal capsules (Endometrin) vs progesterone IM
Outcomes	Ongoing pregnancy, miscarriage
Notes	Only abstract available No reply from study author Support from Ferring Pharmaceuticals Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"With randomization prior to stimulation" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"A multicenter, randomized, open-label exploratory study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"A multicenter, randomized, open-label exploratory study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available
Other bias	Low risk	No specific source of other potential bias identified

Mochtar 2006

Methods	Randomised controlled trial
Participants	Women undergoing their first IVF cycle, mean age 34 (n = 355)
Interventions	PD/COH: GnRH agonist LPS: micronised vaginal progesterone 200 mg twice daily starting at the evening of hCG administration for final oocyte maturation vs micronised vaginal progesterone 200 mg twice daily starting at the

Mochtar 2006 *(Continued)*

	evening after oocyte retrieval vs micronised vaginal progesterone 200 mg twice daily starting at the evening after ET
Outcomes	Biochemical pregnancies (serum hCG > 2 IU/mL or a positive pregnancy test at the 18th day after oocyte retrieval), clinical pregnancies (gestational sac seen by transvaginal ultrasound at day 35 after oocyte retrieval), ongoing pregnancies (positive foetal heartbeat by transvaginal ultrasound 10 weeks after oocyte retrieval), live births
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Envelopes prepared by main investigator, method of preparation and randomisation list not reported
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported with reasons
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Moini 2011

Methods	Randomised, placebo-controlled trial
Participants	Women under 35 undergoing IVF/ICSI, mean age 30 (n = 98)
Interventions	PD/COH: GnRH agonist SC from 21st day until complete suppression + hMG or rFSH ET: day 2 or 3, mean 2.8 embryos transferred LPS: vaginal progesterone 400 mg 2× daily + placebo vs vaginal progesterone 400 mg 2× daily + oral oestradiol valerate 2 mg daily. Both from OPU until 10th week
Outcomes	Clinical pregnancy (presence of at least 1 gestational sac with detectable foetal heartbeat)
Notes	

Risk of bias

Moini 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Nallapeta 2013

Methods	Randomised controlled trial
Participants	Women age 18 to 39 undergoing IVF/ICSI (n = 309)
Interventions	LPS: progesterone 100 mg 1× daily IM vs vaginal progesterone 400 mg 1× daily. Both from OPU until 10th week
Outcomes	PR (not defined) and OHSS
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Nallapeta 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	High risk	Abstract only

Ng 2003

Methods	Randomised controlled trial, sample size calculation based on rate of perineal irritation (primary outcome of study)
Participants	Women undergoing ICVF/ICSI with high risk of OHSS because of E2 level on day of hCG administration > 10,000 pmol/L or > 15 oocytes obtained (n = 60)
Interventions	PD/COH: GnRH agonist long protocol ET: max 3 embryos transferred LPS: progesterone suppositories (Cyclogest) 400 mg 2× daily vaginally vs progesterone gel (Crinone 8%) 90 mg once daily vaginally. Both for 14 days from day of ET
Outcomes	Clinical pregnancy (not defined)
Notes	Study author contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"They were randomized according to a computer-generated randomization list in sealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported

Ng 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Ng 2007

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI with long protocol GnRH agonist, mean age 35 (n = 132)
Interventions	PD/COH: GnRH agonist 150 µg intranasal 4× daily from midluteal phase preceding cycle + hMG ET: max 3 embryos, most often 2 embryos transferred LPS: progesterone vaginal suppositories 400 mg 2× daily vs progesterone vaginal capsules 100 mg 2× daily. Both from ET for 14 days
Outcomes	Clinical pregnancy (1 or more gestational sacs), ongoing pregnancy (beyond 10 to 12 weeks' gestation), miscarriage, multiple pregnancy
Notes	Study author contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"They were randomized according to a computer-generated randomization list in sealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Nyboe Andersen 2002

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI with long protocol GnRH agonist, mean age 32 (n = 303)
Interventions	PD/COH: long protocol with nafarelin 600 µg/d or buserelin 0.5 mg/d for at least 14 days + rFSH ET: max 3 embryos transferred, mean 2 embryos LPS: progesterone vaginal suppositories 200 mg 3× daily from OPU until pregnancy test after 14 days vs progesterone vaginal suppositories 200 mg 3× daily from OPU until 3 weeks after pregnancy test
Outcomes	Live birth rate, ongoing pregnancy (> 7 weeks' gestational age), multiple pregnancies
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Patki 2007

Methods	Randomised placebo-controlled trial, "dose-finding study" consisting of 2 phases. Phase 1 investigates 20 mg dydrogesterone vs placebo, phase 2 investigates 30 mg dydrogesterone vs placebo
Participants	Women undergoing ART divided into groups with low or high risk of OHSS, down-regulation by long protocol GnRH agonist, excluding all other protocols (phase 1: n = 404; phase 2: n = 555)
Interventions	Phase 1 PD/COH: long protocol GnRH agonist LPS: micronised progesterone vaginal capsules 600 mg daily + dydrogesterone 20 mg daily oral vs micronised progesterone vaginal capsules 600 mg daily from day of oocyte retrieval + placebo

Patki 2007 *(Continued)*

	Phase 2 PD/COH: long protocol GnRH agonist LPS: micronised progesterone vaginal capsules 600 mg daily from day of oocyte retrieval + dydrogesterone 30 mg daily oral vs micronized progesterone vaginal capsules 600 mg daily from day of oocyte retrieval + placebo All progesterone from day of oocyte retrieval, dydrogesterone or placebo from day of ET until pregnancy test or continued when pregnant
Outcomes	Pregnancy (intrauterine viable pregnancy)
Notes	Phase 1 investigates vaginal progesterone + oral dydrogesterone vs vaginal progesterone + placebo. This does not fit into any of our comparisons; therefore phase 1 is excluded Both phases included an extra group; both examined participants in a donor oocyte programme and therefore were not included in our data analysis Study author contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant receives intervention or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcome reported
Other bias	Low risk	No specific source of other potential bias identified

Perino 1997

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET for the first time for tubal factor infertility, age < 38, mean age 31 (n = 300)
Interventions	PD/COH: GnRH agonist + FSH ET: day 2, max 4 embryos transferred

Perino 1997 *(Continued)*

	LPS: micronised progesterone 50 mg IM daily vs natural progesterone 200 mg vaginally daily. Both from day before ET until pregnancy test
Outcomes	Clinical pregnancy (not defined), ongoing pregnancy (term), miscarriage (not defined)
Notes	No reply from study author in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Porcu 2003

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET (n = 224)
Interventions	PD/COH: GnRH agonist LPS: natural progesterone 50 mg IM daily vs micronised progesterone 200 mg vaginally daily
Outcomes	Pregnancy per transfer (not defined)
Notes	No reply from study author in 2004 Only abstract available

Risk of bias

Bias	Authors' judgement	Support for judgement

Porcu 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Pouly 1996

Methods	Multi-centre (6) randomised controlled trial
Participants	Women undergoing IVF/ET for tubal, idiopathic or endometriosis-related infertility, age < 38, mean age 32 (n = 283)
Interventions	PD/COH: GnRH agonist + hMG ET: mean 3 embryos transferred LPS: progesterone 90 mg vaginal gel daily vs micronised progesterone 100 mg oral, 1 in morning, 2 in evening. Both from day after ET for 14 days or 30 days in case of pregnancy
Outcomes	Clinical pregnancy (gestational sac or β-hCG > 1000 IU), miscarriage, multiple pregnancy, ongoing pregnancy (13 weeks)
Notes	Study author contacted in 2004

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer generated random assignment schedule for each centre"
Allocation concealment (selection bias)	Unclear risk	Not reported

Pouly 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Unclear risk	No specific source of other potential bias identified

Propst 2001

Methods	Randomised controlled trial, sample size calculation based on LBR
Participants	Women undergoing IVF or ICSI/ET, no cryopreserved ET or donor recipients were included, mean age 35 (n = 201)
Interventions	PD/COH: GnRHa in 76%, rest had different protocols IVF (64%), ICSI (36%)/ET: 79% on day 3, mean 3.5 embryos transferred, 21% on day 5, 2 embryos transferred LPS: progesterone gel 90 mg vaginally once daily vs progesterone 50 mg IM daily. Both from day after oocyte retrieval until pregnancy test +10 weeks in case of pregnancy
Outcomes	Clinical pregnancy (gestational sac), miscarriage (loss of clinical pregnancy before 20 weeks' gestation), live birth
Notes	Recruitment terminated after interim results showed high rate of early bleeding in Crinone group Crinone 8% was provided by Serono Laboratories, Inc., Randolph, Massachusetts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomized by permuted blocks of four in sealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label study"
Blinding of outcome assessment (detection bias)	High risk	"Open-label study"

Propst 2001 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Qublan 2008

Methods	Randomised placebo-controlled trial
Participants	Women undergoing IVF/ICSI-ET, excluding PCO, endometriosis, hydrosalpinx thrombophilia, abnormal uterine cavity, women receiving any other form of hormonal treatment and women with ≥ 3 previous cycles. Age between 19 and 36, mean age 29 (n = 120)
Interventions	PD/COH: long protocol GnRH agonist + hMG IVF/ICSI-ET: day 3, 1 to 3 embryos transferred LPS: progesterone pessaries (Cyclogest) + GnRH agonist triptorelin 0.1 mg SC on day of oocyte retrieval, day of ET and day +3 vs progesterone pessaries (Cyclogest) + placebo (solvent) on day of oocyte retrieval, day of ET and day +3
Outcomes	Clinical pregnancy (positive foetal heartbeat), miscarriage, live birth rate
Notes	Dosage/frequency of Cyclogest usage not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was accomplished by using a selection from a table of random numbers available in a standard statistics textbook"
Allocation concealment (selection bias)	Low risk	"Allocation to the groups was concealed from both researchers and patients. The randomization sequence was placed into sealed, numbered opaque envelopes that were only opened once the consent form was signed"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded by using placebo in control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	234 participants recruited, 120 analysed, no reasons for withdrawal reported

Qublan 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	High risk	Dosage/frequency of Cyclogest usage not mentioned

Rodriguez-Pezino 2004

Methods	Randomised controlled trial
Participants	Women undergoing IVF (n = 124)
Interventions	PD/COH: GnRH antagonist 0.25 mg SC + rFSH + LH + hCG ET: day 3 LPS: vaginal progesterone gel 90 mg daily vs vaginal progesterone capsules (Utrogestan) 200 mg twice daily vs vaginal progesterone suppositories 200 mg daily. All from oocyte retrieval
Outcomes	Pregnancy (not defined), miscarriage
Notes	Only abstract available No reply from study author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Were randomised" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Objective states same outcome as reported outcome
Other bias	Low risk	No specific source of other potential bias identified

Salehpour 2013

Methods	Randomised controlled trial
Participants	Women undergoing IVF because of male factor infertility, mean age 30 (n = 80)
Interventions	PD/COH: GnRH agonist 500 µg SC 1× daily + rFSH or FSH highly purified ET: day 2 or 3, mean 3 embryos transferred LPS: oral dydrogesterone 10 mg 4× daily vs vaginal progesterone 400 mg 2× daily. Both from OPU until 12 weeks of pregnancy
Outcomes	Clinical pregnancy (viable foetus on ultrasound 6 weeks after ET), miscarriage (loss of a fetus before the 20th week of pregnancy), ongoing pregnancy (at least 1 viable foetus at 12 weeks' gestation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly divided" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Saucedo 2000

Methods	Randomised controlled trial
Participants	Women undergoing ART (n = 60)
Interventions	ET: day 3, average of 3 embryos transferred LPS: progesterone 400 mg oral daily vs progesterone vaginal gel 90 mg daily vs progesterone 50 mg IM daily

Saucedo 2000 *(Continued)*

Outcomes	Clinical pregnancy (not defined)
Notes	Only abstract available No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomized" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Saucedo 2003

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET, mean age 35 (n = 86)
Interventions	PD/COH: GnRH agonist + rFSH ET: day 3 LPS: progesterone 50 mg IM daily vs vaginal progesterone gel 90 mg daily. Both from day of oocyte retrieval
Outcomes	Pregnancy (not defined)
Notes	Only abstract available No reply from study author

Risk of bias

Saucedo 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available

Serna 2008

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ICSI-ET with at least 2 good quality embryos available for ET, age < 42, excluding women with FSH > 12 IU/L, liver or renal disease, alcoholism, drug abuse, abnormal thyroid function tests or hyperprolactinaemia, mean age 34 (n = 160)
Interventions	PD/COH: long protocol GnRH agonist or GnRH antagonist + rFSH IVF/ICSI-ET: 2 embryos transferred LPS: vaginal progesterone 200 mg 2× daily + transdermal E2 10 µg daily vs vaginal progesterone 200 mg 2× daily. Progesterone from oocyte retrieval until 10th week of gestation, E2 from ET until 10th week of gestation
Outcomes	Ongoing pregnancy (> 12 weeks' gestation), miscarriage (positive test, failed to develop > 12 weeks)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated random number list was created, and patients were included consecutively"
Allocation concealment (selection bias)	Low risk	"Sequence was concealed—opaque consecutively numbered envelopes—until intervention was assigned; a study nurse generated the allocation sequence, enrolled the participants, and assigned participants to their group"

Serna 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Serour 2012

Methods	Randomised controlled trial
Participants	Women undergoing ICSI (n = 147)
Interventions	LPS: progesterone-in-oil 50 mg IM daily vs progesterone-in-oil 50 mg IM daily + rectal progesterone 400 mg 2× daily from pregnancy test for 2 weeks vs progesterone-in-oil 50 mg IM daily + rectal progesterone 400 mg 2× daily from pregnancy test until 12 weeks' gestation. Progesterone-in-oil in all groups from ET until pregnancy test
Outcomes	Clinical pregnancy (not defined), miscarriage rate (not defined)
Notes	Abstract only No reply from study author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Dark sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	Withdrawal and reasons not reported

Serour 2012 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Abstract only Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Stadtmauer 2013

Methods	Multi-centre randomised controlled trial
Participants	Women undergoing ART, mean age 31 (n = 1297)
Interventions	PD/COH: long down-regulation protocol GnRH agonist + FSH 75 to 450 IU daily + LH 75 to 150 IU daily ET: day 3 or 5 LPS: progesterone weekly vaginal ring vs progesterone vaginal gel 90 mg daily. Birth from day after OPU for 10 weeks
Outcomes	Live birth rate, clinical pregnancy (gestational sac and foetal heartbeat), ongoing pregnancy (intrauterine gestation with foetal heartbeat at 12 weeks' gestation), miscarriage rate (not defined)
Notes	Supported by Teva Pharmaceuticals T&D

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	After 1:1 randomisation by third party
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported, participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	High risk	Supported by Teva Pharmaceuticals T&D

Strehler 1999

Methods	Randomised controlled trial
Participants	Women undergoing IVF, mean age 32 (n = 99)
Interventions	PD/COH: short GnRH agonist protocol + hMG IVF/ET: day 2, mean 2.8 embryos transferred LPS: progesterone vaginal gel 90 mg daily vs progesterone vaginal suppositories 200 mg 3× daily. Both from oocyte retrieval until eighth week of pregnancy
Outcomes	Clinical pregnancy (foetal sac), miscarriage and multiple pregnancy
Notes	Only abstract available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were prospectively randomized" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Correct blinding was used for researchers"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Sumita 2003

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET, mean age 34 (n = 100)
Interventions	PD/COH: GnRH agonist + FSH IVF/ET: 2 embryos transferred

Sumita 2003 *(Continued)*

	LPS: progesterone 50 mg IM daily vs vaginal micronised progesterone 600 mg daily, both from day of oocyte retrieval until 12th week of pregnancy
Outcomes	Clinical pregnancy (not defined)
Notes	Additional information obtained in 2004 from poster presentation Only abstract available No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A randomized prospective trial" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Tay 2005

Methods	Randomised controlled trial
Participants	Women undergoing IVF for tubal disease, male factor, ovulatory dysfunction, endometriosis or unexplained infertility, excluding women with pre-ovulatory oestradiol concentration ≥ 15,000 pmol/L and/or total oocyte number ≥ 15. Age between 21 and 41, mean 32.4 (n = 168)
Interventions	PD/COH: long protocol stimulated IVF regimens IVF/ET: mean 2.3 embryos transferred LPS Group 1: natural progesterone 200 mg rectally twice daily vs Group 2: natural progesterone vaginal gel 90 mg daily vs

Tay 2005 *(Continued)*

	Group 3: natural progesterone vaginal capsules, 200 mg once, twice or 3× daily vs Group 4: hCG 1500 IU SC on days 4 and 7 after oocyte retrieval All progesterone supplements were administered from day 4 until 14 days after oocyte retrieval
Outcomes	Expected live birth rate (> 14 weeks' gestation)
Notes	5 egg donor cycles and 5 natural cycle frozen embryo replacement cycles were recruited as controls. None of them conceived and none were given any form of luteal support. These are not included in our data analysis No reply from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomised on the day of embryo transfer" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Tesarik 2006

Methods	Randomised placebo-controlled trial, including 2 separate participant groups: participants undergoing a GnRH agonist protocol and participants undergoing a GnRH antagonist protocol; this is subjectively decided depending on clinical context
Participants	Women undergoing ICSI/ET excluding women with age > 40 and non-obstructive azoospermia requiring testicular sperm retrieval, mean age in agonist group 35, in antagonist group 31 (agonist: n = 283; antagonist: n = 289)
Interventions	Agonist PD/COH: GnRH agonist, triptorelin 0.1 mg SC daily starting in luteal phase of preceding cycle, reduced to 0.05 mg after first bleeding + rFSH and hMG

Tesarik 2006 *(Continued)*

	ET: day 3, mean 2.2 embryos transferred LPS: single-dose GnRH agonist 0.1 mg 6 days after ICSI (3 days after ET) vs placebo Antagonist PD/COH: rFSH + hMG from day 2 of menstrual bleeding, followed by withdrawal of a contraceptive pill. GnRH antagonist 0.25 mg SC daily from started on day 5 until trigger ET: day 3, mean 2.3 embryos transferred LPS: single-dose GnRH agonist 0.1 mg 6 days after ICSI (3 days after ET) vs placebo All women received vaginal micronised progesterone 400 mg and E2 valerate 4 mg daily from oocyte retrieval for 17 days and an injection of 250 µg human rhCG on day of embryo transfer
Outcomes	Live birth, clinical pregnancy (not defined), ongoing pregnancy (not defined)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done with the use of a computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	"Sealed envelopes with treatment allocation instructions were opened on the day of embryo transfer by a nurse who assigned participants to their groups"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The doctor and the biological team performing the ART were blinded to group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The doctor and the biological team performing the ART were blinded to group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Tonguc 2011

Methods	Randomised controlled trial
Participants	Women undergoing IVF treatment with a long GnRH agonist protocol, excluding women thought to be at risk for the development of OHSS and patients with endometriosis. Mean age 30 (n = 285)
Interventions	PD/COH: long GnRH agonist protocol ET: mean 2.6 embryos transferred

Tonguc 2011 *(Continued)*

	LPS: vaginal progesterone gel 90 mg daily + oestradiol 2 mg daily vs vaginal progesterone gel 90 mg daily + oestradiol 4 mg daily vs vaginal progesterone gel 90 mg daily + oestradiol 6 mg daily
Outcomes	Clinical pregnancy rate (positive serum b-hCG result with ultrasound evidence of a gestational sac and foetal heartbeat), miscarriage rate (proportion of participants with initially positive hCG or ultrasound evidence of a gestational sac with or without a foetal pole in whom pregnancy failed to develop before 12 weeks' gestation) and multiple pregnancy rate (not defined)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Third party", method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Identical sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Personnel blinded, participant blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Torode 1987

Methods	Randomised placebo-controlled trial
Participants	Women undergoing IVF (n = 131)
Interventions	PD/COH: clomiphene citrate + hMG ET: day 2 LPS: hCG 1500 IU every other day vs placebo
Outcomes	Pregnancy (not defined)
Notes	No reply from study author

Risk of bias

Torode 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Ugur 2001

Methods	Randomised controlled trial
Participants	Women undergoing IVF with high and normal risk of developing OHSS (n = 375)
Interventions	High risk PD/COH: GnRH agonist LPS: vaginal micronised progesterone 400 mg daily vs vaginal micronised progesterone 400 mg daily + hCG 3000 IU on day 7 Low risk PD/COH: GnRH agonist LPS: vaginal micronised progesterone 400 mg daily vs hCG 1500 IU every 3 days vs vaginal micronised progesterone 400 mg daily + hCG 1500 IU every 3 days
Outcomes	Clinical pregnancy
Notes	Only abstract available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated"

Ugur 2001 *(Continued)*

		Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Only abstract available Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Vimpeli 2001

Methods	Randomised controlled trial
Participants	Women undergoing IVF, excluding women with PCO, previous case of OHSS or > 20 oocytes (n = 89)
Interventions	PD/COH: GnRH agonist + hMG LPS: hCG 1500 IU IM on days 3, 6 and 9 after oocyte retrieval vs vaginal micronised natural progesterone 200 mg 3× daily. from day of oocyte retrieval for 2 weeks, or 4 when pregnant
Outcomes	Pregnancy (not defined)
Notes	No reply in 2004 Supported by a grant from Organon, the Netherlands

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly assigned" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Vimpeli 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported
Other bias	Low risk	No specific source of other potential bias identified

Williams 2001

Methods	Randomised controlled trial
Participants	Women undergoing IVF, mean age 34.5 (n = 126)
Interventions	PD/COH: individual protocol per participant including GnRH agonist protocol or microdose GnRH agonist flare protocol or no GnRH protocol ET: day 3, mean 3 embryos transferred LPS: vaginal progesterone 200 mg 3× daily from day 3 after OPU until 10th week of gestation vs vaginal progesterone 200 mg 3× daily from day 6 after OPU until 10th week of gestation
Outcomes	Clinical pregnancy rate (presence of a gestational sac by ultrasound with appropriately rising b-hCG levels)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization occurred using a sealed-envelope technique"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported

Williams 2001 *(Continued)*

Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Wong 1990

Methods	Randomised controlled trial
Participants	Women undergoing IVF/ET for tubal factor (n = 30)
Interventions	PD/COH: clomiphene citrate + hMG ET: day 2 LPS: progesterone 50 mg IM daily from day 2 until day 11 vs progesterone 50 mg IM daily from day 2 until day 11 + hCG 1500 IU alternate days from day 5 to day 15 vs no luteal support
Outcomes	Pregnancy (not defined)
Notes	No reply from study author in 2004

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	High risk	Given outcome (pregnancy) not stated in Methods section
Other bias	Low risk	No specific source of other potential bias identified

Yanushpolsky 2010

Methods	Randomised controlled trial
Participants	Women undergoing IVF with fewer than 3 prior unsuccessful cycles, mean age 34 (n = 407)
Interventions	ET: mean 2.1 embryos transferred LPS: progesterone 50 mg IM daily from day after oocyte retrieval vs progesterone vaginal gel 90 mg daily from 48 hours after oocyte retrieval. In both arms, 51 women received E2 3 mg oral daily
Outcomes	Pregnancy (not defined), failed pregnancy (chemical pregnancy + spontaneous abortion + ectopic pregnancy)
Notes	Study author contacted; the article, published in *Fertility & Sterility* (2011) describes a retrospective analysis of women receiving LPS with E2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized with equal probability to receive either [...]" Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Via onsite computer system utilising locked files
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

Yildiz 2014

Methods	Randomised study of infertile women having ICSI
Participants	infertile women having ICSI
Interventions	COS: long agonist protocol LPS: all women had 600 mg/day vaginal micronized progesterone plus 4 mg 17beta estradiol for LPS starting from the day of oocyte retrieval until the pregnancy test was performed at day 12 after embryo transfer

Yildiz 2014 *(Continued)*

	Group A (n=100) received leuprolide acetate 1 mg s.c. injection 3 days after ET in addition to routine LPS. Group B (n=100) received two sequential doses of leuprolide acetate 1 mg s.c. injections 3 and 6 days after ET in addition to routine LPS. Control group (n=100) received only the routine LPS. RESULTS: A total of 279 patients completed the study.
Outcomes	Clinical pregnancy rate, ongoing pregnancy rate, multiple pregnancy, OHSS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomisation model"
Allocation concealment (selection bias)	Unclear risk	not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	some losses to follow up
Selective reporting (reporting bias)	High risk	did not report live birth data
Other bias	Unclear risk	nil

Zegers-Hochschild 2000

Methods	Multi-centre (3) randomised controlled trial, including 2 different studies: IVF-embryo transfer trial and oocyte donation trial. Only the IVF-ET trial is included in the review
Participants	Women undergoing ICSI/IVF-ET (n = 505)
Interventions	PD/COH: GnRH agonist + hMG ET: day 2 or 3, mean 3.7 embryos transferred LPS: 1 gram progesterone vaginal ring vs 50 mg progesterone IM daily
Outcomes	Clinical pregnancy (gestational sac), multiple gestation (2 or more gestational sacs visualised 5 weeks after embryo transfer), live birth

Zegers-Hochschild 2000 *(Continued)*

Notes	Laboratorios Silesia S.A. provided the vaginal rings

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"On day of oocyte retrieval patient were randomly allocated..." Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported
Other bias	Low risk	No specific source of other potential bias identified

ART: assisted reproduction techniques.
BMI: body mass index.
CC: clomifene citrate.
COH: controlled ovarian hyperstimulation.
CPR: clinical pregnancy rate, pregnancy diagnosed by ultrasonographic visualisation of 1 or more gestational sacs or definitive clinical signs of pregnancy.
ET: embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotropin-releasing hormone.
hCG: human chorionic gonadotropin.
hMG: human menopausal gonadotropin.
ICSI: intracytoplasmic sperm injection.
IVF: in vitro fertilisation.
LH: luteinising hormone.
LS: luteal support.
OHSS: ovarian hyperstimulation syndrome.
OPR: ongoing pregnancy rate, pregnancy proceeding beyond 20th gestational week.
OPU: ovum pick up.
PCO: polycystic ovary.
PCOS: polycystic ovarian syndrome.
PD: pituitary desensitisation.
RCT: randomised controlled trial.
rFSH: recombinant follicle stimulating hormone
TESA: testicular sperm aspiration.
TESE: testicular sperm extraction.
US: ultrasound.

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

Study	Reason for exclusion
Abu-Musa 2008	This RCT investigated the role of 17a-hydroxyprogesterone caproate given before embryo transfer to decrease uterine contractions and thereby improve implantation rates
Abu-Musa 2008a	This RCT investigated the role of 17a-hydroxyprogesterone caproate given before embryo transfer to decrease uterine contractions and thereby improve implantation rates
Aleyasin 2012	This RCT investigated methods of final oocyte maturation
Allahbadia 2004	This comparative study investigated pregnancy outcomes with IM progesterone (n = 94) vs oral dydrogesterone (n = 30) for luteal phase support in cycles using donated eggs
Allen 2004	This RCT included ZIFT cycles only (n = 99)
Alsanie 2005	This retrospective case control study compared serum hCG levels when progesterone and oestrogen were used (n = 15) vs progesterone alone (n = 15) for luteal phase support in IVF-ET cycles
Andersen 2014	Not a primary study; a literature review
Anserini 2001	This is a quasi-RCT
Anthony 1993	This is a quasi-RCT
Araujo 1994	This RCT investigated IVF and ZIFT cycles but did not describe the distribution of these interventions Study authors previously contacted (in 2004)
Araujo Filho 1996	Study did not report the percentage of ZIFT cycles
Baber 1988	This study was excluded from the previous version of this review, as in this RCT, allocation to hCG or no treatment included only women with a positive pregnancy test; thus treatment did not truly consist of luteal phase support
Beckers 2006	This RCT investigated high doses of steroids administered after the LH surge in normo-ovulatory volunteers to investigate whether this would give rise to endocrine changes and shortening of the luteal phase
Belaisch-Allart 1988	This was an interim analysis of 295 cases in a total of 525 women. Data included 451 transfers Study author contacted in 2004 but not able to provide any information
Ben-Nun 1990	This study was excluded from the previous version of this review, as it was not a randomised trial - compared IM progesterone vs historical controls receiving no progesterone. Treatment was given for only 6 days around the time of oocyte retrieval
Berjis 2008	This study included only rapid-ZIFT procedures
Bjuresten 2011	This RCT investigated the effects of luteal phase support in frozen embryo transfers only (n = 435)
Blake 2010	This pharmacokinetic study did not include patients undergoing ART
Buvat 1988	This was a quasi-RCT
Buvat 1990	This was a quasi-RCT

Study	Reason for exclusion
Casini 2003	This study was excluded from the previous version of this review because in this RCT, some women contributed more than 1 cycle to the study (n = 201 women, 436 cycles) Study author was unable to provide first cycle data
Chakravarty 2012	Abstract only, no data reported No reply from study author
Chang 2008	Not a randomised trial; review about intramuscular progesterone for luteal phase support in IVF
Chang 2009	Not a randomised trial; retrospective analysis of outcomes of IVF cycles with GnRH antagonist administration on ovulation triggering day
Chantilis 1999	This study was excluded from the previous version of this review, as it was not a randomised trial - compared vaginal progesterone vs historical controls using IM progesterone
Check 2010	This RCT investigated the dosage of progesterone supplementation in frozen embryo transfers only (n = 408)
Check 2012	Not a primary study; literature review
Check 2013	Not a randomised controlled trial; retrospective cohort study
Claman 1992	This RCT included IVF/ETcycles (n = 121) rather than women (n = unknown) Study author contacted in 2004 and was not able to provide first cycle data
Costabile 2001	This RCT was excluded because it included more cycles (n = 300) than women (n = 220) No reply from study author
Daya 2009	Not a randomised trial; review about progestogens for luteal support
Demir 2013	This article pertains to a subset of women with a thin endometrium; therefore the results cannot be generalised
Demirel 2003	This RCT was excluded, as the abstract does not provide details on the number of participants allocated to each intervention group No reply from study author
Ding 2005	This RCT was excluded because it included more cycles (n = 114) than women (n = 95) No reply from study author
Ellenbogen 2011	This study investigated in vitro maturation of oocytes
Erman Akar 2005	This RCT was excluded because it included more cycles (n = 115) than women (n = 95) No reply from study author
Escriba 2006	This RCT investigated initiation of progesterone supplementation in donated oocyte transfers only (n = 300)
Farhi 2000	This study was excluded from the previous version of this review because in this RCT, some women contributed more than 1 cycle to the study (n = 271 women, 285 cycles)

Study	Reason for exclusion
Farrag 2008	This RCT investigated the use of recombinant hCG to induce final oocyte maturation in ICSI cycles
FeiYang 2013	Abstract of an RCT investigating different LH and luteal phase protocols. Limited information on outcomes reported, no contact details available
Feliciani 2004	This RCT compared the effects of intravaginal (n = 14) and IM progesterone (n = 14) in frozen/thawed embryo transfers only
Gallardo 2004	This study was excluded as only the abstract is available, and it provides no details on participants allocated to each intervention group and no contact details for study authors
Garcia-Velasco 2009	This RCT investigated the effects of letrozole administered during the luteal phase after oocyte retrieval in oocyte donors only
Gazvani 2012	This is a study protocol only
Germond 2002	Not a randomised trial. This cohort study investigated 2 types of micronised progesterone as luteal phase support
Ghanem 2009	This study was quasi-randomised, as randomisation was performed using a sequential allocation method
Gibbons 1998	This study was excluded from the previous version of this review, as this RCT compared vaginal and IM progesterone only in women receiving donated oocytes (n = 72)
Griesinger 2006	Not a randomised trial; review
Herman 1990	This was a quasi-RCT
Herman 1996	This was a quasi-RCT
Ho 2008	Not a randomised trial; retrospective case control study
Hokenstad 2013	This RCT included frozen embryo transfers only (n = 71)
Humaidan 2010	This RCT was excluded, as it investigated only 1 dose of hCG as a trigger; not a luteal phase support study
Humaidan 2013	This study investigated risk of OHSS
Hutchinson-Williams 1990	This study was excluded from the previous version of this review, as it was not a randomised trial - the treatment group was "randomly" selected, but the control group was retrospectively selected and was age-matched to the treatment group
Iliodromiti 2013	Not a randomised trial; retrospective study on the effects of GnRH agonist trigger and modified intensive luteal phase support on pregnancy outcomes and risk of OHSS
Jee 2010	Not a randomised trial; meta-analysis
Johnson 1999	This study was excluded from the previous version of this review, as this RCT compared hCG vs no treatment, with primary objective of measuring relaxin levels during the luteal phase Complete pregnancy outcomes by groups were not reported
Jung 2010	Randomisation unclear No reply from study author

Study	Reason for exclusion
Kahraman 2010	This was a quasi-RCT
Kaser 2012	This study investigated intramuscular progesterone vs Crinone 8% in cryopreserved embryos (n = 738)
Kol 2011	This proof-of-concept study investigated an hCG-based, progesterone-free luteal phase
Koper 2008	This randomised trial investigated the dose-response relationship of corifollitropin alfa to initiation of multi-follicular development for the first 7 days of controlled ovarian stimulation
Krause 2006	This RCT investigated the efficiency and safety of different luteal support regimens in non-IVF cycles (n = 36)
Krischker 1998	This study was excluded from the previous version of this review, as this RCT compared progesterone IM, 2 types of oral progesterone and hCG, using long GnRHa (n = 30) or ultrashort GnRHa (n = 273). Pregnancy rates by group were provided, but numbers of transfers in each group were not provided. Attempts to contact study authors were unsuccessful
Kwon 2012	This randomised study investigated the effects of intravenous immunoglobulin treatment on pregnancy outcomes
Kyrou 2011a	Not a randomised trial; meta-analysis on addition of GnRH agonist for luteal phase support
Lainas 2012	Not a randomised trial; observational cohort study on outpatient management of severe early OHSS
Lam 2003	This study was excluded from the previous version of this review, as this RCT compared hCG plus vaginal progesterone administered only between oocyte retrieval and embryo transfer vs hCG alone (n = 102). This was the only identified study that made this comparison
Lan 2007	This RCT compared the efficacy and tolerability of 2 formulations of vaginal progesterone - Crinone 8% (n = 100) and Utrogestan (n = 100) - in frozen embryo transfers only
Lee 2013	Not a randomised trial; retrospective analysis on frozen-thawed cycles
Lee 2013a	This retrospective study investigated the effects of additional hCG with vaginal progesterone in luteal phase support
Leeton 1985	This was a quasi-RCT
Lightman 1999	This was a quasi-RCT
Lin 2013a	This report investigated the effects of delayed initiation of gonadotropin in luteal long protocol on outcomes of in vitro fertilisation
Liu 2012	Not a randomised trial; meta-analysis about duration of luteal phase support
Lukaszuk 2005	This RCT was excluded because it included more cycles (n = 231) than women (n = 166) No reply from study author
Mahadevan 1985	This was a quasi-RCT
Marianowski 2000	This study was excluded from the previous version of this review, as it was not a randomised trial - compared IM and vaginal progesterone vs allocation by the woman's preference (n = 79)

Study	Reason for exclusion
Martins 2010	Not a randomised trial; review about luteal phase support
McBain 1987	This was a quasi-RCT
Michnova 2011	Not a primary study; literature review
Miller 2013	Abstract only; no details on number of participants randomly assigned to each intervention group No reply from study author
Mochtar 1996	This study was excluded from the previous version of this review because in this RCT, some women contributed more than 1 cycle to the study (n = 98 women, 176 cycles) An attempt was made to contact study authors, but no reply was received
Moraloglu 2008	This study compared the effects of GnRH agonist (n = 48) and GnRH antagonist (n = 45) use in 2 matched groups of women undergoing IVF/ICSI
Munoz 2013	Not a primary study; literature review
Nader 1988	This study was excluded from the previous version of this review, as this RCT compared progesterone vs hCG but was excluded because some women contributed more than 1 cycle to the study (n = 17 women, 20 cycles) Study author was unable to provide first cycle data
NCT01007851 2006	NCT01007851 https://ClinicalTrials.gov/show/NCT01007851 Study terminated for lower than anticipated recruitment.
Nikkanen 1992	This was a quasi-RCT
Nyboe Andersen 2012	This was not a primary study - data from 2 other studies were reported
Osmanagaoglu 2013	This randomised study investigated differences in the numbers of metaphase 2 oocytes after triggering with hCG vs triggering with the combination of hCG and GnRH agonist
Ozcimen 2004	This cross-over study investigated the effects of luteal phase support on non-IVF gonadotropin induction of ovulation
Papanikolaou 2010	This RCT compared recombinant hCG (n = 59) vs urinary hCG (n = 60) as a final oocyte maturation trigger
Papanikolaou 2011	This was a proof-of-concept study on use of luteal phase support as a final oocyte maturation trigger
Paredes 2004	Abstract only available - does not provide details on outcomes No reply from study author
Pirard 2005	This randomised trial included IUI only
Pirard 2006	Comparison did not meet inclusion criteria
Polson 1992	This was a quasi-RCT
Priyadharshini 2013	Not a randomised trial; observational study

Study	Reason for exclusion
Propst 2012	This study investigated intrauterine insemination
Santibanez 2014	This randomised study investigated the effects of human chorionic gonadotropin on clinical pregnancy before embryo transfer
Satir 2013	This retrospective study investigated intramuscular progesterone vs vaginal progesterone gel
Schwarzler 2003	This study was excluded from the previous version of this review because in this RCT, some women contributed more than 1 cycle to the study (n = 603 women, 945 cycles)
Shamma 1992	Abstract only - no contact details for study authors
Silverberg 2010	Not a true randomised trial; study investigating vaginal progesterone vs intramuscular progesterone Study author contacted
Simunic 2007	Not a randomised trial; cohort study investigating the efficacy and tolerability of Crinone 8% gel vs Utrogestan capsules
Singh 2010	This randomised trial investigated supplementation of GnRH agonists during the luteal phase in IUI only
Smith 1989	This was a quasi-RCT
Smitz 1988	Study did not report the percentage of GIFT cycles
Smitz 1992	Study included > 20% GIFT/ZIFT cycles
Smitz 1993	This was a quasi-RCT
Sordal 1993	This study was excluded from the previous version of this review, as this RCT compared progesterone IM, 2 doses of vaginal progesterone and no treatment (n = 40) but did not provide pregnancy rates by group Attempts to contact study author were unsuccessful
Stadtmauer 2009	This randomised trial compared the effects of progesterone in a vaginal ring (n = 10) vs progesterone vaginal gel (n = 10) in donor oocytes
Stovall 1998	Not a randomised trial - this study investigated selective early elimination of luteal phase support
Tay 2003	This study divided study population into 2 groups; group A underwent GnRH-a/rFSH ovarian stimulation followed by IVF, and group B underwent CC/rFSH ovarian stimulation and IUI After ET or insemination, participants were randomly assigned to 2 different luteal phase support protocols No reply from study author in 2004
Tomic 2011	Not a randomised trial; case control study investigating oral micronised progesterone combined with vaginal progesterone
Trounson 1986	This study was excluded from the previous version of this review, as this RCT assessed luteal support with progesterone IM or hCG given only around the time of oocyte retrieval (n = 42)
Unfer 2004	This RCT was excluded because it included more cycles (n = 284) than women (n = 213) No reply from study author

Study	Reason for exclusion
Unfer 2004a	This RCT was excluded because it included more cycles (n = 734) than women (n = 320) No reply from study author
Vaisbuch 2012	This was a World Wide Web-based survey
Valentino 2004	This study was excluded from the previous version of this review, as this RCT compared vaginal and IM progesterone (n = 40) but did not provide pregnancy rates (main outcome measures were side effects and convenience) Attempts to contact study author were unsuccessful
van Steirteghem 1988	Study did not report percentage of GIFT procedures
Var 2011	This was a quasi-RCT - allocation was based on application number
Wang 2009	Not a randomised trial; cohort study comparing Crinone 8% gel vs Utrogestan capsules
Wilcox 2001	This study was excluded from the previous version of this review, as this RCT compared luteal support with progesterone vaginal gel alone or in combination vs IM progesterone in frozen embryo transfer cycles (n = 97)
Yazici 2014	This randomised study investigated the role of luteal phase support in ovulation induction and intrauterine insemination
Ye 2009	This RCT investigated luteal oestradiol pretreatment before the GnRH antagonist protocol and the GnRH agonist protocol
Yigit 2002	This study was excluded from the previous version of this review, as it was not a randomised trial According to information received from study author, this was a retrospective study comparing vaginal gel vs IM progesterone
Yovich 1984	This was a quasi-RCT with allocation based on study number Study author contacted in 2004
Yovich 1985	This was a quasi-RCT
Yovich 1991	This RCT included ZIFT cycles only

ART: assisted reproduction techniques.
CC: clomifene citrate.
ET: embryo transfer.
GIFT: gamete intrafallopian transfer.
GnRH: gonadotropin-releasing hormone.
hCG: human chorionic gonadotropin.
ICSI: intracytoplasmic sperm injection.
IVF: in vitro fertilisation.
LH: luteinising hormone.
OHSS: ovarian hyperstimulation syndrome.
RCT: randomised controlled trial.
rFSH: recombinant follicle stimulating hormone.
ZIFT: zygote intrafallopian transfer.

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

Pirard 2015

Methods	Computer-generated randomization was applied (2/1; group A/B). Treatment allocation instructions were placed in individually sealed envelopes to be opened at the center in chronological order on the day of signing the informed consent form.
Participants	Women undergoing IVF/ICSI after stimulation of multiple follicular development with human menopausal gonadotropin (hMG). Inclusion criteria were the age between 18 and 39 and BMI ≥ 18 but ≤35, while exclusion criteria were a history of poor response, systemic disease (diabetes, severe migraine, hepatic, renal, or cardiovascular disease, and corticodependent asthma), and ovarian cysts ≥11 mm.
Interventions	In study group A, GnRH agonist (buserelin) was administered IN to trigger final follicular maturation and support the luteal phase. In control group B, hCG was administered to trigger final follicular maturation and vaginal progesterone to support the luteal phase.
Outcomes	The primary end-point was the comparison of pregnancy rates between the two groups. Pregnancy was diagnosed by measuring serum hCG levels on day 14 of the luteal phase (day of first hCG/buserelin administration = D0). Clinical pregnancy was defined as the presence of an intrauterine gestational sac with a positive heartbeat visual-ized by vaginal ultrasound.
Notes	Single-center, prospective, randomised, open, parallel group study.

Tomic 2015

Methods	Patients were randomly assigned at the day of oocyte retrieval following computerized random number generator in procedure, to study or control group. Random allocation concealment with intervention drug was ensured by sequentially numbered, sealed, opaque envelopes. Patients were aware of the allocated arm since the treatment drugs have different route of administration, but investigators and outcome assessor were kept blinded to the allocation.
Participants	Eligible participants were all women undergoing controlled ovarian stimulation for IVF/ICSI treatment who met the following inclusion criteria: aged 18–45 years, a body mass index (BMI) < 35 kg/m2 , applied routine short ovulation induction protocol with GnRH agonist, with less than three prior IVF cycles and at least one aspirated oocyte. Exclusion criteria included: a history of dysfunctional uterine bleeding, recurrent miscarriage (defined as three or more spontaneous miscarriage), acute urogenital disease, transfer of frozen embryos and previous allergic reactions to progesterone products.
Interventions	Study group: recieved 2 10 mg of oral dydrogesterone (Duphaston1, Abbot Biologicals B.V., Olst, Netherlands) from the day of oocyte retrieval until a pregnancy test or in the case of pregnancy until week 10. Control group: recieved 1 90 mg of vaginal progesterone gel (Crinone 8%, Fleet Laboratories Ltd., Watford, UK) in the same fashion i.e. from the day of oocyte retrieval until pregnancy test or in the case of pregnancy until week 10.
Outcomes	The primary outcome was ongoing pregnancy rate, defined by the presence of gestational sac(s) with viable fetal heart beats at 12 weeks' gestation by transvaginal ultrasound. Secondary outcome measures were satisfaction score, determinate on the 5-point level scale (with 1 being ''absolutely unsatisfied'' and 5 being ''absolutely dissatisfied'') and tolerability accessed by questionnaire with different side effects that the supplements could cause.
Notes	The prospective, randomized, double-blinded clinical trial was conducted from October 2010 to October 2013 in a tertiary infertility unit at University Hospital Center ''Sisters of Mercy'', Zagreb, Croatia.

Tomic 2015 *(Continued)*

	Corresponding author at: DZ Zagreb Centar, Department of Gynecology and Obstetrics, Runjaninova 4, 10 000 Zagreb, Croatia. Fax: +385 1 37 68 272. E-mail address: tomic.vlatka@gmail.com (V. Tomic)

Zafardoust 2015

Methods	Computer-generated randomization list was used for randomization. Selection was performed on the day of OCP admin-istration for GnRH antagonist cycle.
Participants	100 infertile couples with history of 2 or more previous IVF-ET or ICSI-ET failures treated by GnRH antagonist protocol for ICSI. Inclusions: Women with history of 2 or more previous IVF-ET or ICSI-ET failures; women were under 42 years old and had FSH levels <12 mIU/ml on 2nd or 3rd day of menstrual bleeding with normal thyroid and prolactin levels and the couples had at least one embryo available for transfer. Exclusions: Women with hydrosalpinx or anatomical uterine disorders or those with thrombophilia disorders; couples suffering from azoospermia who required testicular sperm retrieval; those who had undergone Preimplantation Genetic Diagnosis (PGD) 100 couples; 17 dropouts, 83 analysed - 43 in intervention group and 40 in control.
Interventions	There were two groups. Intervention group received Decapep-til (Ferring, Germany) 0.1 mg S.C., 6 days after oocyte retrieval and control group did not receive Decapeptil. All women received routine luteal phase support with 800 mg vaginal progesterone daily.
Outcomes	Pregnancy was tested by measuring serum beta-hCG levels 14 days after ET. The implantation rate was calculated as the ratio of the number of embryonic sacs detected by ultrasonography to the total number of embryos transferred. Clinical pregnancy was defined as the presence of a fetus with a heart beat by vaginal ultrasonography at 6 weeks of pregnancy. Multiple pregnancies were defined by presence of more than one fetus in vaginal ultrasonography.
Notes	This study was conducted between February 2013 and January 2014 in Avicenna infertility Clinic affiliated to Avicenna Research institute, Tehran, Iran. This study was approved by the Ethical Commit-tee of Avicenna Research Institute and informed consent was obtained from all participants.

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

EUCTR2012-002215-26-BE 2013

Trial name or title	A Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg Daily Versus Intravaginal Micronized Progesterone Capsules 600 mg Daily for Luteal Support in In-Vitro Fertilization (Lotus I)
Methods	A Double-Blind, Double-Dummy, Randomized, Two-arm, Multicenter Study
Participants	Infertile women undergoing IVF
Interventions	Oral dydrogesterone 10 mg TID versus micronized progesterone vaginal capsules 200 mg TID

EUCTR2012-002215-26-BE 2013 *(Continued)*

Outcomes	Primary Outcome: Pregnancy Rate, defined as the presence of fetal heart beats at 12 weeks gestation determined by transvaginal ultrasound Secondary Outcome: Positive Pregnancy test rate, defined as positive biochemical pregnancy test on Day 14 after embryo transfer, Rate of successful completion of pregnancy, Incidence of live births and healthy newborns, Adverse Events, Status newborn. The gender, APGAR score, height, weight and head circumference, physical examination and any malformations of the newborn(s) will be recorded, Adverse Events At Study Completion (about 10 months after IVF)
Starting date	2013
Contact information	Simone Schicker Email: simone.schicker@quintiles.com Contact telephone: +496102 296 213
Notes	Sponsorship:Quintiles GmbH and Abbott Laboratories GmbH https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-002215-26 NB: This trial has a second registration NCT01850030 https://clinicaltrials.gov/ct2/show/NCT01850030

EUCTR2013-001105-81-2013

Trial name or title	Randomized Clinical Trial to Compare the Pregnancy Rates of Vaginally Applied Cyclogest® Pessary and Crinone® 8% Gel After In-vitro Fertilization
Methods	Randomized clinical parallel group trial
Participants	Women having IVF, age 18-40
Interventions	Cyclogest® Pessary or Crinone® 8% Gel for luteal phase support after IVF
Outcomes	Clinical pregnancy rate (Clinical pregnancy rate achieved after 38 days of luteal phase support (primary), Clinical pregnancy rate achieved after 70±3 days (10 weeks) of luteal phase support (secondary), Clinical pregnancy rate achieved after 70 ±3 days (10 weeks) of luteal phase support (fetal heart movement measured by TVUS), Clinical implantation rates per number of embryos transferred after 38 days of luteal phase support (fetal heart movement measured by TVUS), Biochemical pregnancy rate at Day 18 and 38 after OR The patient's evaluation of treatment convenience, The patient's evaluation of bleeding and leakage (diary), Incidence of adverse events.
Starting date	31 July 2013
Contact information	Email: iklingmann@pharmaplex.be
Notes	Sponsorship: Actavis Group PTC ehf. https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-001105-81 http://adisinsight.springer.com/trials/700235403

IRCT201402191141N18 2015

Trial name or title	Subcutaneous progesterone (Prolutex) versus vaginal (Cyclogest) for luteal phase support in IVF/ICSI cycles: a randomized controlled clinical trial study phase 3

IRCT201402191141N18 2015 *(Continued)*

Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	Intervention: Luteal phase support during ART treatment with subcutaneous injections of progesterone (Prolutex): since ovum pick up day, a daily subcutaneous injection of progesterone (25 mg) (Prolutex®; IBSA Institut, SA Biochimique) will be used and if pregnancy is occurred it continues until 10 weeks of pregnancy. Control group : Luteal phase support during ART treatment using a vaginal suppository (Cyclogest) : Since ovum pick up day, one vaginal suppository every 12 hours will be used (Cyclogest ®; Actavis, Barnstaple, UK), If pregnancy is occurred it continues until 10 weeks of pregnancy.
Outcomes	Clinical pregnancy rate: evidence of pregnancy by clinical (fetal heartbeat) or ultrasound parameters (ultrasound visualization of a gestational sac, embryonic pole with heartbeat) after 7-6 weeks after embryos transfer. Early miscarriage rate.
Starting date	2015
Contact information	Dr Ashraf Moini Email: a_moini@royaninstitute.org Contact telephone: 00982123562640
Notes	Sponsorship: Royan Institute and Shafayab gostar pharmaceutical company http://www.irct.ir/searchresult.php?keyword=&id=1141&number=18&prt=6166&total=10&m=1

IRCT2014030916912N1 2014

Trial name or title	Comparison administration single dose GNRH agonist (Triptrolin) with placebo in the luteal phase on clinical pregnancy rate in ART cycle in the infertile women.
Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	Intervention: Three days after embryo transfer, 0.1 mg (1ml) triptrolin subcutaneous injected Control: 1ml normal saline subcutaneous injection three days after embryo transfer
Outcomes	Clinical pregnancy, 8 week after intervention. Implantation rate, 10 weeks after intervention.
Starting date	2014
Contact information	Saeedeh Gharahjeh Tehran University of Medical Sciences Email: s-gharahgeh@razi.ac.ir, Dr.gharahgeh_1388@yahoo.com Contact telephone: 00982184902421
Notes	http://www.irct.ir/searchresult.php?keyword=stimulatio&id=16912&field=&number=1&prt=171&total=10&m=1

IRCT2014071212494N2 2014

Trial name or title	Comparison of oral progesterone with vaginal and subcutaneous progesterone for luteal phase support on pregnancy rate of infertile patients underwent intracytoplasmic sperm injection - Embryo transfer cycles
Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	Intervention 1: Duphaston(Oral Didrogesterone 10mg, Abbott, Netherland) 20mg , Twice daily until 12 weeks Intervention 2: Subcutaneous progesterone (Prolutex, 25mg, IBSA company, Switzerland) daily injection until 12 weeks Control: Vaginal suppository cyclogest, (A kind of vaginal progesterone, 400 mg, actover company, Britain) 400mg twice daily until 12 weeks.
Outcomes	Clinical pregnancy rate, five weeks after start of intervention by transvaginal ultrasonography. Miscarriage rate, until 24 weeks after start of intervention. Patients acceptance, until 12 weeks by questionnaire
Starting date	2014
Contact information	Nasrin Saharkhiz Reproductive Health Research Centre - Shahid Beheshti of Medical Science Email: saharkhiz1377@yahoo.com; www.irhrc.sbmu.ac.ir Contact telephone: 00982122432558
Notes	Sponsorship: Vice chancellor for research, Shahid Beheshti University of Medical Science; Shafayab Gostar company http://www.irct.ir/searchresult.php?keyword=&id=12494&number=2&prt=7064&total=10&m=1

NCT00490308 2007

Trial name or title	Blinded Randomised Trial About the Influence of Estradiol Supplementation During the Luteal in Patients Undergoing in Vitro Fertilization (IVF) Treatment
Methods	RCT
Participants	Inclusion Criteria: Women treated for infertility with controlled ovarian hyperstimulation using daily GnRH agonist Exclusion Criteria: Women younger then 18 or older then 40, Women with systemic disease, Women with a family or personal history of thromboembolic event
Interventions	Treatment with estradiol valerate
Outcomes	Secondary Outcome Measures: E2 and progesterone levels
Starting date	2007
Contact information	Ran Svirsky, MD

NCT00490308 2007 *(Continued)*

	Assaf-Harofeh Medical Center Email: rsvirs@gmail.com Contact telephone: +972-0523-859521
Notes	https://ClinicalTrials.gov/show/NCT00490308

NCT01081652

Trial name or title	A Study Using Micronised Progesterone (Crinone® 8%) in the Luteal Phase Support of Women Undergoing in Vitro Fertilisation (IVF) and Embryo Transfer (ET)
Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	Intervention: Micronised progesterone administered intravaginally once daily from the day of ET. If pregnancy was confirmed on day 14 of progesterone administration, progesterone was continued for another 45 days. Comparison: Progesterone 60 mg administered intramuscular once daily from the day of ET. If pregnancy was confirmed on day 14 of progesterone administration, progesterone was continued for another 45 days.
Outcomes	The difference in hCG positive rate in the two arms 14 days after embryo transfer. The difference in pregnancy rates in the two arms 30 and 60 days after embryo transfer. The difference in implantation rate in the two arms 30 days after embryo transfer.
Starting date	2014
Contact information	Huafei Li Serono Pharmaceutical Limited
Notes	https://ClinicalTrials.gov/show/NCT01081652 Completed with no results available.

NCT01237535

Trial name or title	Luteal Phase Support With Progesterone Versus Estrogen and Progesterone on Pregnancy Rates
Methods	RCT
Participants	Infertile women undergoing IUI, age 20-40 years
Interventions	Intervention 1: Luteal support with progesterone only (they will received vaginal P gel (Crinone 8% vaginal gel; Serono, Israel) Intervention 2: Luteal support with estrogen + progesterone [(Crinone 8% vaginal gel; Serono, Israel) and Estrofem 4mg] Control: No luteal support

NCT01237535 *(Continued)*

Outcomes	Clinical Pregnancy, a pregnancy test will be performed 2 weeks after insemination (Serum hCG) an intrauterine pregnancy will be confirmed using a transvaginal ultrasound 2 weeks after a positive pregnancy test
Starting date	2010
Contact information	Dr. Galia Oron Rabin Medical Center, Petach-Tikva, Israel Email: orong@clalit.org.il Contact telephone: 972-3-9377492
Notes	https://ClinicalTrials.gov/show/NCT01237535

NCT01504139 2012

Trial name or title	The Luteal Phase After GnRHa Trigger - a Proof of Concept Study
Methods	RCT
Participants	Women undergoing IVF, age 25-40 years
Interventions	Intervention 1: hCG in the late follicular phase + luteal phase, when the follicles are over 12 mm FSH is replaced by hCG Intervention 2: hCGi n the follicular phase + luteal phase, hCG is given together with FSH from the beginning of the FSH stimulation. Intervention 3: LH in the luteal phase, LH replaces progesterone and estradiol in the luteal phase. Control: vaginal progesterone and estradiol in the luteal phase.The usual dose of vaginal progesterone and estradiol is given in the luteal phase.
Outcomes	Levels of progesterone in the mid-luteal phase
Starting date	2012
Contact information	Helen Olesen Elbaek The Fertility Clinic, Skive Regional Hospital, Denmark
Notes	Sponsor: Regionshospitalet Viborg, Skive https://ClinicalTrials.gov/show/NCT01504139

NCT01638026 2012

Trial name or title	Final Oocyte Maturation Via Administration of GnRH Agonists Followed By Luteal Support With hCG
Methods	RCT
Participants	Inclusion Criteria: patients who are eligible for in vitro fertilization using an antagonist protocol

NCT01638026 2012 *(Continued)*

	Exclusion Criteria: patients diagnosed with hypogonadotrophic hypogonadism, sensitivity to any of the drugs used in the study A patient enrolled in the study who, as a result of ovarian stimulation, responds in a way that puts her in risk of developing ovarian hyperstimulation, will be ultimately excluded from the study.
Interventions	In the study group women will receive GnRH agonist (decapeptyl 0.2 mg) for oocyte maturation, followed by ovum pick-up which will be performed 35 hours later. Embryo transfer will be performed 48-72 hours after ovum pick-up. Luteal support will include HCG 1500 IU.
Outcomes	Primary Outcome Measures: fertilization rate Secondary Outcome Measures: satisfaction, no. of oocyte, pregnancy rate, no. of embryos, quality of embryos
Starting date	2012
Contact information	Ronit Beck Fruchter, MD HaEmek Medical Center, Israel Contact telephone: 0097246494475 Email: beck_r@clalit.org.il
Notes	https://ClinicalTrials.gov/show/NCT01638026

NCT01790282 2013

Trial name or title	Is Adding E2 to P4 Luteal Support In High Responder Long Gn-RH Agonist ICSI Cycles Detrimental to Outcome?
Methods	RCT
Participants	Inclusion criteria: age<40 years, first ICSI cycle, third day FSH< 10 mIU/mL, serum E2 level on day of hCG administration <4,000 pg/mL, number of ova obtained >15 Exclusion Criteria: age 40 years or more, basal FSH 10 mIU/mL or more, eggs retrieved 15 or less, E2 level on day of hCG administration 4000 or more pg/ mL or more, repeat ICSI , need for PGD, presence of myoma, hydrosalpinx (unless disconnected)
Interventions	Estradiole - progesterone arm: estradile valaerate 2mg plus progesterone 100 mg/day support arm :E2 valerate 2mg three times /day are given to the arm cases plus P4 100 IM/day for 14 days starting on day of ovum pickup and single IM injection of 0.1 mg decapeptyl on day of ET Progesterone only arm: Starting on day of ovum pickup ICSI cases are given prontogest 100 mg IM / day plus single dose dose of treptorline 0.1mg is given sc on day of embryo transfer
Outcomes	Primary Outcome Measures: cycle pregnancy rate, pregnancy rate per started cycle Secondary Outcome Measures: implantation rate, multiple pregnancy rate, ongoing pregnancy rate ,live birth rate, implantation rate, multiple pregnancy rate, abortion rate
Starting date	2013
Contact information	Mohamad E GHanem, MD Mansoura Integrated Fertility Center Email: meghanem87@gmail.com

NCT01790282 2013 *(Continued)*

	Contact telephone: 00201223366955
Notes	http://clinicaltrials.gov/show/NCT01790282

NCT01850030

Trial name or title	A Double-Blind, Double-Dummy, Randomized, Two-arm, Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg Daily Versus Intravaginal Micronized Progesterone Capsules 600 mg Daily for Luteal Support in In-Vitro Fertilization (Lotus I)
Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	Intervention 1: Oral Dydrogesterone 10 mg tablets tid, Placebo intravaginal micronized progesterone 200 mg capsules tid Intervention 2: Intravaginal micronized progesterone 200 mg capsules tid, placebo oral dydrogesterone 10 mg tablets tid
Outcomes	Primary Outcome Measures: Pregnancy Rate Secondary Outcome Measures: Positive Pregnancy test rate, Rate of successful completion of pregnancy, Adverse Events, Status newborn - The gender, APGAR score, height, weight and head circumference, physical examination and any malformations of the newborn(s) will be recorded, Adverse Events At Study Completion (about 10 months after IVF)
Starting date	2015
Contact information	Darline Cheatham-Seitz, MD, PhD Abbott
Notes	Sponsors: Abbott, Quintiles https://ClinicalTrials.gov/show/NCT01850030

NCT01863680 2013

Trial name or title	Open-label, Single-arm, Multicenter Phase III Trial to Evaluate the Efficacy and Safety of COL-1620 8% Vaginal Progesterone Gel for Luteal Phase Support in In-vitro Fertilization and Embryo Transfer (IVF/ET) Cycles in Japanese Women
Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	COL-1620 vaginal progesterone gel (1.125 grams of progesterone gel containing 90 milligram that is 8% gel) will be administered by the vaginal route once daily, from the day of ovum pick-up (OPU) until Week 12, or until the confirmation of miscarriage or extra-uterine pregnancy.
Outcomes	Primary Outcome Measures: Percentage of subjects with Clinical pregnancy per Embryo Transfer Secondary Outcome Measures: Percentage of subjects with Biochemical pregnancy per Embryo Transfer, Serum progesterone level

NCT01863680 2013 *(Continued)*

Starting date	2013
Contact information	Unknown
Notes	Sponsorship: Merck KGaA Based in Japan http://clinicaltrials.gov/show/NCT01863680

NCT01980680 2013

Trial name or title	The Exogenous Progesterone Free Luteal Phase After GnRHa Trigger - a Randomized Controlled Pilot Study in Normo-responder IVF Patients
Methods	RCT
Participants	Inclusion Criteria: Age between 20 and 40, Normal menstrual cycles: 25-34 days Oligomenorrhea/amenorrhea or polycystic syndrome (defined according to the Rotterdam criteria 2004), BMI >18 and <35 kg/m2 Exclusion Criteria: Patients with >14 follicles on day of trigger, Previous hyperresponse with OHSS development, Previous low response (less than 3 oocytes on a high dose of FSH stimulation), Endocrine disorders
Interventions	Intervention: Agonist trigger Buserelin 0,5 mg and Pregnyl (hCG) Control: hCG trigger Pregnyl (hCG) and Progesterone and Estradiol
Outcomes	Primary Outcome Measures: Ongoing pregnancy rate per patient
Starting date	2013
Contact information	Peter S Humaidan, MD Email: peter.humaidan@sygehusviborg.dk Contact telephone: +45 89 27 40 13
Notes	http://clinicaltrials.gov/show/NCT01980680

NCT02053779 2014

Trial name or title	The Impact of a Single Dose of GnRH Agonist (Triptorelin 0,1 mg) at the Time of Implantation on the Reproductive Outcome in IVF Cycles Triggered by a GnRH Agonist Followed by a Small Bolus of HCG the Day of Oocyte Retrieval
Methods	RCT
Participants	Inclusion Criteria: Female age < 40 years, Baseline FSH and LH < 12 IU/l, Body Mass Index > 18 and < 35 kg/m2, No uterine (fibroids, mullerian malformations), ovarian (endometrioma) or adnexa (hydrosalpinx) abnormalities, Patients with at least one embryo at transfer time Exclusion Criteria: Very high risk of OHSS (> 30 follicles > 12 mm the day of ovulation triggering), Reduced ovarian reserve, Fertilization failure, Severe endocrinopathy, Azoospermia

NCT02053779 2014 *(Continued)*

Interventions	Intervention: Triptorelin 0.1 mg administered subcutaneously 6 days after ovum pick-up (OPU) in IVF/ICSI cycles triggered by triptorelin 0.2 mg followed by hCG 1500 iu the day of OPU. Control: Placebo (1 ml Nacl 0.9% solution) administered subcutaneously 6 days after ovum pick-up (OPU) in IVF/ICSI cycles triggered by triptorelin 0.2 mg followed by hCG 1500 iu the day of OPU.
Outcomes	Primary Outcome Measures: implantation rate, number of gestational sacs per number of embryos transferred Secondary Outcome Measures: chemical pregnancy, confirmed by beta-hCG 14 days post embryo transfer, clinical pregnancy, appearance of yolk sac with foetal heart beat at 7 weeks of gestation, live birth, birth of baby beyond 28 weeks of gestation Other Outcome Measures: ovarian hyperstimulation syndrome OHSS
Starting date	2014
Contact information	Dr Abdelhamid benmachiche Ibn roch infertility centre, cité boussouf, Constantine Algeria Email: benmachiche@gmail.com Contact telepgone: 00213773112786
Notes	http://clinicaltrials.gov/show/NCT02053779

NCT02114645 2014

Trial name or title	To Evaluate the Effect of GnRH Agonist Administered in the Luteal Phase on ART Cycle Outcomes in Both GnRH Agonist and GnRH Antagonist Treated Ovarian Stimulation Protocols
Methods	RCT crossover
Participants	Inclusion Criteria: Couples undergoing ART with their own gametes, Couples having at least one good embryo available for transfer, Normoresponder, Infertility etiology is unexplained, ovulation triggered by intramuscular injection of 10000 IU of HCG Exclusion Criteria: Patients older than 38 years old, High and poor responder patients
Interventions	Intervention 1: Long GnRH agonist protocol, Luteal Phase Support: Vaginal progesterone+oral estradiol valerate subcutaneous 0.5mg leuprolide acetate fifth and tenth day after embryo transfer Control 1: Long GnRH agonist protocol, Luteal Phase Support: Vaginal progesterone + 4mg oral estradiol valerate Intervention 2: GnRH antagonist protocol, Luteal Phase Support: Vaginal progesterone + 4mg oral estradiol valerate + subcutaneous 0.5mg leuprolide acetate fifth and tenth day after embryo transfer Control 2: GnRH antagonist protocol, Luteal Phase Support: Vaginal progesterone + 4mg oral estradiol valerate
Outcomes	Primary Outcome Measures: Live Birth Rate Secondary Outcome Measures: Ongoing pregnancy, miscarriage, OHSS
Starting date	2014
Contact information	Nagihan Cengaver, MD

NCT02114645 2014 *(Continued)*

	Zekai Tahir Burak Women's Health Research and Education Hospital Email: nagihancengaver@gmail.com Contact telephone: +905556309298
Notes	http://clinicaltrials.gov/show/NCT02114645

NCT02262416 2014

Trial name or title	A Prospective Randomised Controlled Trial of GnRH Agonist and Progesterone Versus Progesterone Only for Luteal Phase Support in Antagonist Cycles
Methods	RCT
Participants	Inclusion Criteria: Single embryo transfer, Antagonist cycle with HCG trigger, Use of progesterone as luteal phase support (crinone or progesterone pessary), Women undergoing their first IVF cycle with TFC, Age 18-42 inclusive Exclusion Criteria: No or frozen embryo transfer planned, Use of other luteal support, Known contraindication to the use of GnRH analogue
Interventions	Intervention: 0.5mg Leuprolide acetate injection Control: Normal saline of equivalent volume
Outcomes	Primary Outcome Measures: live birth, ongoing pregnancy Secondary Outcome Measures: pregnancy, ovarian hyperstimulation syndrome
Starting date	2014
Contact information	Queensland Fertility Group, Brisbane, Queensland, Australia, 4000
Notes	http://clinicaltrials.gov/show/NCT02262416

NCT02312076 2014

Trial name or title	Gonadotropin Releasing Hormone Agonist for Luteal Phase Support in Long Gonadotropin Releasing Hormone Agonist Protocol Cycles
Methods	RCT
Participants	Inclusion Criteria: Women subjected to ICSI through controlled ovarian hyperstimulation (COH) with pituitary downregulation by GnRHa. Exclusion Criteria: Moderate or severe endometriosis, Hydrosalpinx, Uterine abnormalities, Myoma, Previous uterine surgery.
Interventions	Intervention: Luteal phase support will be continued by the same regimen started on the day of oocytes retrieval until 2 weeks after embryo transfer (ET) with subcutaneous administration of a single dose (0.2 mg) of GnRHa (Triptorelin) 6 days after oocyte retrieval Control: No GnRHa administration in luteal phase
Outcomes	Primary Outcome Measures: Clinical pregnancy rate, Number of clinical pregnancies

NCT02312076 2014 *(Continued)*

	Secondary Outcome Measures: Implantation rate, Miscarriage rate
Starting date	2014
Contact information	Dr Mohamed S Abdelhafez Mansoura University Email: msabdelhafez@gmail.com Contact telephone: +201124442800
Notes	http://clinicaltrials.gov/show/NCT02312076

NCT02312089 2014

Trial name or title	Gonadotropin Releasing Hormone Agonist for Luteal Phase Support in Gonadotropin Releasing Hormone Antagonist Protocol Cycles
Methods	RCT
Participants	Inclusion Criteria: Women subjected to ICSI through controlled ovarian hyperstimulation (COH) with pituitary downregulation by GnRH antagonist. Exclusion Criteria: Moderate or severe endometriosis, Hydrosalpinx, Uterine abnormalities, Myoma, Previous uterine surgery.
Interventions	Intervention: Luteal phase support will be continued by the same regimen started on the day of oocytes retrieval until 2 weeks after embryo transfer (ET) with subcutaneous administration of a single dose (0.2 mg) of GnRHa (Triptorelin) 6 days after oocyte retrieval Control: No GnRHa administration in luteal phase
Outcomes	Primary Outcome Measures: Clinical pregnancy rate, Number of clinical pregnancies Secondary Outcome Measures: Implantation rate, Miscarriage rate
Starting date	2014
Contact information	Dr Mohamed S Abdelhafez Mansoura University Email: msabdelhafez@gmail.com Contact telephone: +201124442800
Notes	http://clinicaltrials.gov/show/NCT02312089

NCT02316626 2014

Trial name or title	Subcutaneous Progesterone Versus Vaginal Progesterone Gel for Luteal Phase Support in Gonadotropin Ovarian Stimulation for Intrauterine Insemination: a Pilot Randomized Controlled Study
Methods	RCT

NCT02316626 2014 *(Continued)*

Participants	Inclusion Criteria: <38 years of age with either primary or secondary infertility for at least 1 years; body mass index between 19 and 30 kg/m2; Day 2 serum FSH <15 IU/ml; normal serum prolactin level; normal uterine cavity on hysterosalpingography or hysteroscopy. Exclusion Criteria: female partners with previous ovarian surgery, one ovary, polycystic ovaries on ultrasound examination, other endocrine abnormalities (i.e., polycystic ovarian syndrome, thyroid disorders, hyperprolactinemia, hypogonadotropic hypogonadism), diminished ovarian reserve (basal FSH level >15 IU/mL), or age of >38 years
Interventions	Intervention: Luteal phase support cycles will involve once-daily administration of 25 mg of SC P from the day after insemination for 14 days. Control: Luteal phase support cycles will involve once-daily administration of 90 mg vaginal gel from the day after insemination for 14 days.
Outcomes	Primary Outcome Measures: Clinical pregnancy Secondary Outcome Measures: Side effects
Starting date	2014
Contact information	Fulvio Zullo, MD, PhD Magna Graecia University of Catanzaro; Email: zullo@unicz.it Contact telephone: 00390961883234
Notes	http://clinicaltrials.gov/show/NCT02316626

NCT02357654 2015

Trial name or title	GnRH for Luteal Support in IVF/ICSI/FET Cycles
Methods	RCT
Participants	Inclusion Criteria: women undergoing IVF/ICSI or frozen embryo transfers (FET) that less than 40 years old. Exclusion Criteria: day 3 transfers
Interventions	Intervention: GnRH agonist Control: placebo
Outcomes	Primary Outcome Measure: Live birth per transfer Secondary Outcome Measure: Implantation rates, clinical pregnancy, rates of OHSS
Starting date	2015
Contact information	Peter G McGovern, MD University Reproductive Associates Email: mcgovepg@gmail.com Contact telephone: 201-288-6330

NCT02357654 2015 *(Continued)*

Notes	https://ClinicalTrials.gov/show/NCT02357654

NCT02491437

Trial name or title	A Randomized, Open-label, Two-arm, Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg Daily Versus Crinone 8% Intravaginal Progesterone Gel 90 mg Daily for Luteal Support in In-Vitro Fertilization (LOTUS II)
Methods	RCT
Participants	Infertile women undergoing IVF
Interventions	Intervention: Dydrogesterone tablets 3x10 mg Control: Crinone 8% intravaginal progesterone gel 90 mg
Outcomes	Primary Outcome Measures: Pregnancy rate Secondary Outcome Measures:Positive Pregnancy test rate, Rate of successful completion of pregnancy, Incidence of live births and healthy newborns Adverse Events, physical examination newborn
Starting date	2015
Contact information	Erik van Leeuwen, MSc The First Affiliated Hospital of Nanjing Medical University Email: erik.vanleeuwen@abbott.com Contact telephone: +31294479241
Notes	Sponsorship: Abbott, PRA Health Sciences, Datamap https://ClinicalTrials.gov/show/NCT02491437

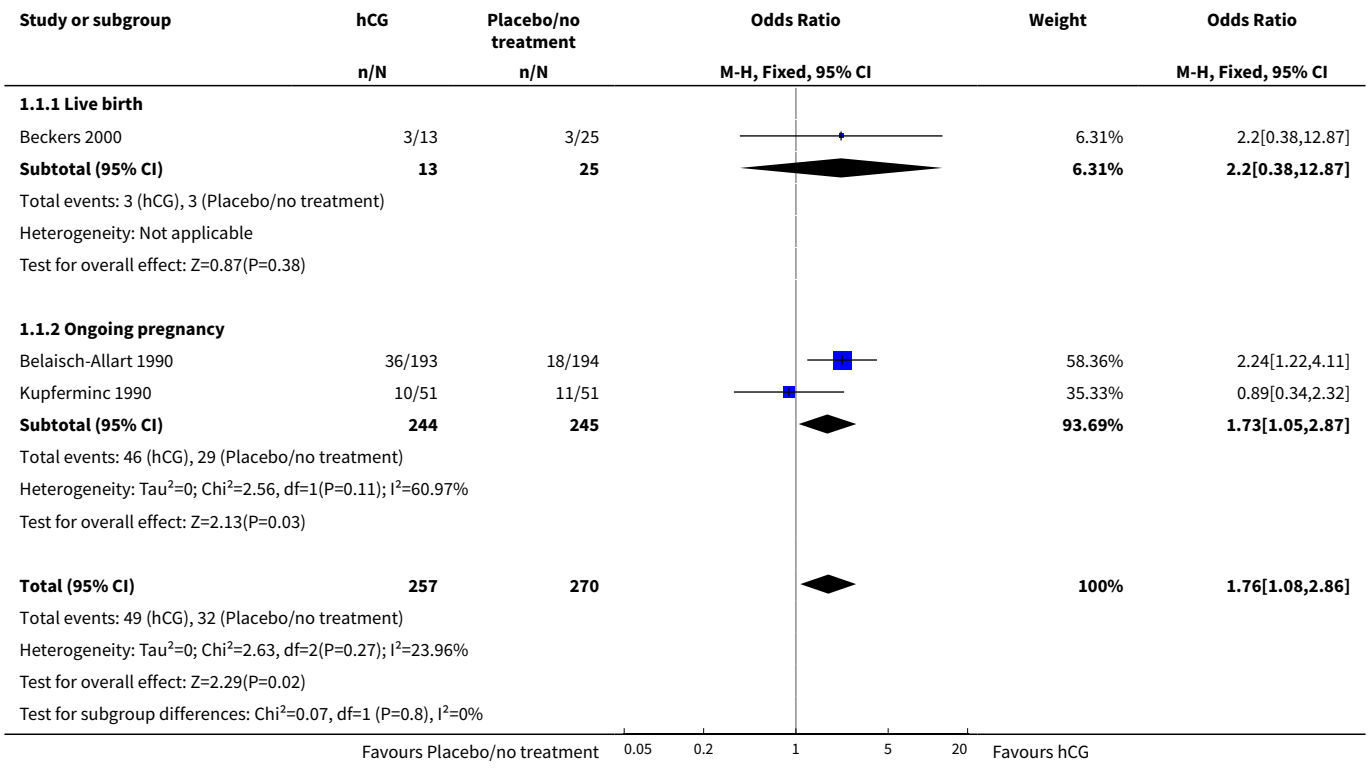
DATA AND ANALYSES

Comparison 1. Human chorionic gonadotropin (hCG) vs placebo or no treatment

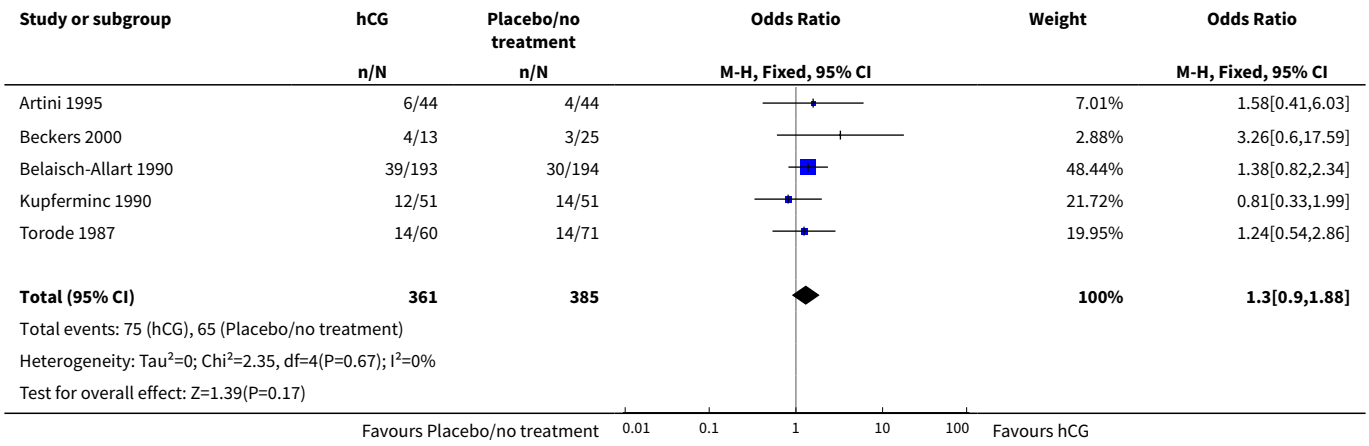
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancy rate	3	527	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [1.08, 2.86]
1.1 Live birth	1	38	Odds Ratio (M-H, Fixed, 95% CI)	2.2 [0.38, 12.87]
1.2 Ongoing pregnancy	2	489	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [1.05, 2.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Clinical pregnancy rate	5	746	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.90, 1.88]
3 Clinical pregnancy rate: subgroup analysis by COH method	5	746	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.90, 1.88]
3.1 Human gonadotropins with clomiphene citrate without GnRH agonists	1	131	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.54, 2.86]
3.2 Human gonadotropins with or without GnRH agonists	3	513	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.94, 2.40]
3.3 Human gonadotropins with or without GnRH antagonists	1	102	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.33, 1.99]
4 Miscarriage rate	2	140	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.37, 6.21]
5 OHSS	1	387	Odds Ratio (M-H, Fixed, 95% CI)	4.28 [1.91, 9.60]

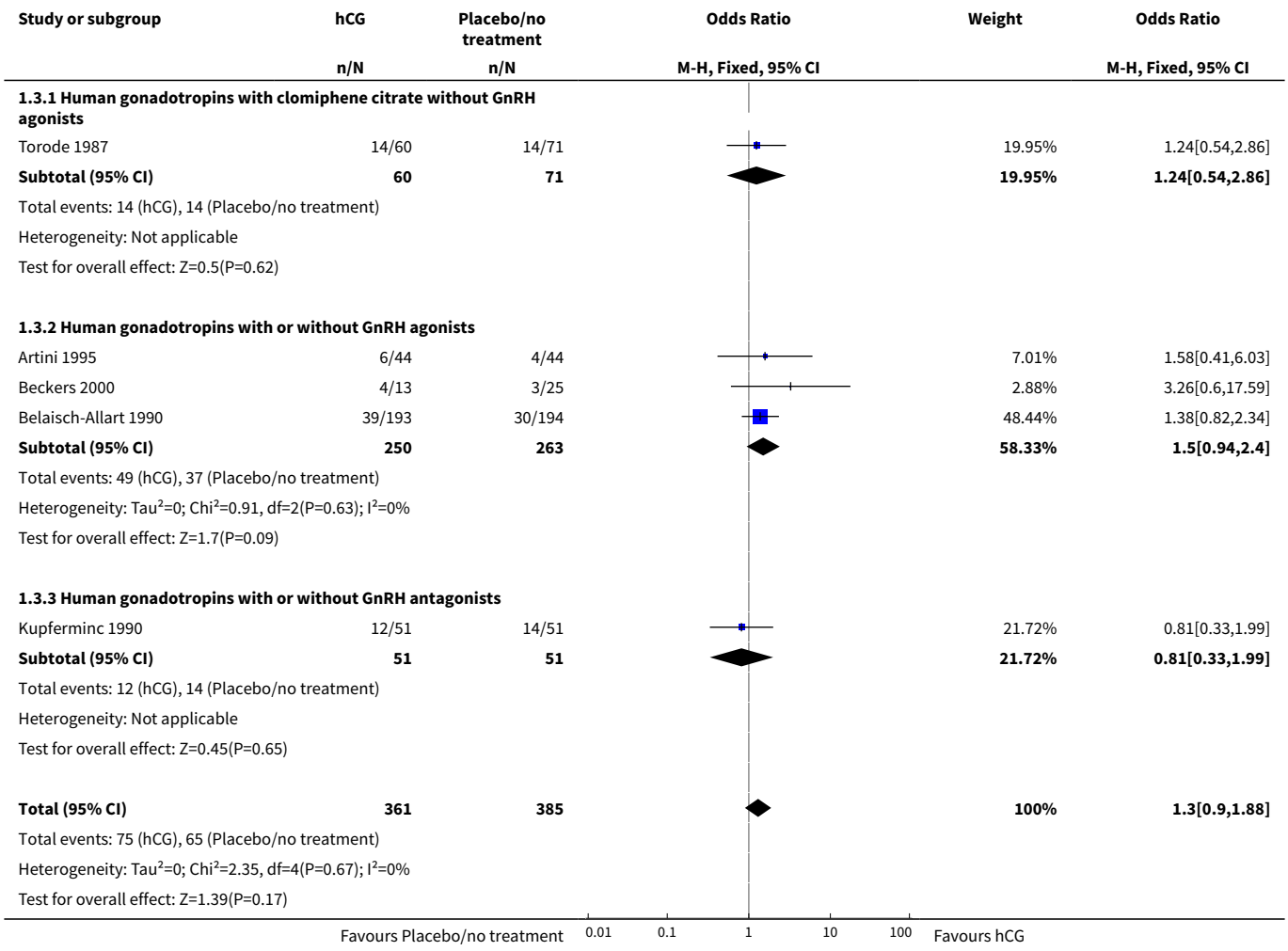
Analysis 1.1. Comparison 1 Human chorionic gonadotropin (hCG) vs placebo or no treatment, Outcome 1 Live birth/ongoing pregnancy rate.

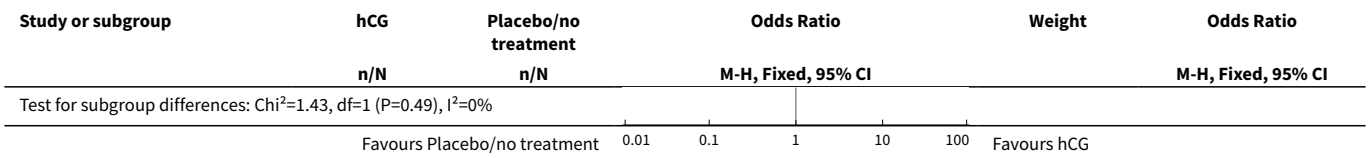


Analysis 1.2. Comparison 1 Human chorionic gonadotropin (hCG) vs placebo or no treatment, Outcome 2 Clinical pregnancy rate.

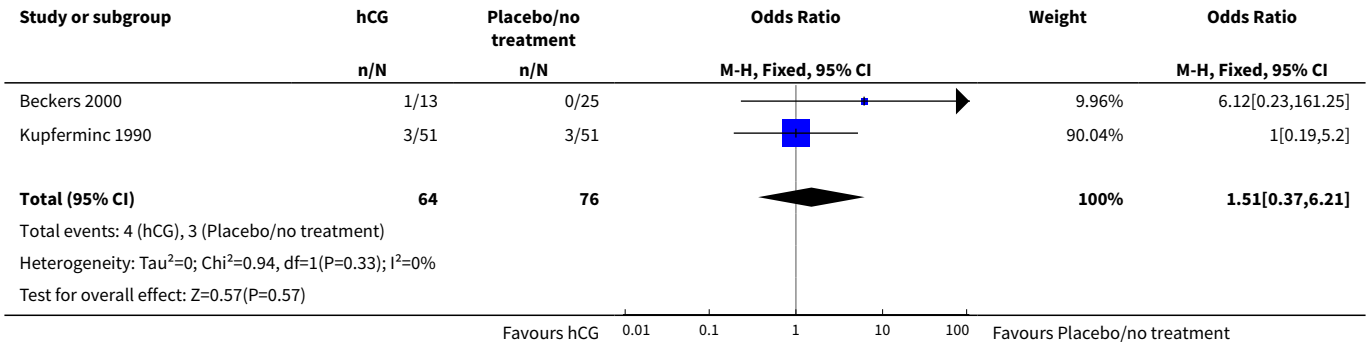


Analysis 1.3. Comparison 1 Human chorionic gonadotropin (hCG) vs placebo or no treatment, Outcome 3 Clinical pregnancy rate: subgroup analysis by COH method.

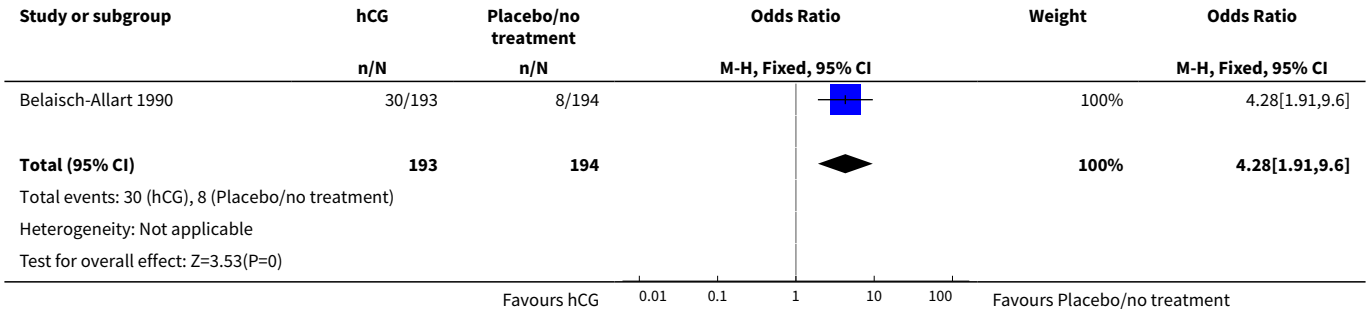




Analysis 1.4. Comparison 1 Human chorionic gonadotropin (hCG) vs placebo or no treatment, Outcome 4 Miscarriage rate.



Analysis 1.5. Comparison 1 Human chorionic gonadotropin (hCG) vs placebo or no treatment, Outcome 5 OHSS.



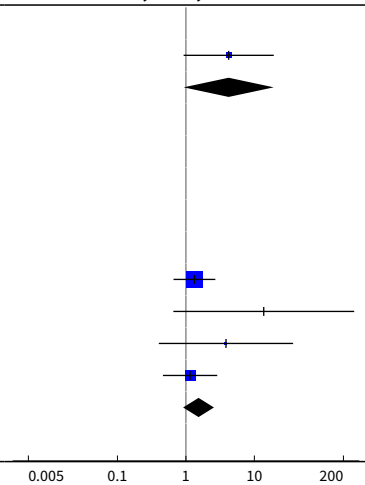
Comparison 2. Progesterone vs placebo or no treatment

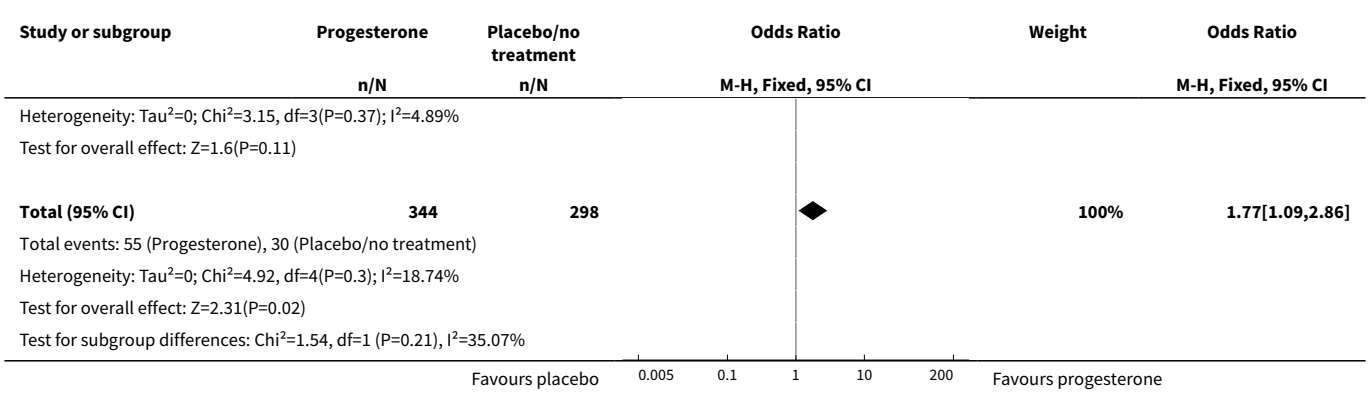
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancy rate	5	642	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.09, 2.86]
1.1 Live birth	1	156	Odds Ratio (M-H, Fixed, 95% CI)	4.21 [0.93, 19.18]
1.2 Ongoing pregnancy	4	486	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.91, 2.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Clinical pregnancy rate	7	841	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.30, 2.75]
3 Clinical pregnancy: subgroup analysis by COH method	7	841	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.30, 2.75]
3.1 Clomiphene citrate alone without GnRH agonists	1	56	Odds Ratio (M-H, Fixed, 95% CI)	5.0 [0.54, 45.92]
3.2 Human gonadotropins with clomiphene citrate without GnRH agonists	2	306	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.86, 2.90]
3.3 Human gonadotropins with or without GnRH agonists	4	479	Odds Ratio (M-H, Fixed, 95% CI)	1.99 [1.22, 3.26]
4 Clinical pregnancy: subgroup analysis by treatment duration	7	841	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.30, 2.75]
4.1 Stop at pregnancy test	3	257	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.74, 2.74]
4.2 Up to 12 weeks	4	584	Odds Ratio (M-H, Fixed, 95% CI)	2.17 [1.37, 3.43]
5 Miscarriage rate	3	425	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.49, 3.03]
6 Multiple pregnancy	1	34	Odds Ratio (M-H, Fixed, 95% CI)	5.87 [0.22, 155.76]

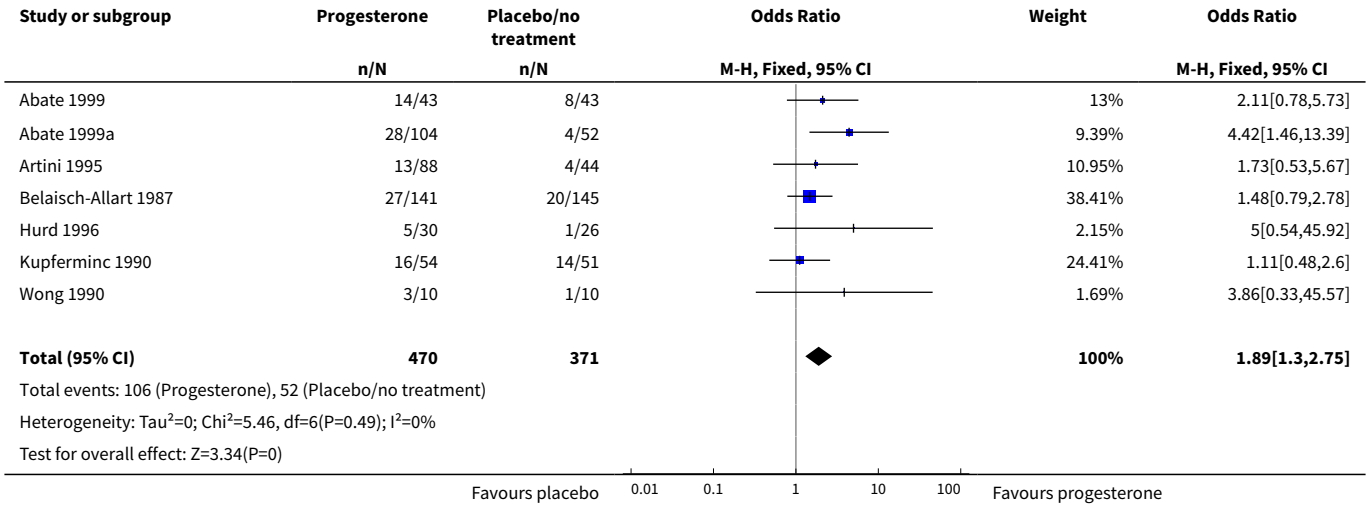
Analysis 2.1. Comparison 2 Progesterone vs placebo or no treatment, Outcome 1 Live birth/ongoing pregnancy rate.

Study or subgroup	Progesterone n/N	Placebo/no treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Live birth					
Abate 1999a	15/104	2/52		8.9%	4.21[0.93,19.18]
Subtotal (95% CI)	**104**	**52**		**8.9%**	**4.21[0.93,19.18]**
Total events: 15 (Progesterone), 2 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.86(P=0.06)					
2.1.2 Ongoing pregnancy					
Belaisch-Allart 1987	20/141	16/145		52.79%	1.33[0.66,2.69]
Colwell 1991	3/15	0/24		1.19%	13.72[0.66,286.96]
Hurd 1996	4/30	1/26		3.62%	3.85[0.4,36.82]
Kupferminc 1990	13/54	11/51		33.5%	1.15[0.46,2.87]
Subtotal (95% CI)	**240**	**246**		**91.1%**	**1.53[0.91,2.57]**
Total events: 40 (Progesterone), 28 (Placebo/no treatment)					

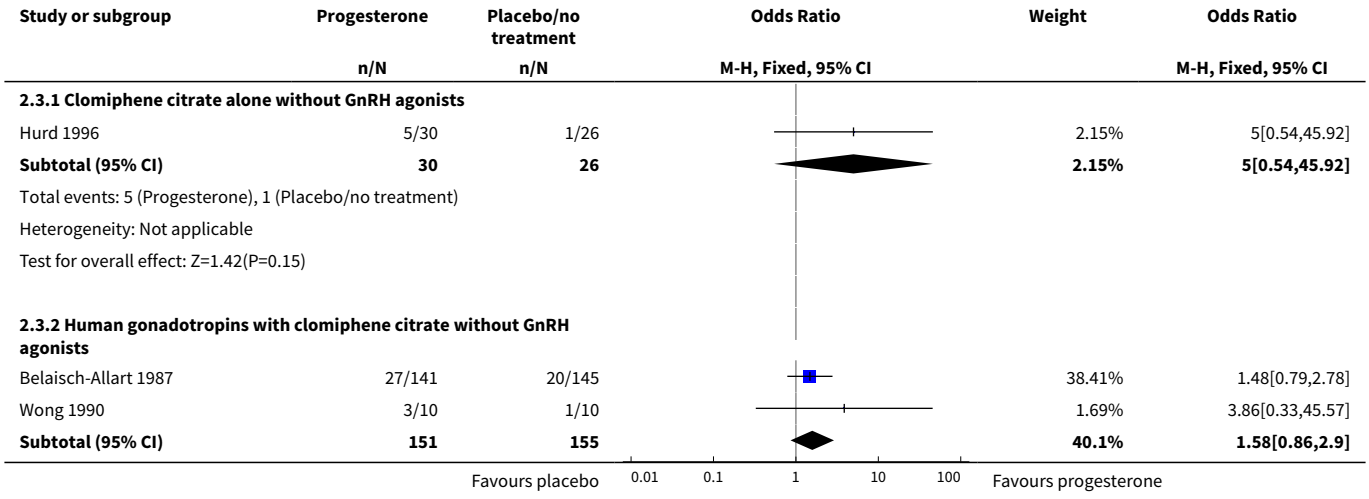


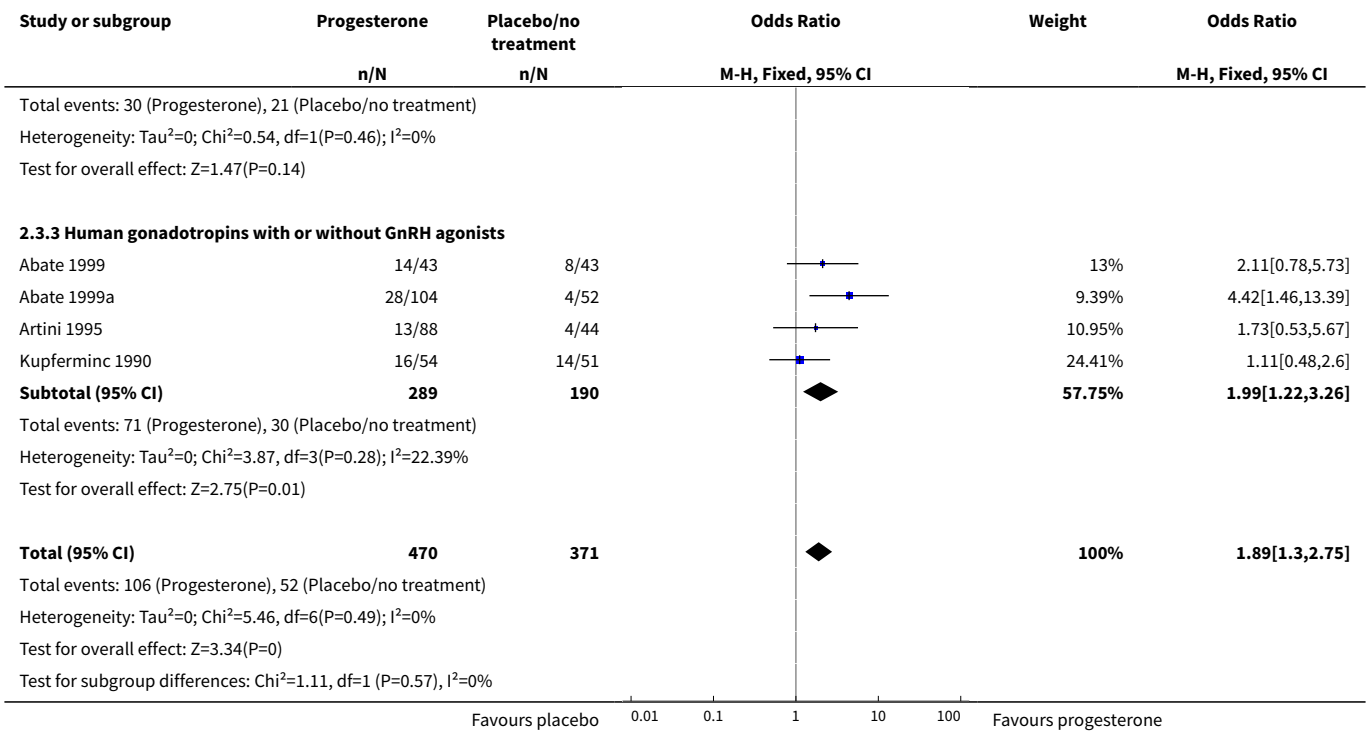


Analysis 2.2. Comparison 2 Progesterone vs placebo or no treatment, Outcome 2 Clinical pregnancy rate.

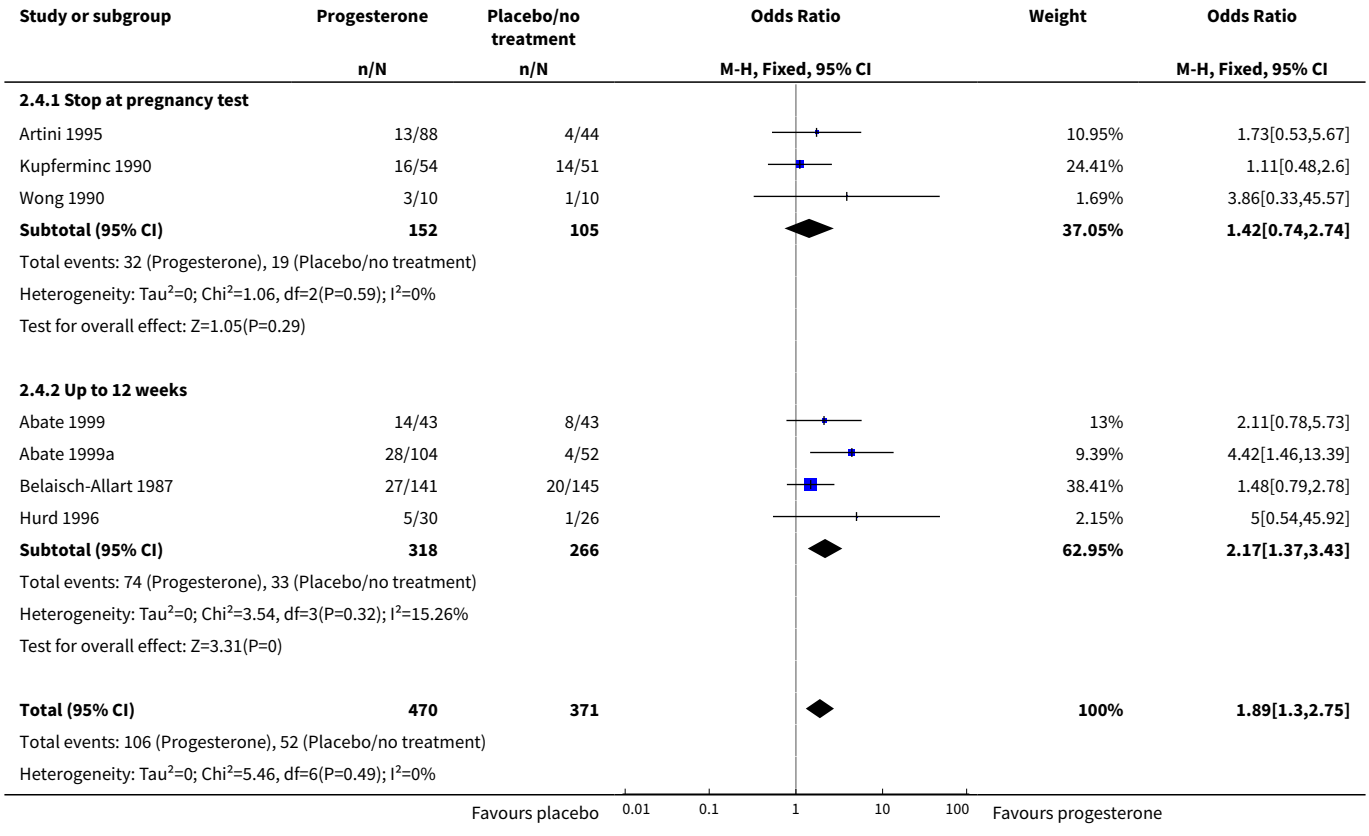


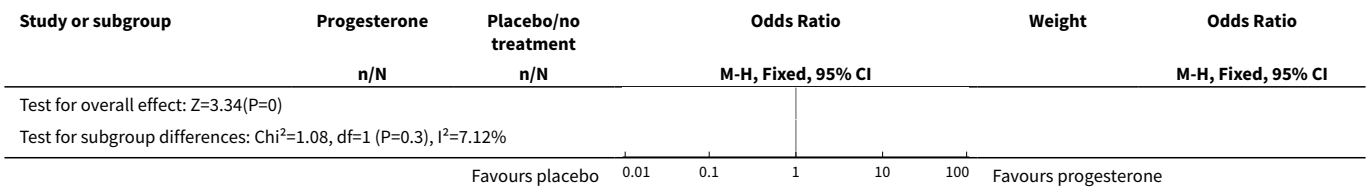
Analysis 2.3. Comparison 2 Progesterone vs placebo or no treatment, Outcome 3 Clinical pregnancy: subgroup analysis by COH method.



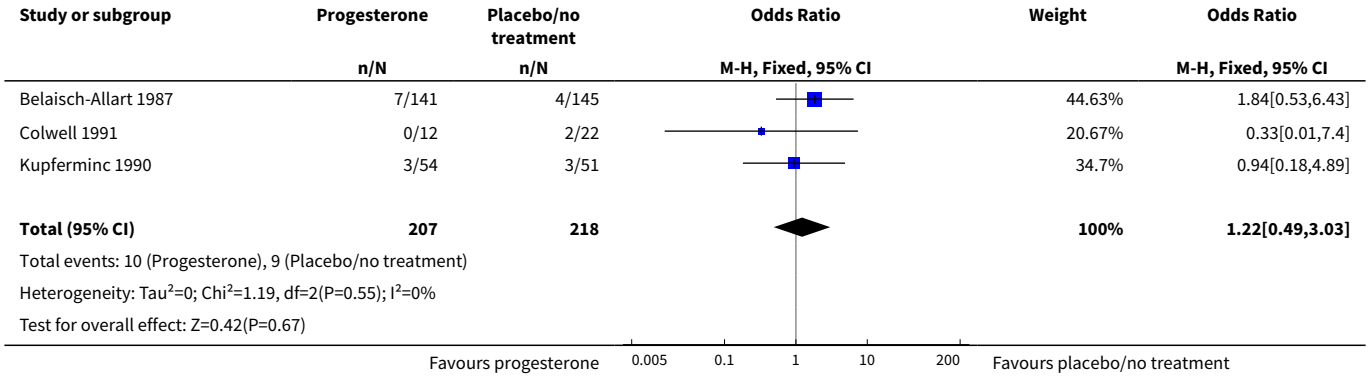


Analysis 2.4. Comparison 2 Progesterone vs placebo or no treatment, Outcome 4 Clinical pregnancy: subgroup analysis by treatment duration.

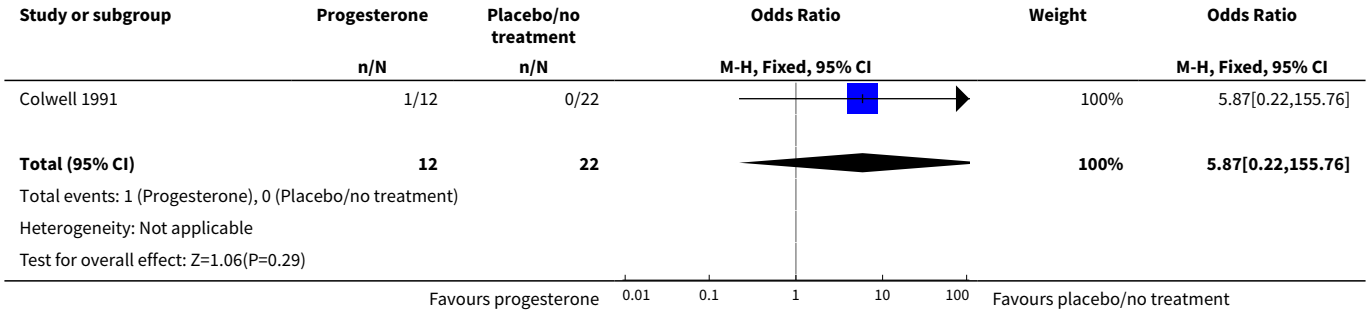




Analysis 2.5. Comparison 2 Progesterone vs placebo or no treatment, Outcome 5 Miscarriage rate.



Analysis 2.6. Comparison 2 Progesterone vs placebo or no treatment, Outcome 6 Multiple pregnancy.



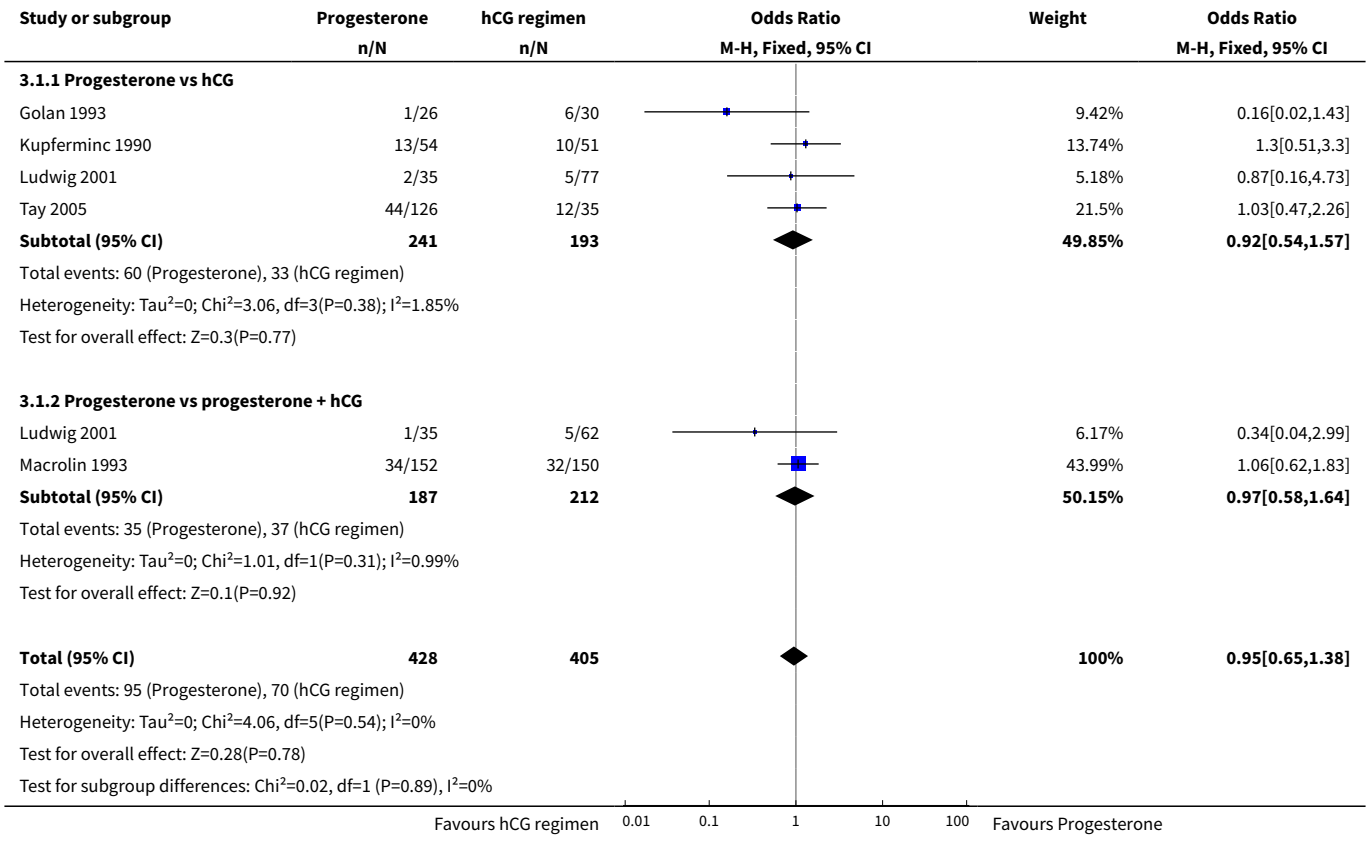
Comparison 3. Progesterone vs hCG regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth or ongoing pregnancy rate	5	833	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.38]
1.1 Progesterone vs hCG	4	434	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.54, 1.57]
1.2 Progesterone vs progesterone + hCG	2	399	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.58, 1.64]

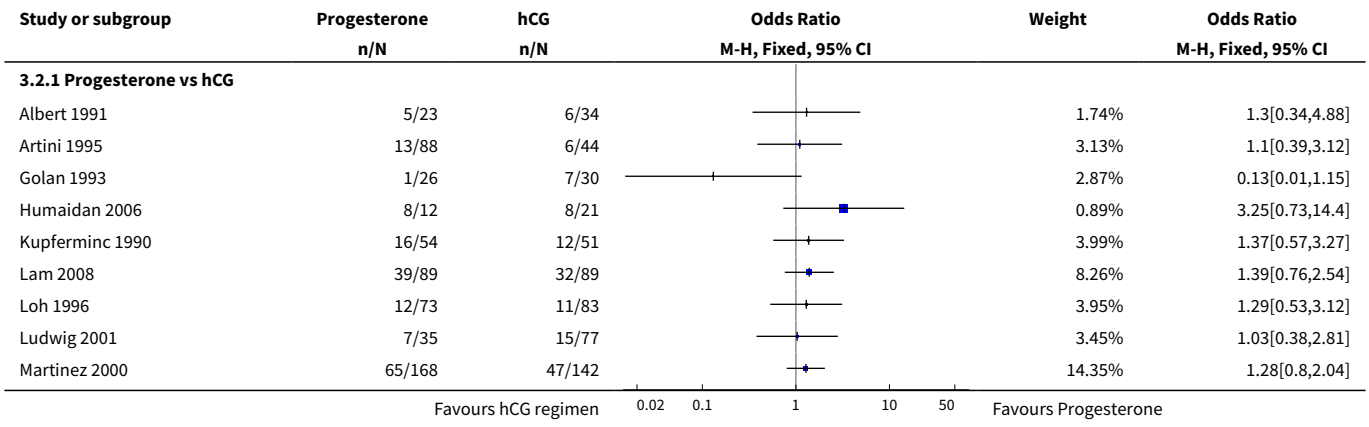
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Clinical pregnancy rate	16	2355	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.90, 1.30]
2.1 Progesterone vs hCG	11	1378	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.94, 1.53]
2.2 Progesterone vs progesterone + hCG	7	977	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.25]
3 Clinical pregnancy: progesterone vs progesterone + hCG: subgroup analysis by COH method	4	722	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.29]
3.1 Human gonadotropins with clomiphene citrate without GnRH agonists	1	20	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.22, 13.41]
3.2 Human gonadotropins with or without GnRH agonists	3	702	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.63, 1.27]
4 Clinical pregnancy: progesterone vs hCG: subgroup analysis by treatment duration	7	872	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.85, 1.58]
4.1 Stop at pregnancy test	6	783	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.84, 1.61]
4.2 Up to 12 weeks when pregnant	1	89	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.46, 2.84]
5 OHSS	5	1293	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.30, 0.71]
5.1 Progesterone vs hCG	4	615	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.32, 1.00]
5.2 Progesterone vs progesterone + hCG	3	678	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.18, 0.69]
6 Miscarriage rate	5	832	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.66, 2.31]
6.1 Progesterone vs hCG	5	735	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.66, 2.55]
6.2 Progesterone vs progesterone + hCG	1	97	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.15, 5.06]
7 Multiple pregnancy	1	209	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.07, 2.65]
7.1 Progesterone vs hCG	1	112	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.07, 7.23]

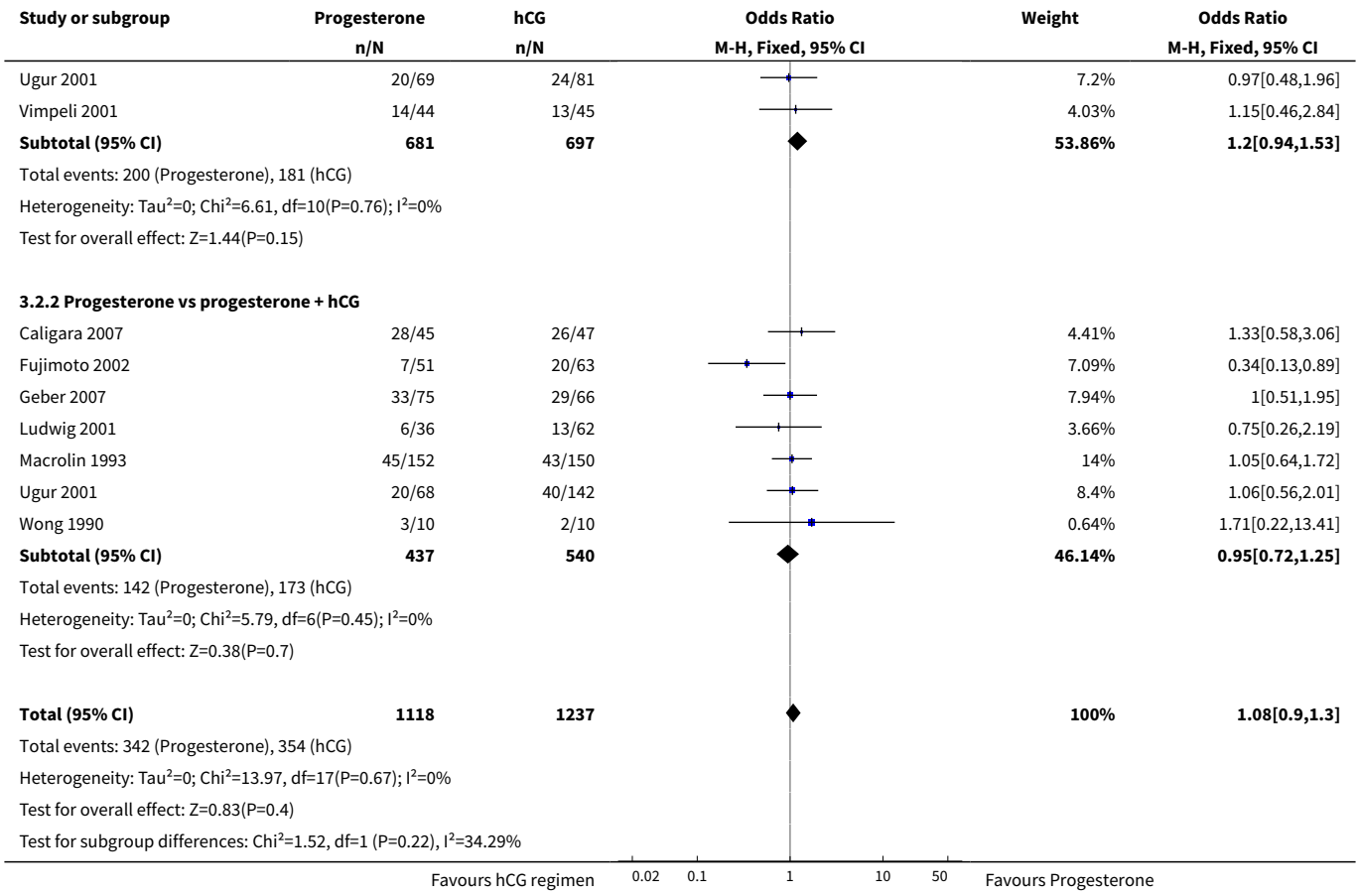
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Progesterone vs progesterone + hCG	1	97	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.01, 4.77]

Analysis 3.1. Comparison 3 Progesterone vs hCG regimens, Outcome 1 Live birth or ongoing pregnancy rate.

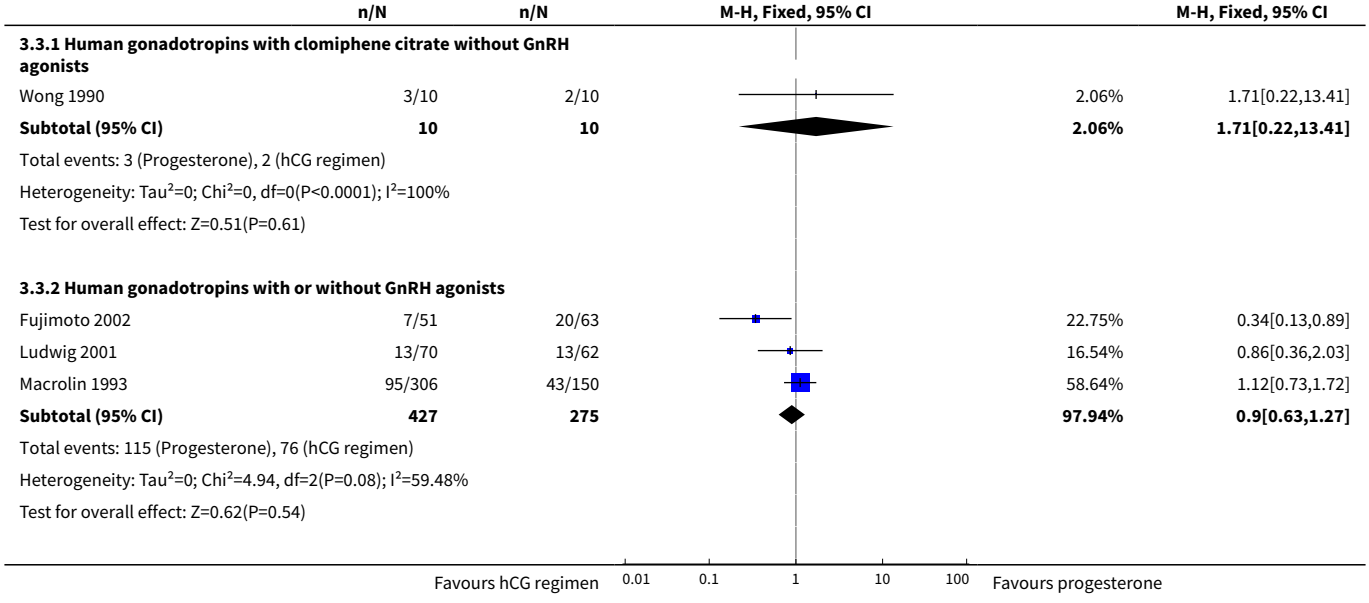


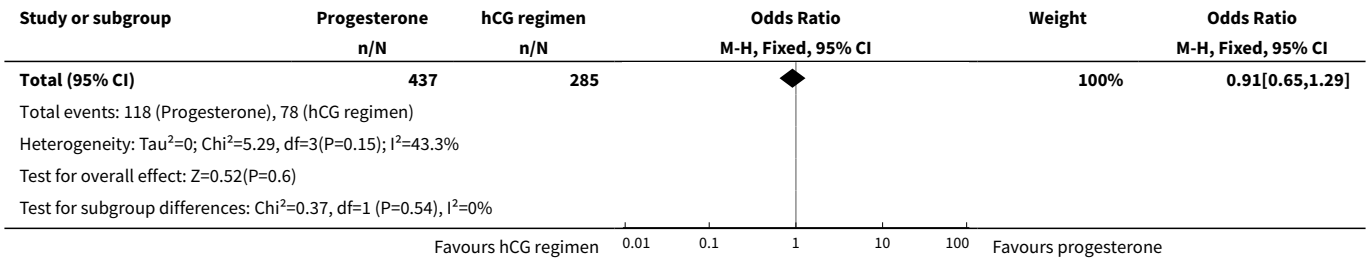
Analysis 3.2. Comparison 3 Progesterone vs hCG regimens, Outcome 2 Clinical pregnancy rate.



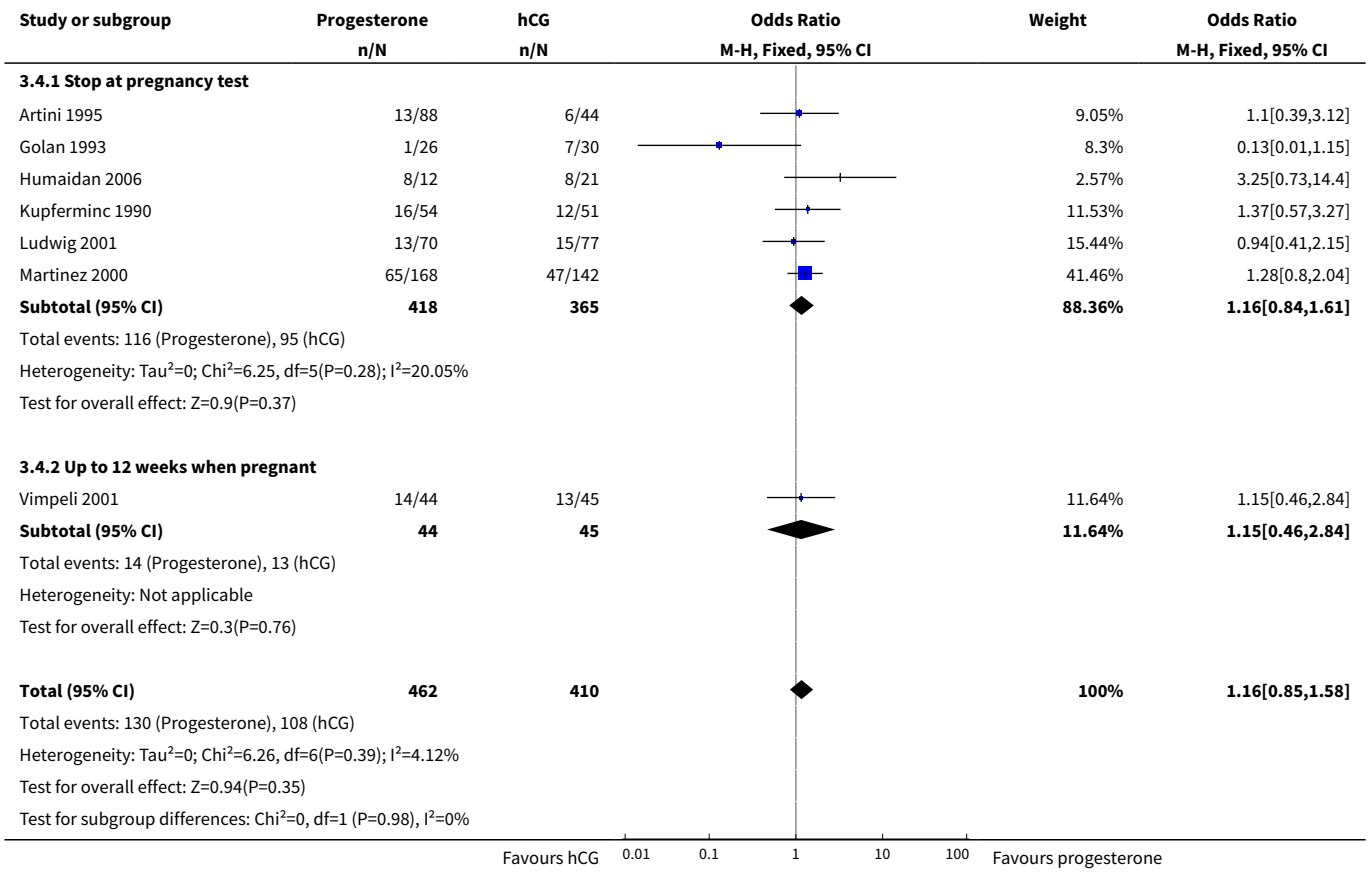


Analysis 3.3. Comparison 3 Progesterone vs hCG regimens, Outcome 3 Clinical pregnancy: progesterone vs progesterone + hCG: subgroup analysis by COH method.

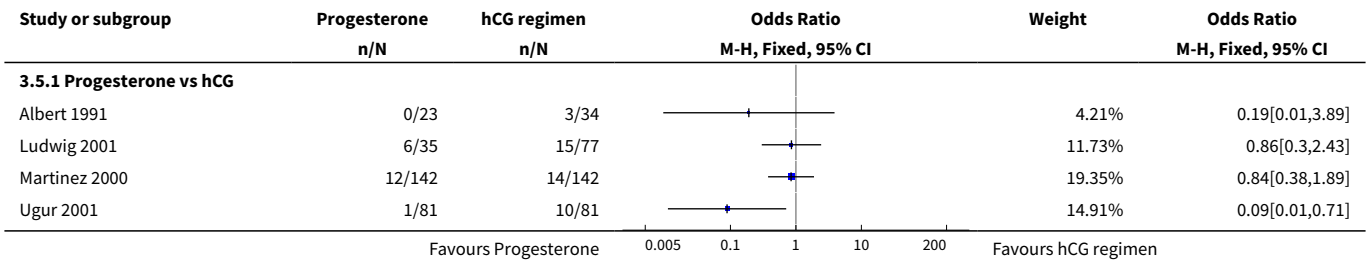


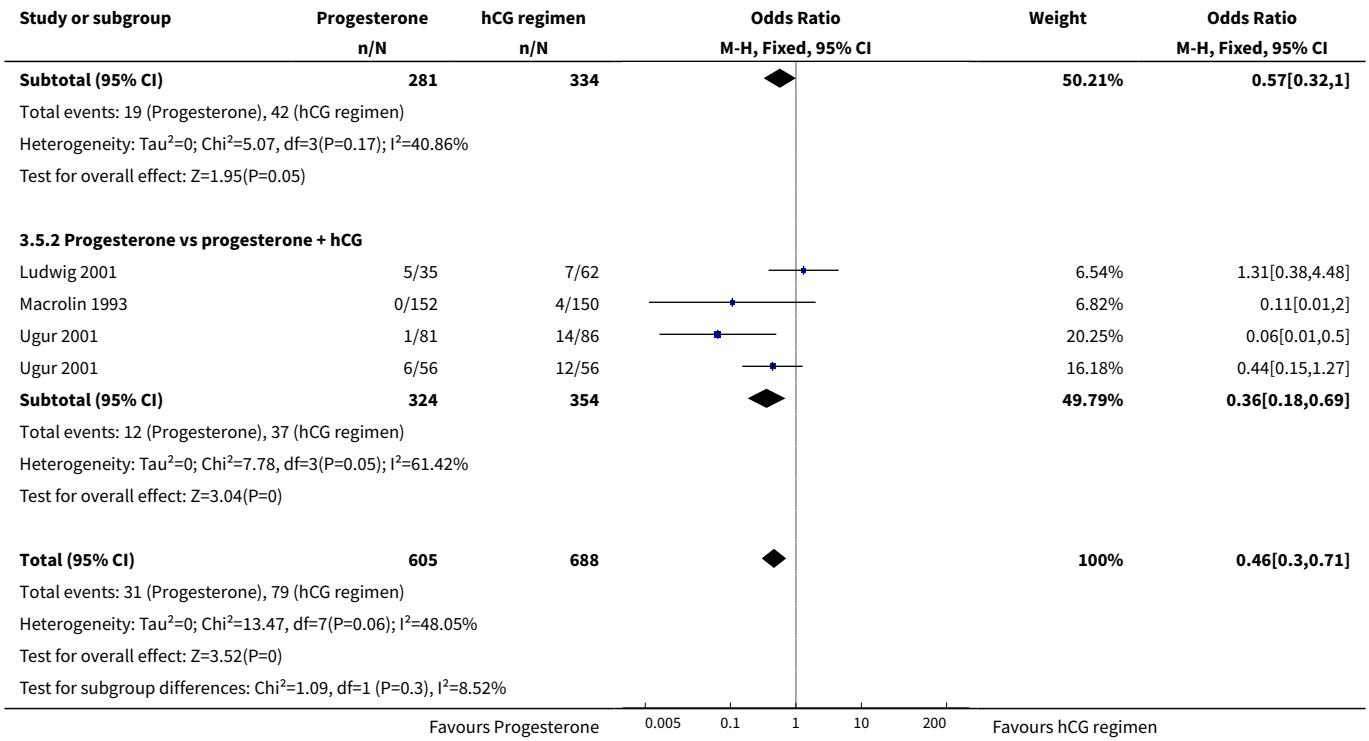


Analysis 3.4. Comparison 3 Progesterone vs hCG regimens, Outcome 4 Clinical pregnancy: progesterone vs hCG: subgroup analysis by treatment duration.

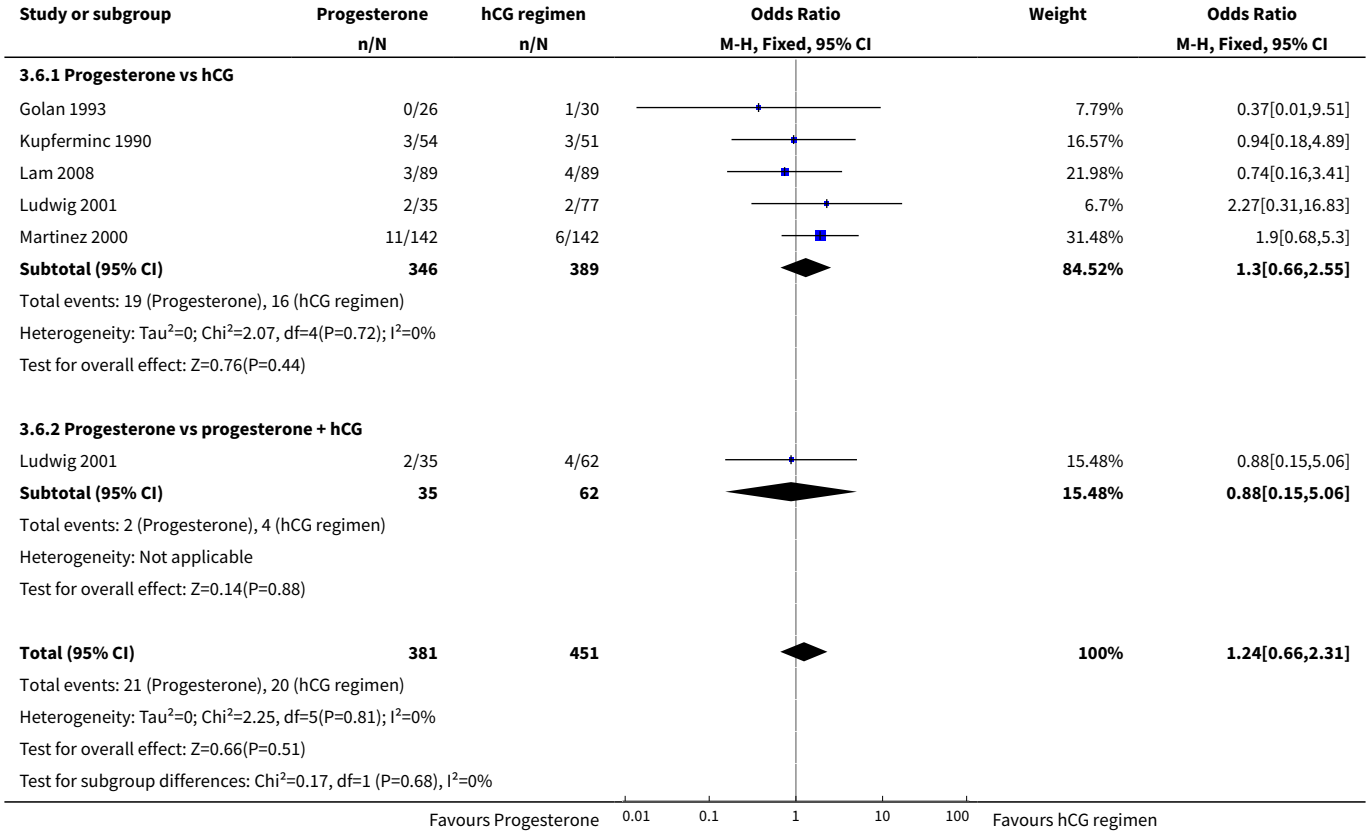


Analysis 3.5. Comparison 3 Progesterone vs hCG regimens, Outcome 5 OHSS.

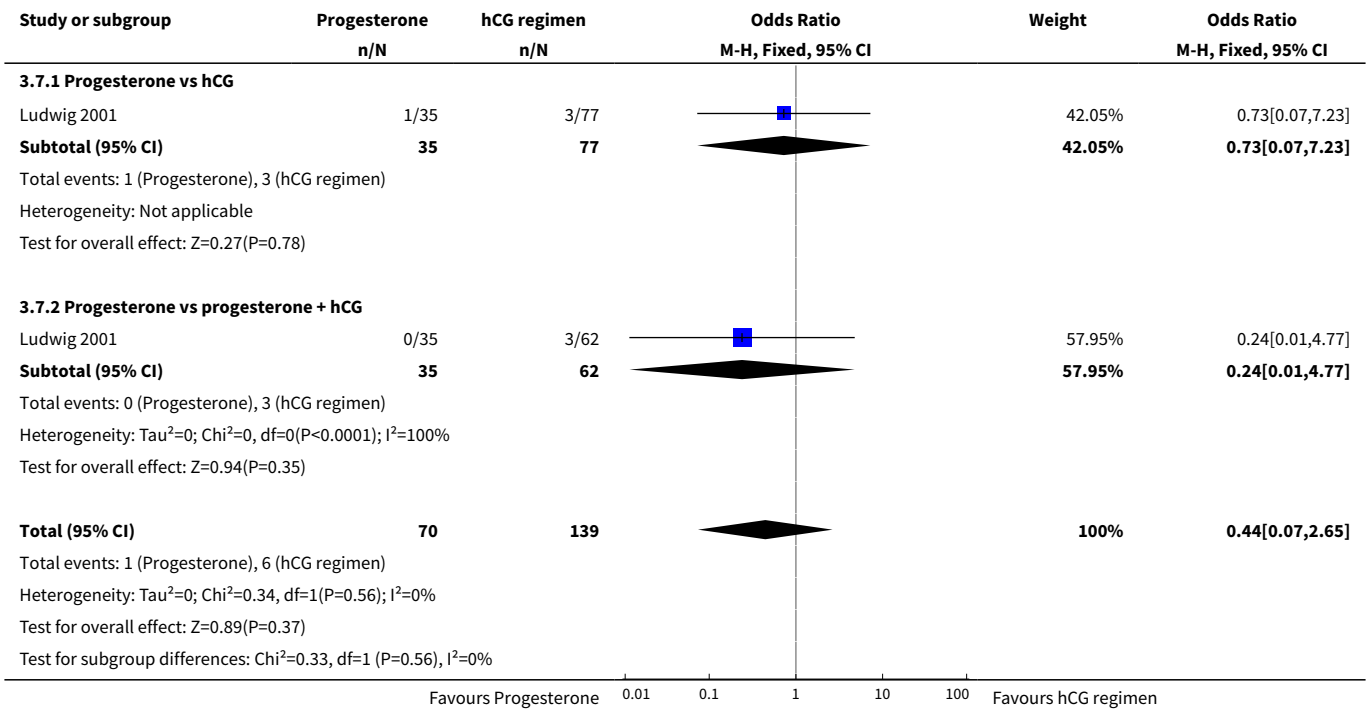




Analysis 3.6. Comparison 3 Progesterone vs hCG regimens, Outcome 6 Miscarriage rate.



Analysis 3.7. Comparison 3 Progesterone vs hCG regimens, Outcome 7 Multiple pregnancy.



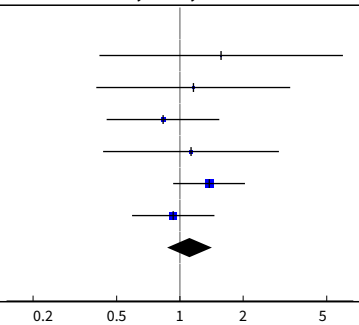
Comparison 4. Progesterone vs progesterone + oestrogen

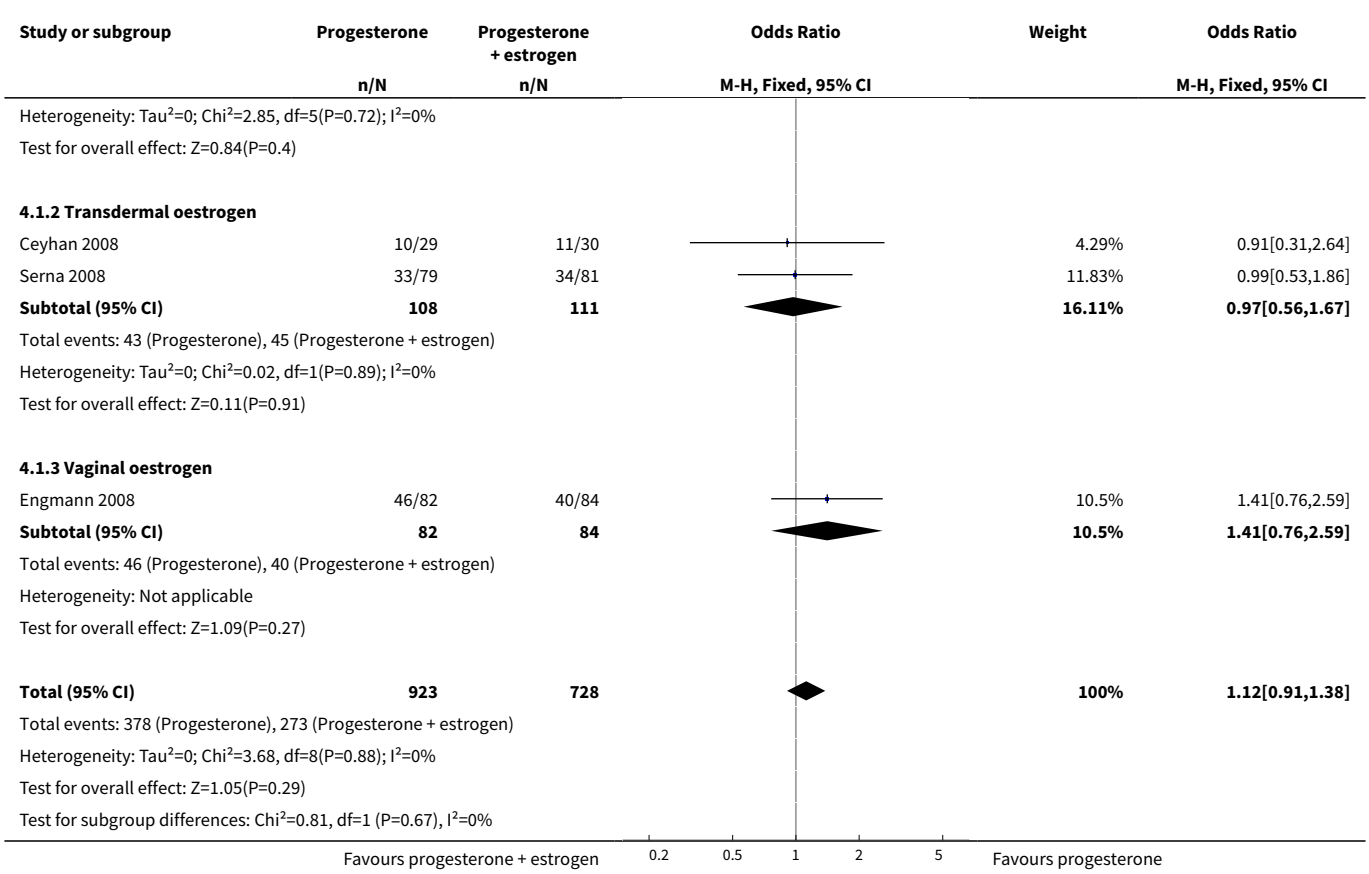
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancy rate	9	1651	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.91, 1.38]
1.1 Oral oestrogen	6	1266	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.87, 1.42]
1.2 Transdermal oestrogen	2	219	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.56, 1.67]
1.3 Vaginal oestrogen	1	166	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.76, 2.59]
2 Clinical pregnancy rate	14	2169	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.04]
2.1 Oral oestrogen	9	1427	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.27]
2.2 Transdermal oestrogen	3	364	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.26, 0.70]
2.3 Vaginal oestrogen	2	301	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.67, 1.71]
2.4 Oral and transdermal oestrogen	1	77	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.10, 0.96]
3 Clinical pregnancy: subgroup analysis by COH method	8	1183	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Human gonadotropins with or without GnRH agonists	7	1080	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.21]
3.2 Human gonadotropins with or without GnRH antagonists	2	103	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.51, 2.44]
4 Clinical pregnancy: subgroup analysis by treatment duration	10	1851	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.08]
4.1 Stop at pregnancy test	2	177	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.32]
4.2 Up to 12 weeks when pregnant	8	1674	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.12]
5 Miscarriage rate	10	1908	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.03]
5.1 Oral oestrogen	7	1370	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.02, 0.04]
5.2 Transdermal oestrogen	1	160	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.09, 0.07]
5.3 Vaginal oestrogen	2	301	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.08, 0.07]
5.4 Oral and transdermal oestrogen	1	77	Risk Difference (M-H, Fixed, 95% CI)	-0.10 [-0.22, 0.01]
6 OHSS	2	461	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.20, 1.68]
6.1 Oral oestrogen	1	402	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.22, 2.29]
6.2 Transdermal oestrogen	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.20]

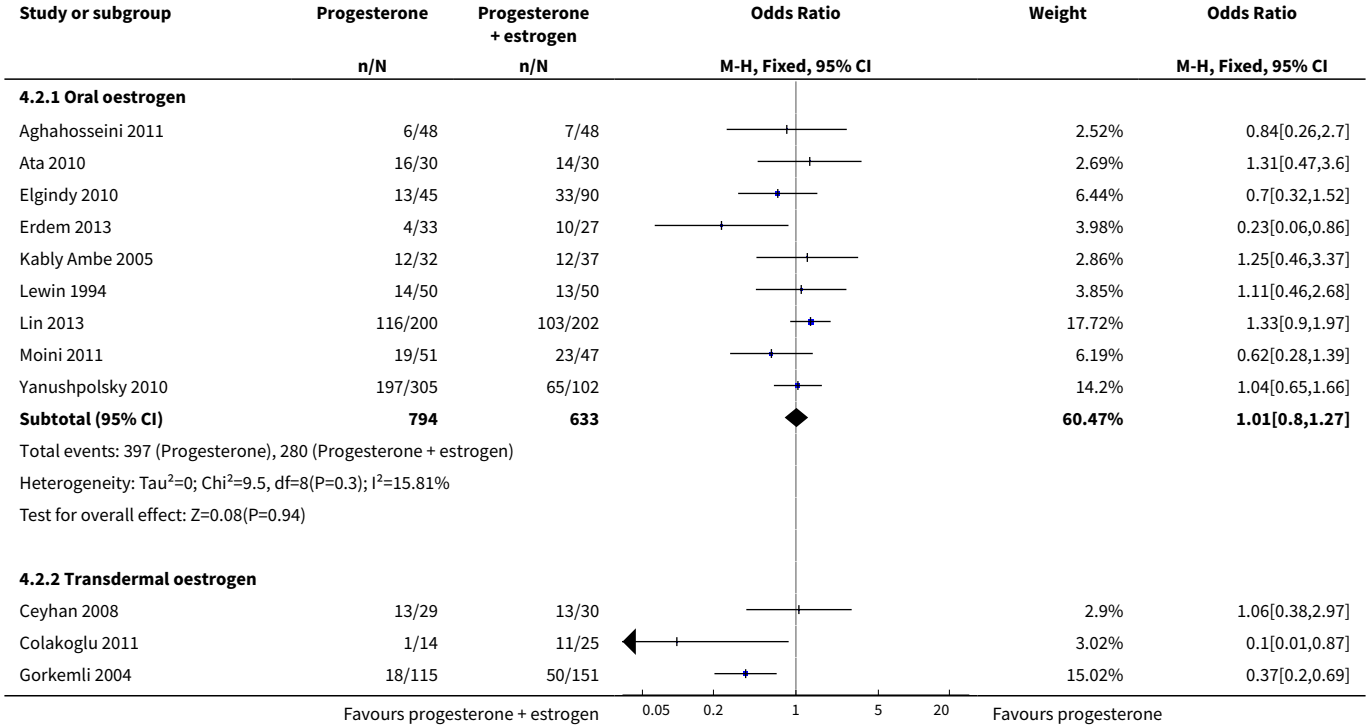
Analysis 4.1. Comparison 4 Progesterone vs progesterone + oestrogen, Outcome 1 Live birth/ongoing pregnancy rate.

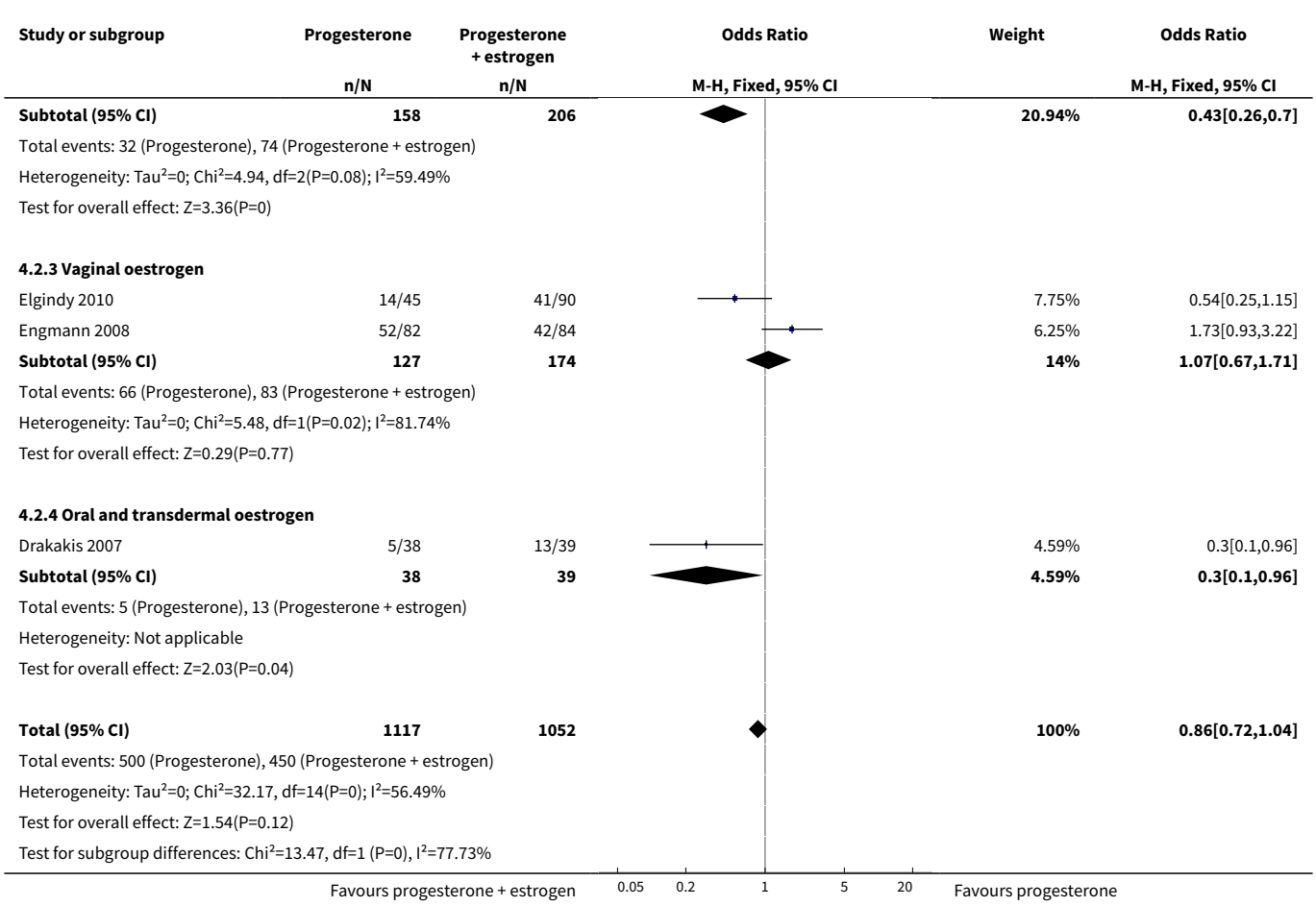
Study or subgroup	Progesterone n/N	Progesterone + estrogen n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Oral oestrogen					
Aghahosseini 2011	6/48	4/48		2.12%	1.57[0.41,5.97]
Ata 2010	11/30	10/30		3.83%	1.16[0.4,3.35]
Fatemi 2006	26/100	30/101		13.36%	0.83[0.45,1.54]
Lewin 1994	11/50	10/50		4.72%	1.13[0.43,2.96]
Lin 2013	103/200	88/202		25.69%	1.38[0.93,2.04]
Yanushpolsky 2010	132/305	46/102		23.66%	0.93[0.59,1.46]
Subtotal (95% CI)	**733**	**533**		**73.39%**	**1.11[0.87,1.42]**
Total events: 289 (Progesterone), 188 (Progesterone + estrogen)					



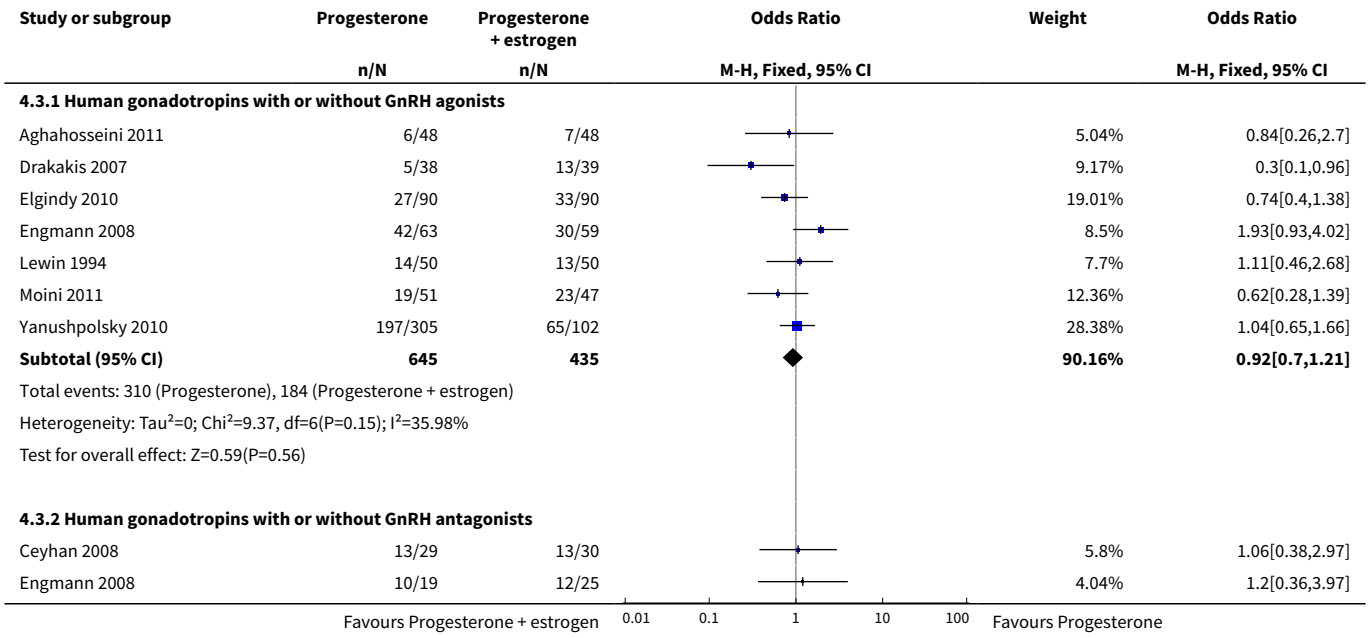


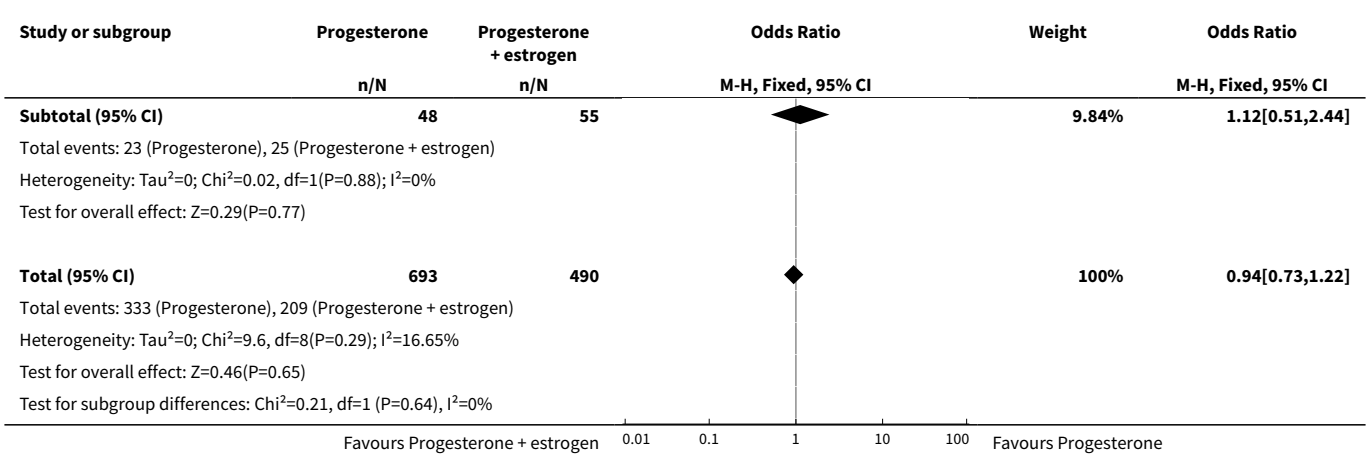
Analysis 4.2. Comparison 4 Progesterone vs progesterone + oestrogen, Outcome 2 Clinical pregnancy rate.



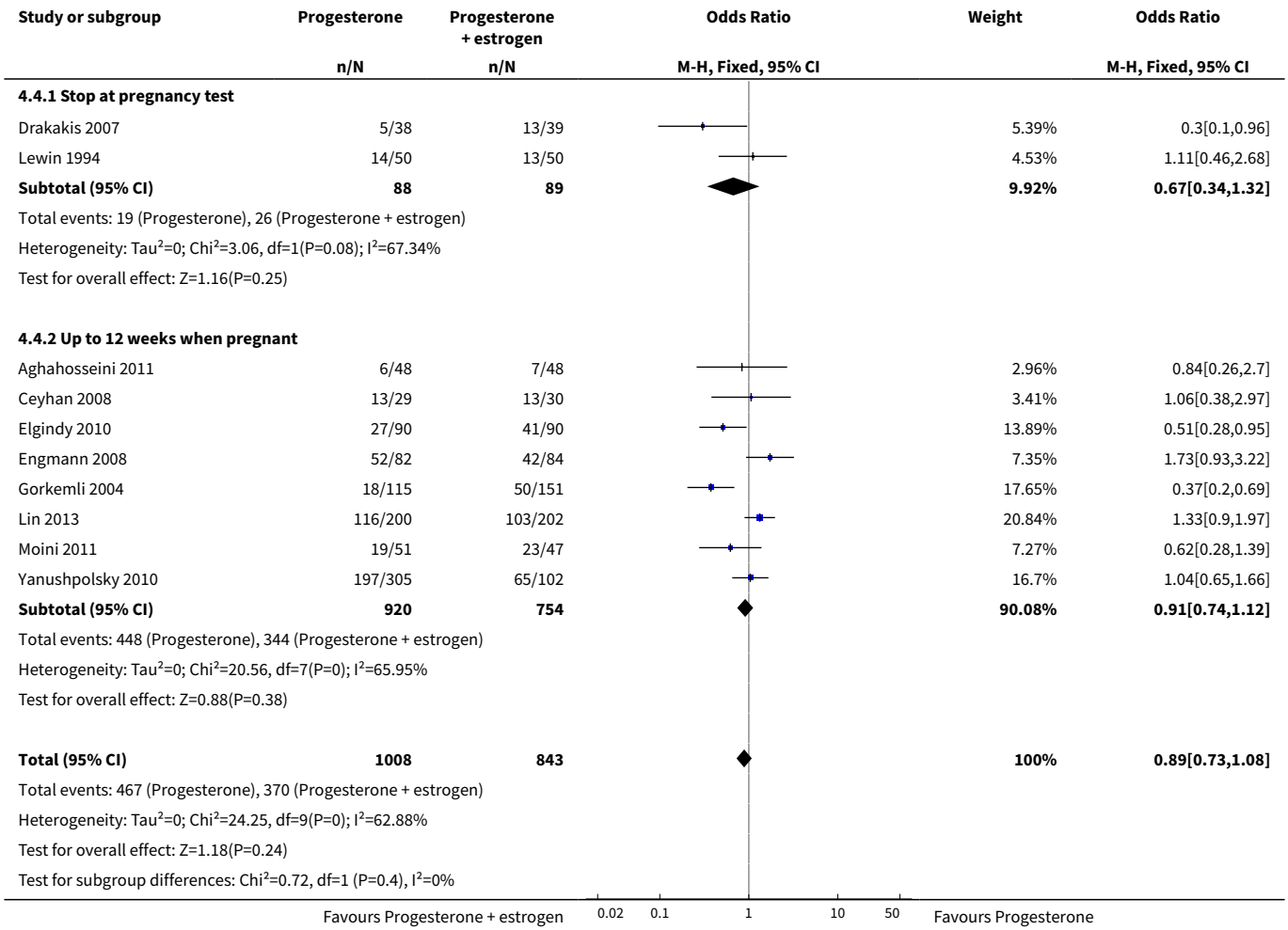


Analysis 4.3. Comparison 4 Progesterone vs progesterone + oestrogen, Outcome 3 Clinical pregnancy: subgroup analysis by COH method.



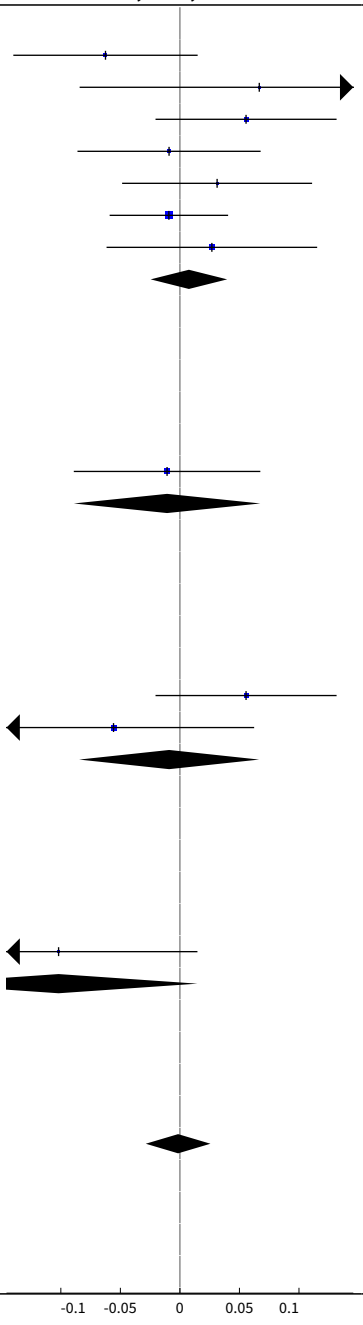


Analysis 4.4. Comparison 4 Progesterone vs progesterone + oestrogen, Outcome 4 Clinical pregnancy: subgroup analysis by treatment duration.

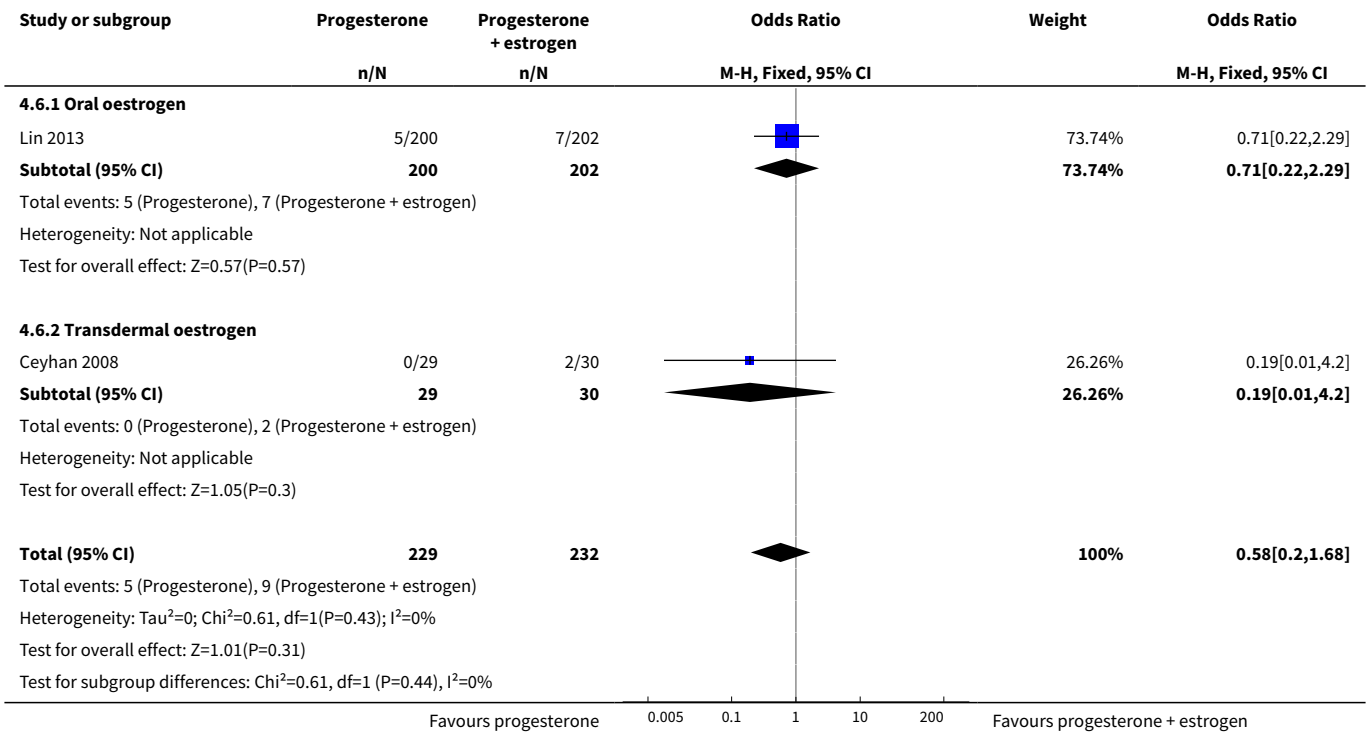


Analysis 4.5. Comparison 4 Progesterone vs progesterone + oestrogen, Outcome 5 Miscarriage rate.

Study or subgroup	Progesterone n/N	Progesterone + estrogen n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
4.5.1 Oral oestrogen					
Aghahosseini 2011	0/48	3/48		5.4%	-0.06[-0.14,0.01]
Ata 2010	4/30	2/30		3.38%	0.07[-0.08,0.22]
Elgindy 2010	3/45	1/90		6.76%	0.06[-0.02,0.13]
Fatemi 2006	8/100	9/101		11.32%	-0.01[-0.09,0.07]
Kably Ambe 2005	1/32	0/37		3.86%	0.03[-0.05,0.11]
Lin 2013	13/200	15/202		22.63%	-0.01[-0.06,0.04]
Yanushpolsky 2010	65/305	19/102		17.21%	0.03[-0.06,0.12]
Subtotal (95% CI)	**760**	**610**		**70.56%**	**0.01[-0.02,0.04]**
Total events: 94 (Progesterone), 49 (Progesterone + estrogen)					
Heterogeneity: Tau²=0; Chi²=6.41, df=6(P=0.38); I²=6.37%					
Test for overall effect: Z=0.46(P=0.65)					
4.5.2 Transdermal oestrogen					
Serna 2008	5/79	6/81		9.01%	-0.01[-0.09,0.07]
Subtotal (95% CI)	**79**	**81**		**9.01%**	**-0.01[-0.09,0.07]**
Total events: 5 (Progesterone), 6 (Progesterone + estrogen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					
4.5.3 Vaginal oestrogen					
Elgindy 2010	3/45	1/90		6.76%	0.06[-0.02,0.13]
Engmann 2008	13/82	18/84		9.34%	-0.06[-0.17,0.06]
Subtotal (95% CI)	**127**	**174**		**16.1%**	**-0.01[-0.08,0.07]**
Total events: 16 (Progesterone), 19 (Progesterone + estrogen)					
Heterogeneity: Tau²=0; Chi²=3.37, df=1(P=0.07); I²=70.36%					
Test for overall effect: Z=0.23(P=0.81)					
4.5.4 Oral and transdermal oestrogen					
Drakakis 2007	1/38	5/39		4.33%	-0.1[-0.22,0.01]
Subtotal (95% CI)	**38**	**39**		**4.33%**	**-0.1[-0.22,0.01]**
Total events: 1 (Progesterone), 5 (Progesterone + estrogen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
Total (95% CI)	**1004**	**904**		**100%**	**-0[-0.03,0.03]**
Total events: 116 (Progesterone), 79 (Progesterone + estrogen)					
Heterogeneity: Tau²=0; Chi²=12.38, df=10(P=0.26); I²=19.23%					
Test for overall effect: Z=0.11(P=0.91)					
Test for subgroup differences: Chi²=3.24, df=1 (P=0.36), I²=7.33%					



Analysis 4.6. Comparison 4 Progesterone vs progesterone + oestrogen, Outcome 6 OHSS.



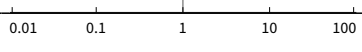
Comparison 5. Progesterone vs progesterone + GnRH agonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth or ongoing pregnancy rate	9	2861	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.48, 0.81]
1.1 Single dose	5	1536	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.87]
1.2 Multiple dose	5	1325	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.42, 0.98]
2 Clinical pregnancy rate	8	2435	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.51, 0.85]
2.1 Single dose	5	1536	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.44, 0.91]
2.2 Multiple dose	4	899	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.44, 1.04]
3 Clinical pregnancy: subgroup analysis by COH method	7	2373	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.56, 0.90]
3.1 Gonadotropins with or without GnRH agonists	6	1919	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.99]
3.2 Gonadotropins with or without GnRH antagonists	2	454	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.30, 0.92]

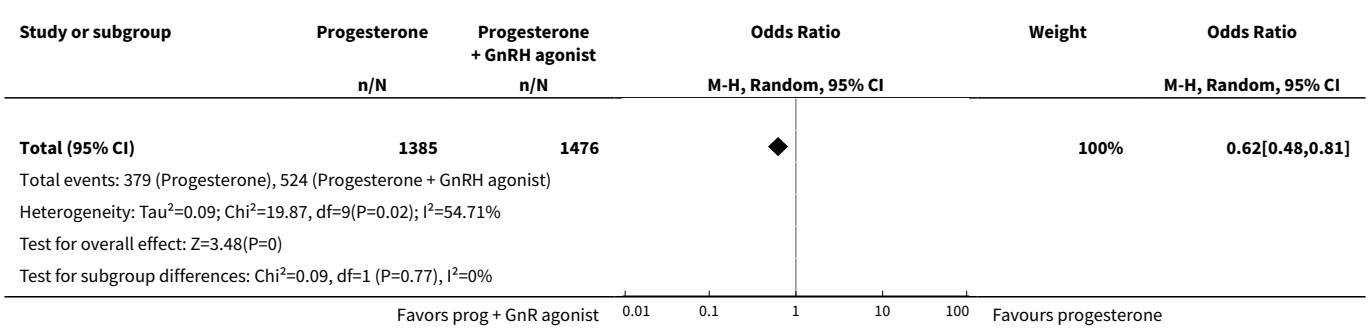
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Clinical pregnancy: subgroup analysis by treatment duration	6	2253	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.95]
4.1 Stop at pregnancy test	5	1683	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.57, 0.89]
4.2 Up to 12 weeks when pregnant	1	570	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.70, 1.35]
5 Miscarriage rate	2	420	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.53, 3.52]
5.1 Single dose	1	150	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.18, 5.65]
5.2 Multiple dose	2	270	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [0.50, 4.92]
6 Multiple pregnancy	4	1450	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.54, 1.05]
6.1 Single dose	3	874	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.52, 1.13]
6.2 Multiple dose	2	576	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.40, 1.36]
7 OHSS	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 1 Live birth or ongoing pregnancy rate.

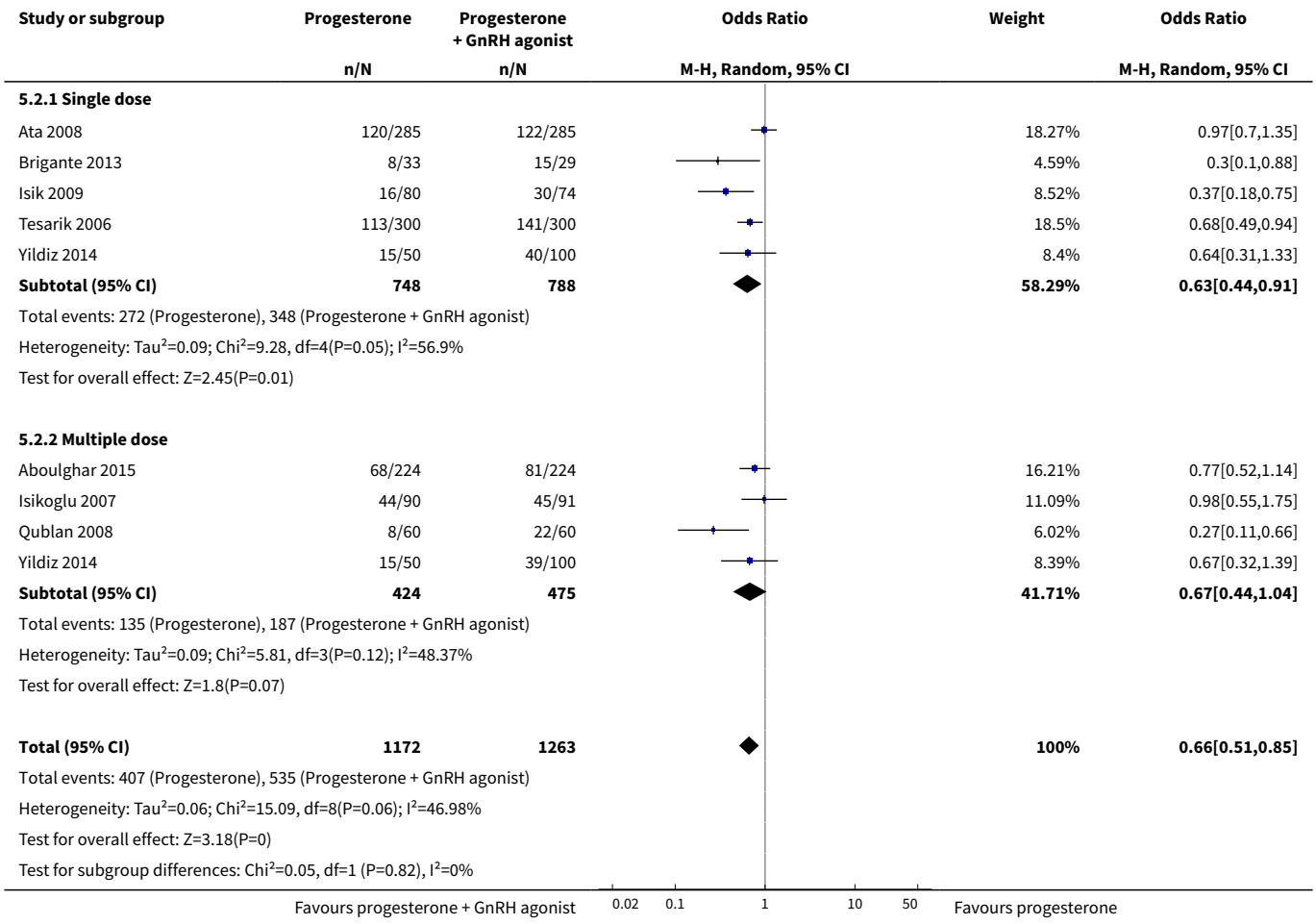
Study or subgroup	Progesterone n/N	Progesterone + GnRH agonist n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
5.1.1 Single dose					
Ata 2008	84/285	89/285		15.17%	0.92[0.64,1.32]
Brigante 2013	6/33	15/29		4.31%	0.21[0.07,0.65]
Isik 2009	13/80	26/74		7.73%	0.36[0.17,0.77]
Tesarik 2006	100/300	131/300		15.77%	0.65[0.46,0.9]
Yildiz 2014	13/50	36/100		7.85%	0.62[0.29,1.33]
Subtotal (95% CI)	**748**	**788**		**50.82%**	**0.59[0.39,0.87]**
Total events: 216 (Progesterone), 297 (Progesterone + GnRH agonist)					
Heterogeneity: Tau^2=0.11; Chi^2=9.74, df=4(P=0.05); I^2=58.92%					
Test for overall effect: Z=2.66(P=0.01)					
5.1.2 Multiple dose					
Aboulghar 2015	57/224	68/224		13.87%	0.78[0.52,1.18]
Inamdar 2012	56/213	59/213		13.57%	0.93[0.61,1.43]
Isikoglu 2007	34/90	45/91		10.29%	0.62[0.34,1.12]
Qublan 2008	3/60	19/60		3.59%	0.11[0.03,0.41]
Yildiz 2014	13/50	36/100		7.85%	0.62[0.29,1.33]
Subtotal (95% CI)	**637**	**688**		**49.18%**	**0.64[0.42,0.98]**
Total events: 163 (Progesterone), 227 (Progesterone + GnRH agonist)					
Heterogeneity: Tau^2=0.13; Chi^2=9.96, df=4(P=0.04); I^2=59.84%					
Test for overall effect: Z=2.07(P=0.04)					



Favors prog + GnR agonist — Favours progesterone

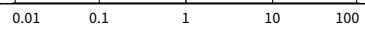


Analysis 5.2. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 2 Clinical pregnancy rate.



Analysis 5.3. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 3 Clinical pregnancy: subgroup analysis by COH method.

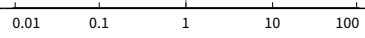
Study or subgroup	Progesterone n/N	Progesterone + GnRH agonist n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 Gonadotropins with or without GnRH agonists					
Aboulghar 2015	68/224	81/224		16.43%	0.77[0.52,1.14]
Ata 2008	120/285	122/285		18.96%	0.97[0.7,1.35]
Isikoglu 2007	44/90	45/91		10.64%	0.98[0.55,1.75]
Qublan 2008	8/60	22/60		5.49%	0.27[0.11,0.66]
Tesarik 2006	59/150	72/150		14.15%	0.7[0.44,1.11]
Yildiz 2014	30/100	72/200		12.37%	0.76[0.45,1.28]
Subtotal (95% CI)	**909**	**1010**		**78.05%**	**0.77[0.61,0.99]**
Total events: 329 (Progesterone), 414 (Progesterone + GnRH agonist)					
Heterogeneity: Tau^2=0.03; Chi^2=7.78, df=5(P=0.17); I^2=35.73%					
Test for overall effect: Z=2.04(P=0.04)					
5.3.2 Gonadotropins with or without GnRH antagonists					
Isik 2009	16/80	30/74		7.96%	0.37[0.18,0.75]
Tesarik 2006	54/150	69/150		14%	0.66[0.42,1.05]
Subtotal (95% CI)	**230**	**224**		**21.95%**	**0.53[0.3,0.92]**
Total events: 70 (Progesterone), 99 (Progesterone + GnRH agonist)					
Heterogeneity: Tau^2=0.08; Chi^2=1.82, df=1(P=0.18); I^2=45.11%					
Test for overall effect: Z=2.24(P=0.02)					
Total (95% CI)	**1139**	**1234**		**100%**	**0.71[0.56,0.9]**
Total events: 399 (Progesterone), 513 (Progesterone + GnRH agonist)					
Heterogeneity: Tau^2=0.05; Chi^2=12.32, df=7(P=0.09); I^2=43.18%					
Test for overall effect: Z=2.87(P=0)					
Test for subgroup differences: Chi^2=1.52, df=1 (P=0.22), I^2=34.39%					



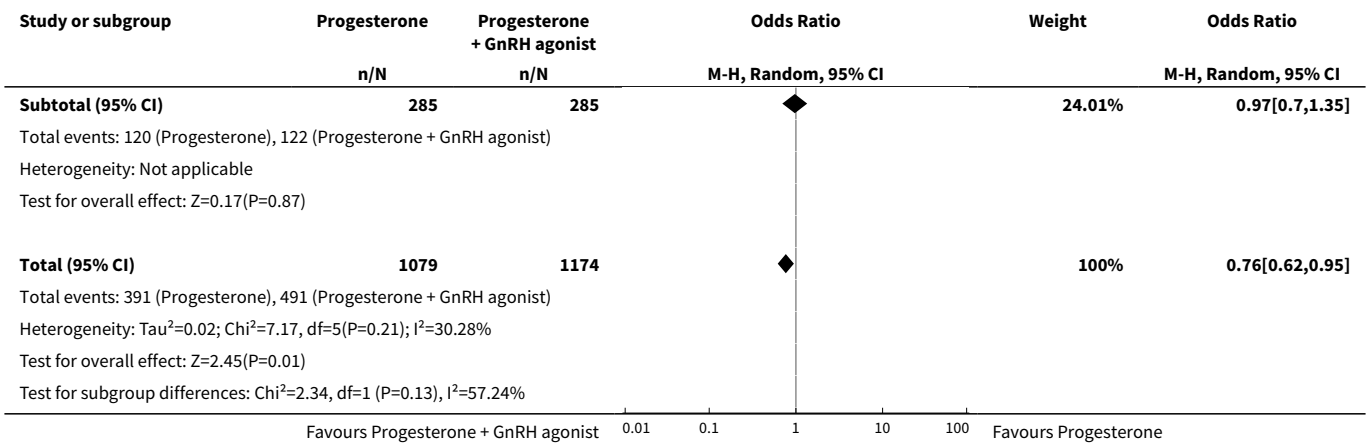
Favours Progesterone + GnRH agonist — Favours Progesterone

Analysis 5.4. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 4 Clinical pregnancy: subgroup analysis by treatment duration.

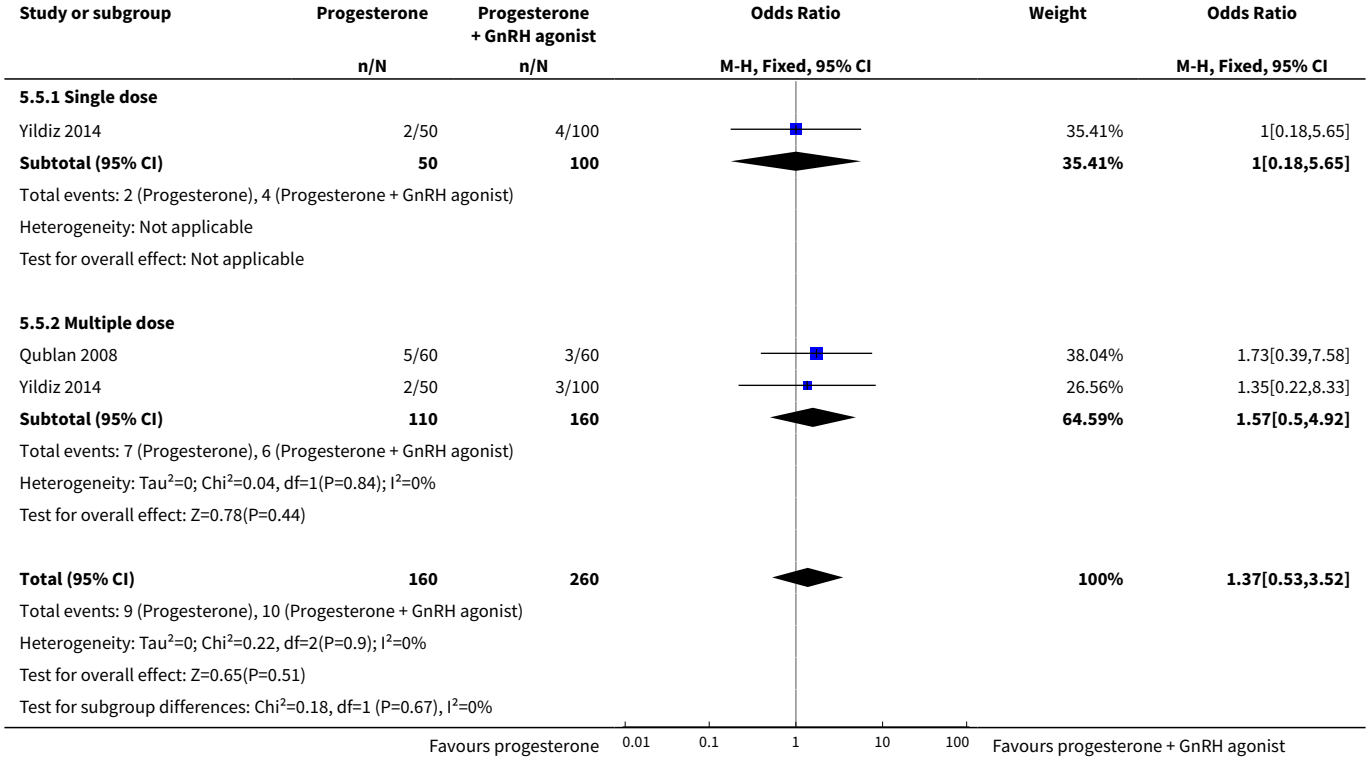
Study or subgroup	Progesterone n/N	Progesterone + GnRH agonist n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
5.4.1 Stop at pregnancy test					
Isik 2009	16/80	30/74		7.73%	0.37[0.18,0.75]
Isikoglu 2007	44/90	45/91		10.96%	0.98[0.55,1.75]
Yildiz 2014	30/100	72/200		13.26%	0.76[0.45,1.28]
Aboulghar 2015	68/224	81/224		19.46%	0.77[0.52,1.14]
Tesarik 2006	113/300	141/300		24.58%	0.68[0.49,0.94]
Subtotal (95% CI)	**794**	**889**		**75.99%**	**0.71[0.57,0.89]**
Total events: 271 (Progesterone), 369 (Progesterone + GnRH agonist)					
Heterogeneity: Tau^2=0.01; Chi^2=4.71, df=4(P=0.32); I^2=14.99%					
Test for overall effect: Z=2.98(P=0)					
5.4.2 Up to 12 weeks when pregnant					
Ata 2008	120/285	122/285		24.01%	0.97[0.7,1.35]



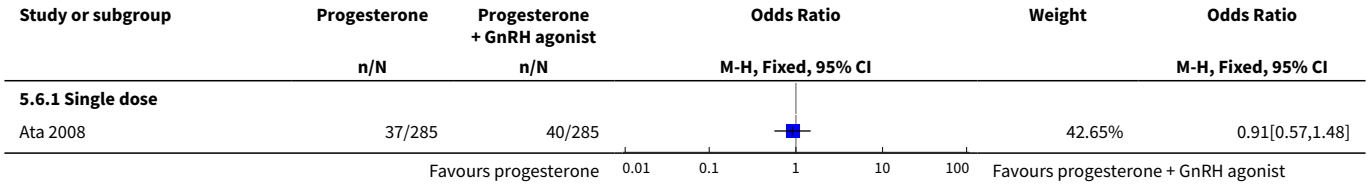
Favours Progesterone + GnRH agonist — Favours Progesterone

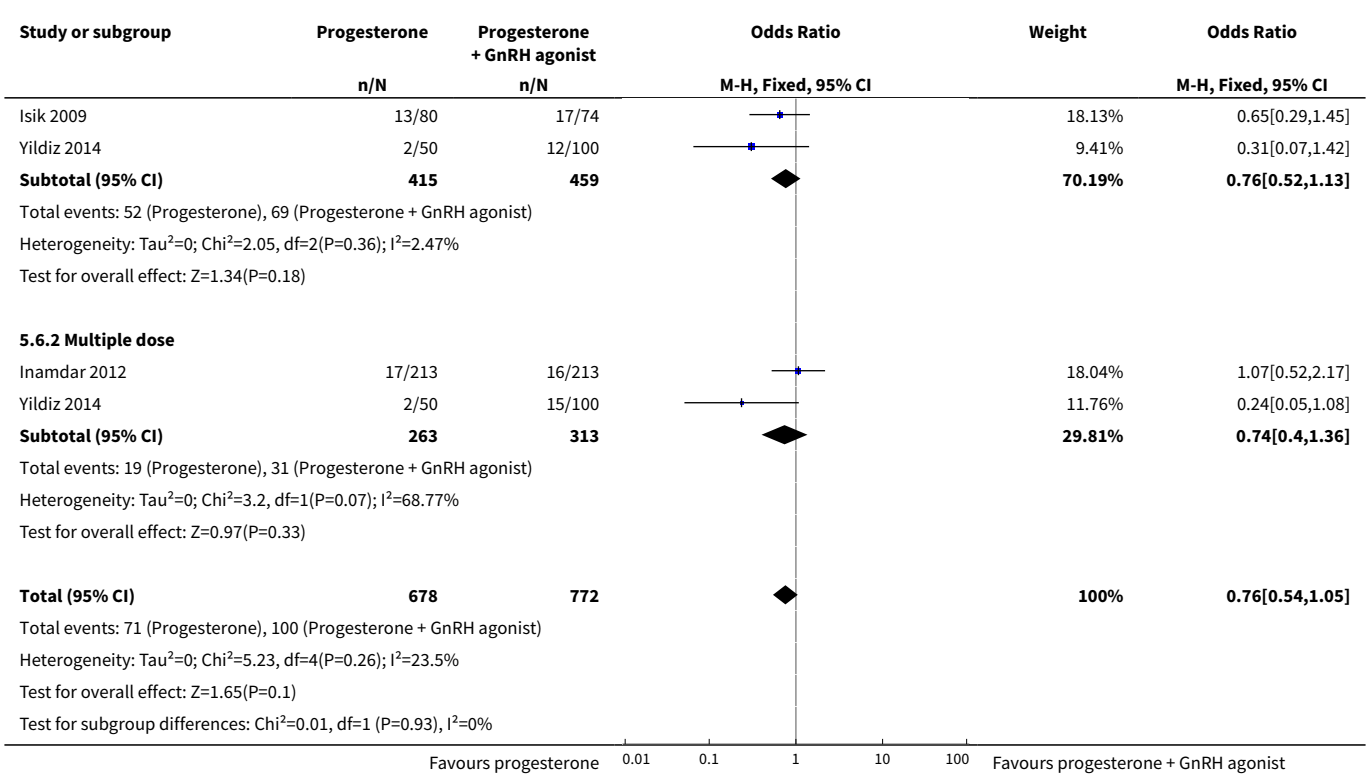


Analysis 5.5. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 5 Miscarriage rate.

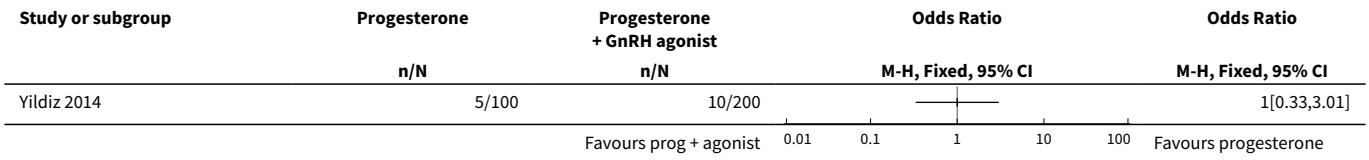


Analysis 5.6. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 6 Multiple pregnancy.





Analysis 5.7. Comparison 5 Progesterone vs progesterone + GnRH agonist, Outcome 7 OHSS.



Comparison 6. Progesterone regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth or ongoing pregnancy rate	25		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 IM vs oral	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.66]
1.2 IM vs vaginal/rectal	7	2039	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [1.03, 1.50]
1.3 Vaginal/rectal vs oral	4	857	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.83, 1.69]

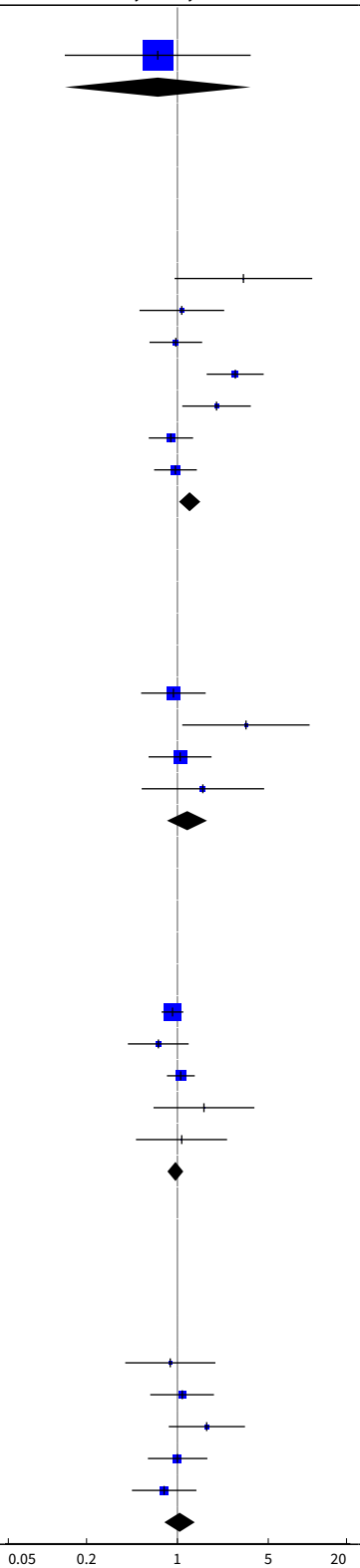
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Low dose vaginal vs high dose vaginal	5	3720	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.11]
1.5 Short protocol vs long protocol	5	1205	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.79, 1.36]
1.6 Micronised vs synthetic	2	470	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.53, 1.55]
1.7 Vaginal ring vs vaginal gel	1	1271	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.88, 1.36]
1.8 Subcutaneous vs vaginal gel	2	1465	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.74, 1.14]
1.9 Vaginal vs rectal	1	147	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.64, 2.54]
2 Clinical pregnancy rate	41		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 IM vs oral	3	123	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [0.89, 4.32]
2.2 IM vs vaginal/rectal	13	2932	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.97, 1.33]
2.3 Vaginal/rectal vs oral	7	2815	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.05]
2.4 Low dose vaginal vs high dose vaginal	12	5659	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.09]
2.5 Short protocol vs long protocol	6	1128	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.87, 1.50]
2.6 Micronised vs synthetic	4	2388	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.96]
2.7 Vaginal ring vs vaginal gel	1	1271	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.31]
2.8 Subcutaneous vs vaginal gel	2	1465	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.71, 1.08]
2.9 Vaginal vs rectal	1	147	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.68, 2.56]
3 Miscarriage rate	26		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 IM vs oral	3	123	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.34, 6.11]

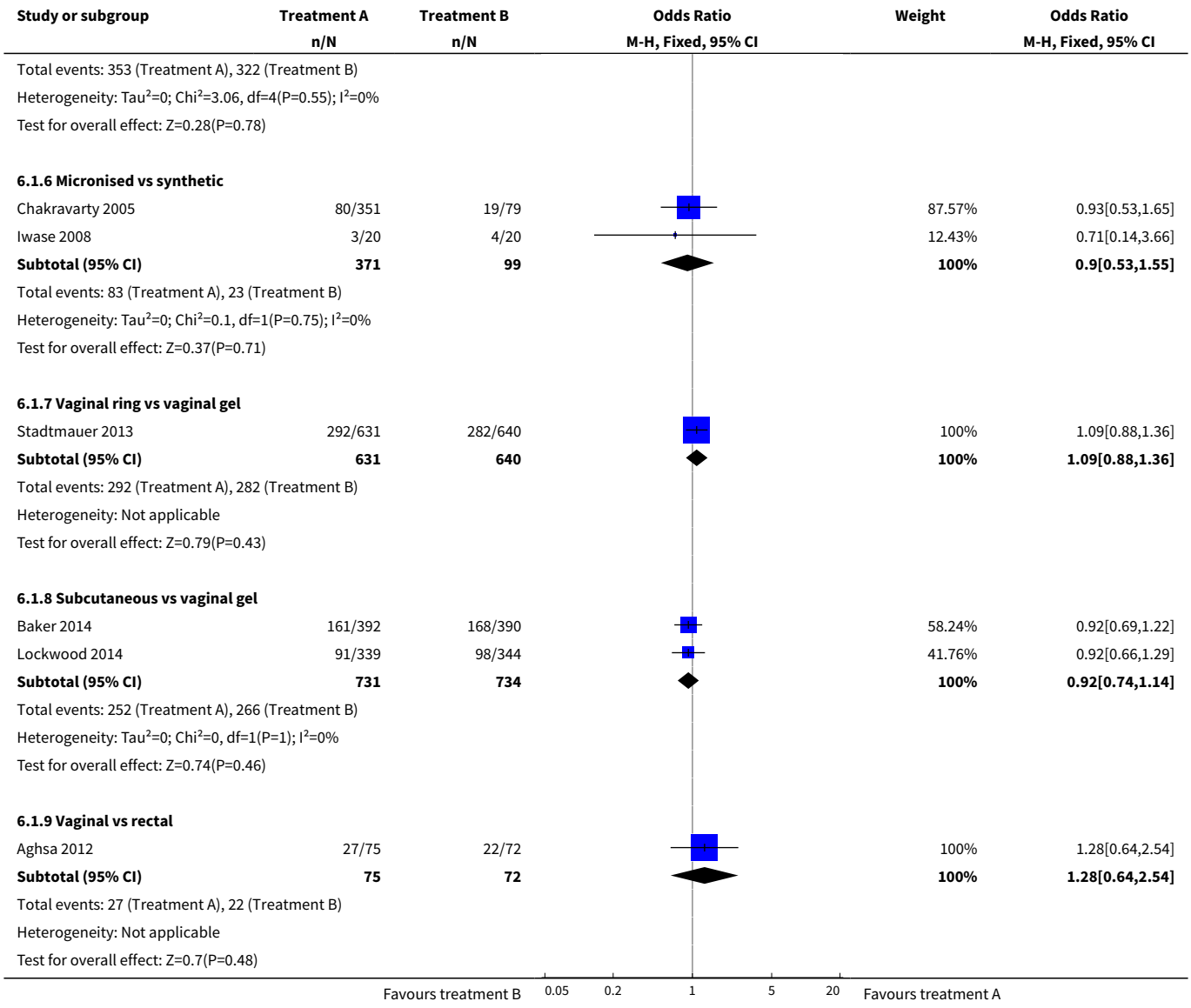
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 IM vs vaginal/rectal	6	1468	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.13]
3.3 Vaginal/rectal vs oral	5	2220	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.76, 1.82]
3.4 Low dose vaginal vs high dose vaginal	9	4333	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.98]
3.5 Short protocol vs long protocol	3	662	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.61, 1.50]
3.6 Micronised vs synthetic	2	1793	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.69, 1.95]
3.7 Subcutaneous vs vaginal gel	2	1465	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.44, 1.54]
3.8 Vaginal vs rectal	1	147	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.31, 4.71]
4 OHSS	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 IM vs oral	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 17.18]
4.2 Low dose vaginal vs high dose vaginal	2	1251	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.57, 1.46]
5 Multiple pregnancy	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 IM vs oral	2	83	Odds Ratio (M-H, Fixed, 95% CI)	4.23 [1.16, 15.40]
5.2 IM vs vaginal/rectal	1	505	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.60, 1.59]
5.3 Vaginal/rectal vs oral	1	283	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.50, 2.58]
5.4 Low dose vaginal vs high dose vaginal	5	2888	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.85, 1.80]
5.5 Short protocol vs long protocol	4	820	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.80, 1.60]
5.6 Vaginal vs rectal	1	147	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.19, 4.91]
6 Clinical pregnancy: IM vs vaginal/rectal: subgroup analysis by COH method	11		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Human gonadotropins with or without GnRH agonists	10		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Human gonadotropins with or without GnRH antagonists	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Clinical pregnancy: IM vs vaginal/rectal: subgroup analysis by treatment duration	7		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Stop at pregnancy test	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Up to 12 weeks when pregnant	5		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Clinical pregnancy: vaginal/rectal vs oral: subgroup analysis by treatment duration	6	2775	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.04]
8.1 Stop at pregnancy test	2	619	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.98]
8.2 Up to 12 weeks when pregnant	4	2156	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.17]
9 Clinical pregnancy: low vs high dose vaginal: subgroup analysis by COH method	9	3512	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.22]
9.1 Human gonadotropins with or without GnRH agonists	8	3388	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.22]
9.2 Human gonadotropins with or without GnRH antagonists	1	124	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.49, 2.22]
10 Clinical pregnancy: low vs high dose vaginal: subgroup analysis by duration of treatment	9	3514	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.24]
10.1 Stop at pregnancy test	3	318	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.67, 1.83]
10.2 Up to 12 weeks when pregnant	6	3196	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.24]
11 Clinical pregnancy: short vs long protocol: subgroup analysis by COH method	4	902	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.75, 1.40]
11.1 Human gonadotropins with or without GnRH agonists	2	482	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.32]
11.2 Human gonadotropins with or without GnRH antagonists	2	420	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.79, 2.05]

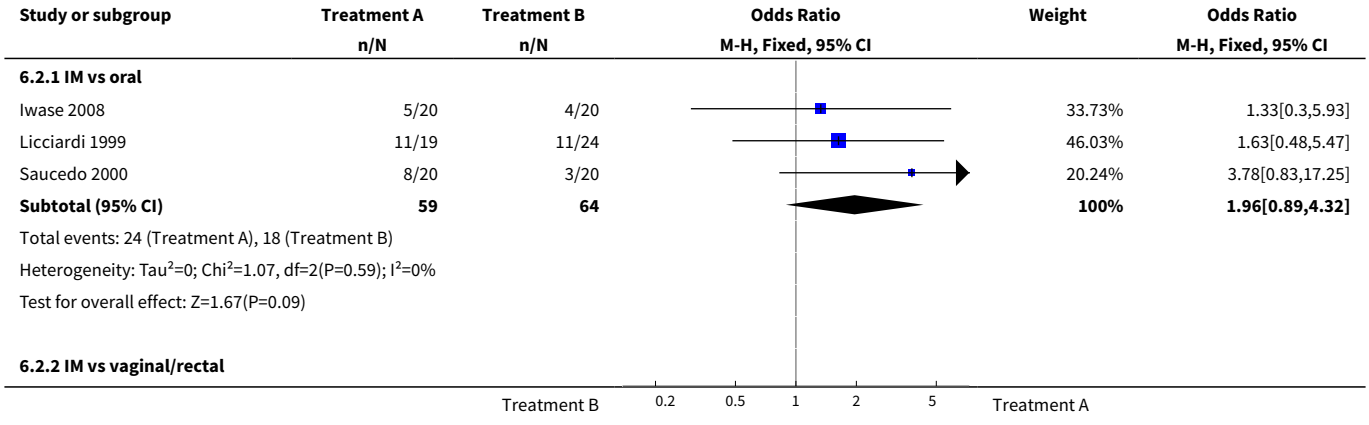
Analysis 6.1. Comparison 6 Progesterone regimens, Outcome 1 Live birth or ongoing pregnancy rate.

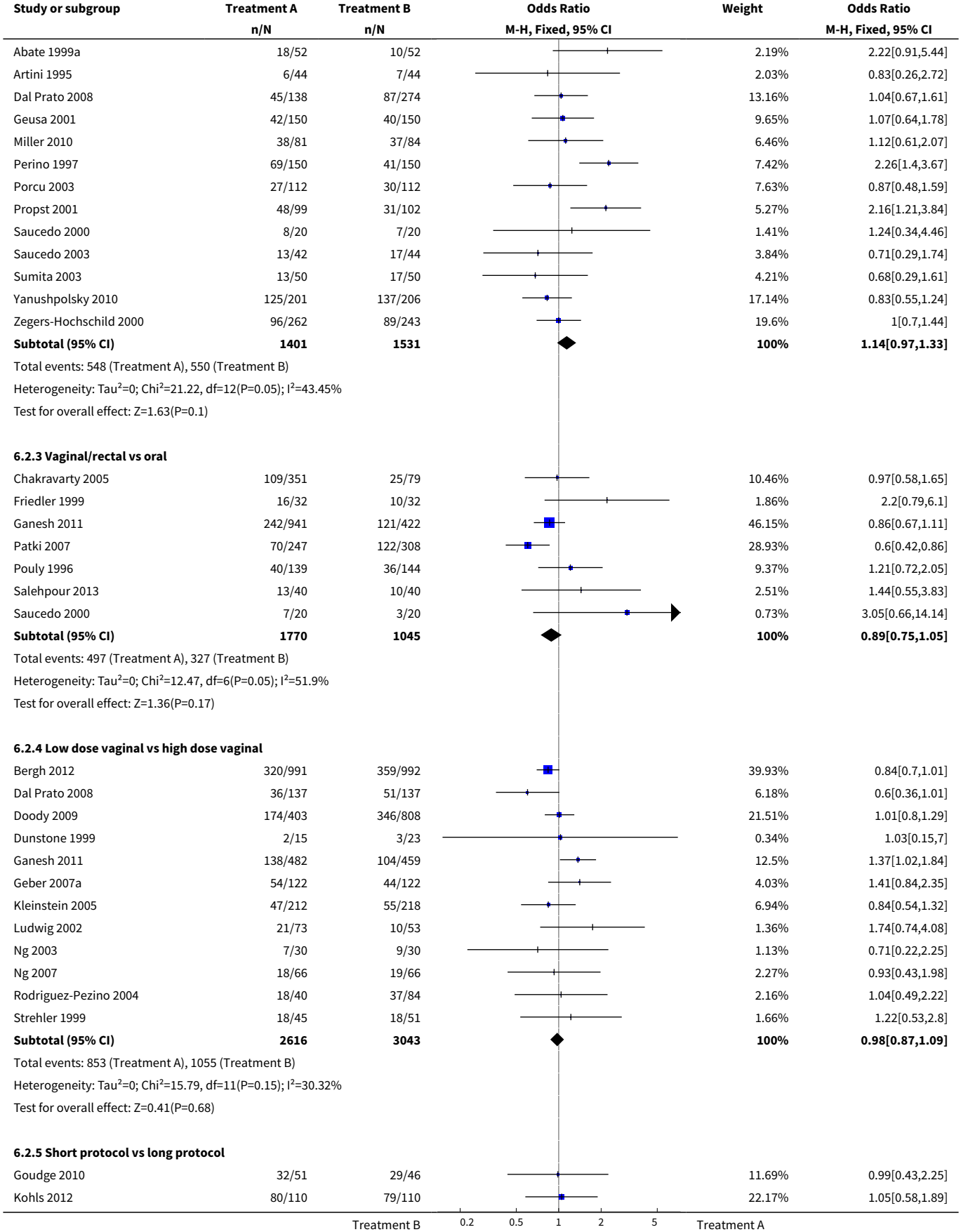
Study or subgroup	Treatment A n/N	Treatment B n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
6.1.1 IM vs oral					
Iwase 2008	3/20	4/20		100%	0.71[0.14,3.66]
Subtotal (95% CI)	**20**	**20**		**100%**	**0.71[0.14,3.66]**
Total events: 3 (Treatment A), 4 (Treatment B)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.41(P=0.68)					
6.1.2 IM vs vaginal/rectal					
Abate 1999a	11/52	4/52		1.62%	3.22[0.95,10.88]
Beltsos 2011	28/57	25/53		6.79%	1.08[0.51,2.29]
Dal Prato 2008	36/138	73/274		18.62%	0.97[0.61,1.55]
Perino 1997	66/150	33/150		9.52%	2.79[1.68,4.61]
Propst 2001	39/99	25/102		7.69%	2[1.09,3.67]
Yanushpolsky 2010	85/201	93/206		27.31%	0.89[0.6,1.32]
Zegers-Hochschild 2000	81/262	77/243		28.44%	0.96[0.66,1.41]
Subtotal (95% CI)	**959**	**1080**		**100%**	**1.24[1.03,1.5]**
Total events: 346 (Treatment A), 330 (Treatment B)					
Heterogeneity: Tau^2=0; Chi^2=20.35, df=6(P=0); I^2=70.51%					
Test for overall effect: Z=2.27(P=0.02)					
6.1.3 Vaginal/rectal vs oral					
Chakravarty 2005	80/351	19/79		42.18%	0.93[0.53,1.65]
Friedler 1999	14/32	6/32		5.94%	3.37[1.09,10.43]
Pouly 1996	32/139	32/144		42.62%	1.05[0.6,1.83]
Salehpour 2013	10/40	7/40		9.25%	1.57[0.53,4.65]
Subtotal (95% CI)	**562**	**295**		**100%**	**1.19[0.83,1.69]**
Total events: 136 (Treatment A), 64 (Treatment B)					
Heterogeneity: Tau^2=0; Chi^2=4.41, df=3(P=0.22); I^2=32.03%					
Test for overall effect: Z=0.94(P=0.35)					
6.1.4 Low dose vaginal vs high dose vaginal					
Bergh 2012	281/991	299/992		55.4%	0.92[0.76,1.11]
Dal Prato 2008	32/137	41/137		8.13%	0.71[0.42,1.22]
Doody 2009	153/403	295/808		31.51%	1.06[0.83,1.36]
Ludwig 2002	18/73	9/53		2.03%	1.6[0.66,3.91]
Tay 2005	13/36	31/90		2.93%	1.08[0.48,2.41]
Subtotal (95% CI)	**1640**	**2080**		**100%**	**0.97[0.84,1.11]**
Total events: 497 (Treatment A), 675 (Treatment B)					
Heterogeneity: Tau^2=0; Chi^2=3.37, df=4(P=0.5); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
6.1.5 Short protocol vs long protocol					
Goudge 2010	25/51	24/46		12.43%	0.88[0.4,1.96]
Kohls 2012	75/110	73/110		22.43%	1.09[0.62,1.91]
Kyrou 2011	82/100	73/100		12.69%	1.68[0.86,3.31]
Mochtar 2006	53/258	26/127		26.74%	1[0.59,1.7]
Nyboe Andersen 2002	118/150	126/153		25.71%	0.79[0.45,1.4]
Subtotal (95% CI)	**669**	**536**		**100%**	**1.04[0.79,1.36]**



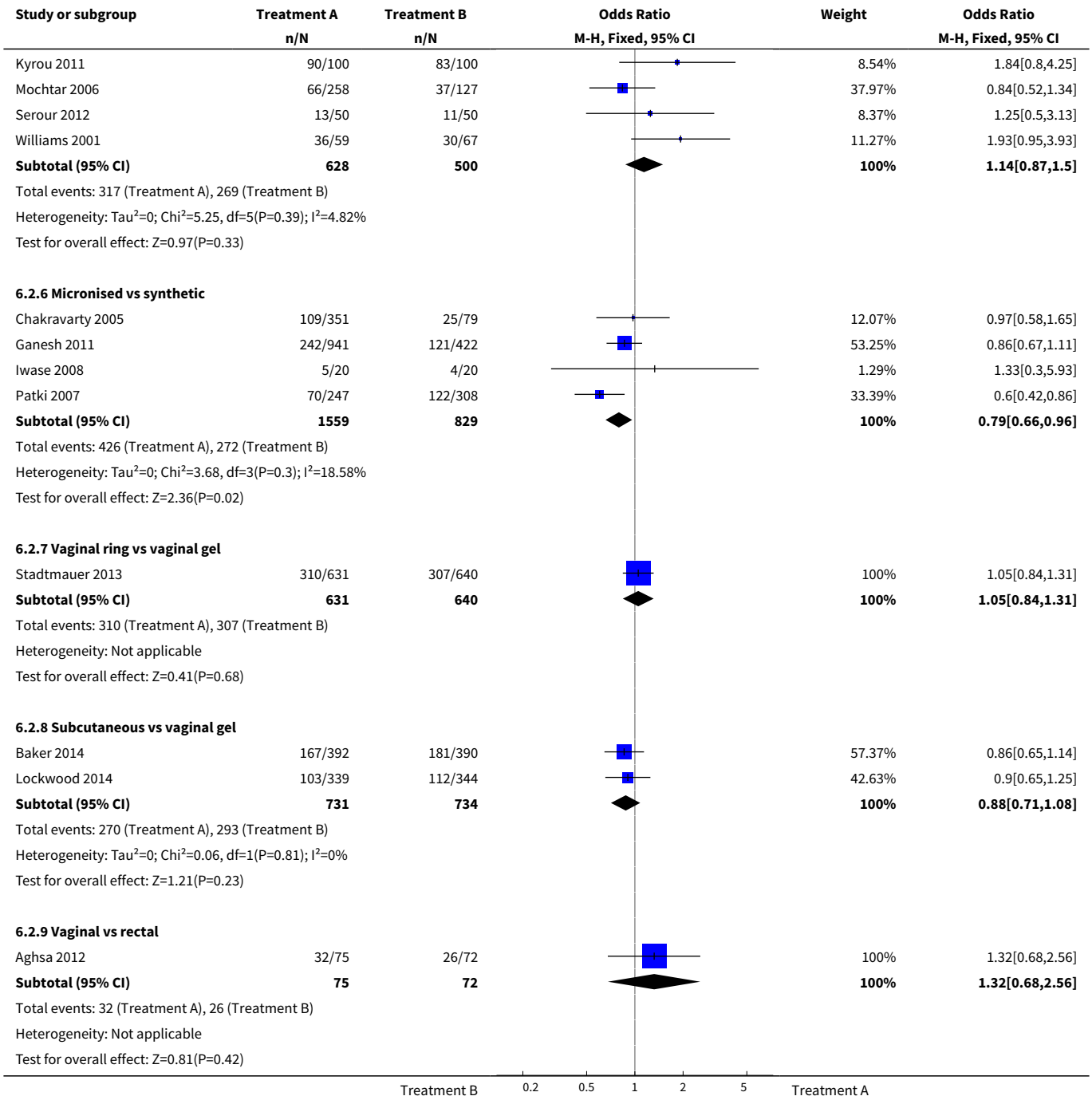


Analysis 6.2. Comparison 6 Progesterone regimens, Outcome 2 Clinical pregnancy rate.

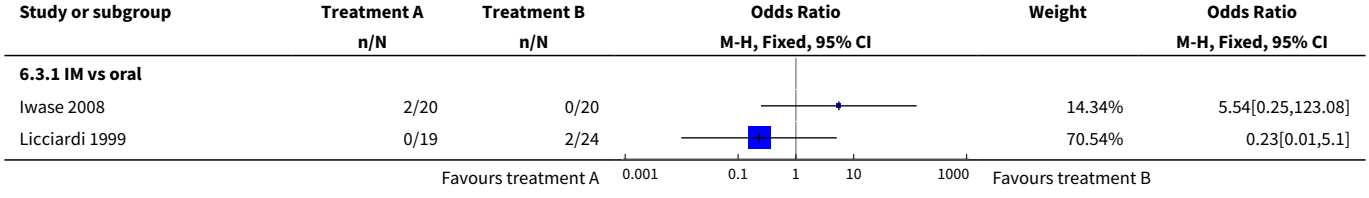


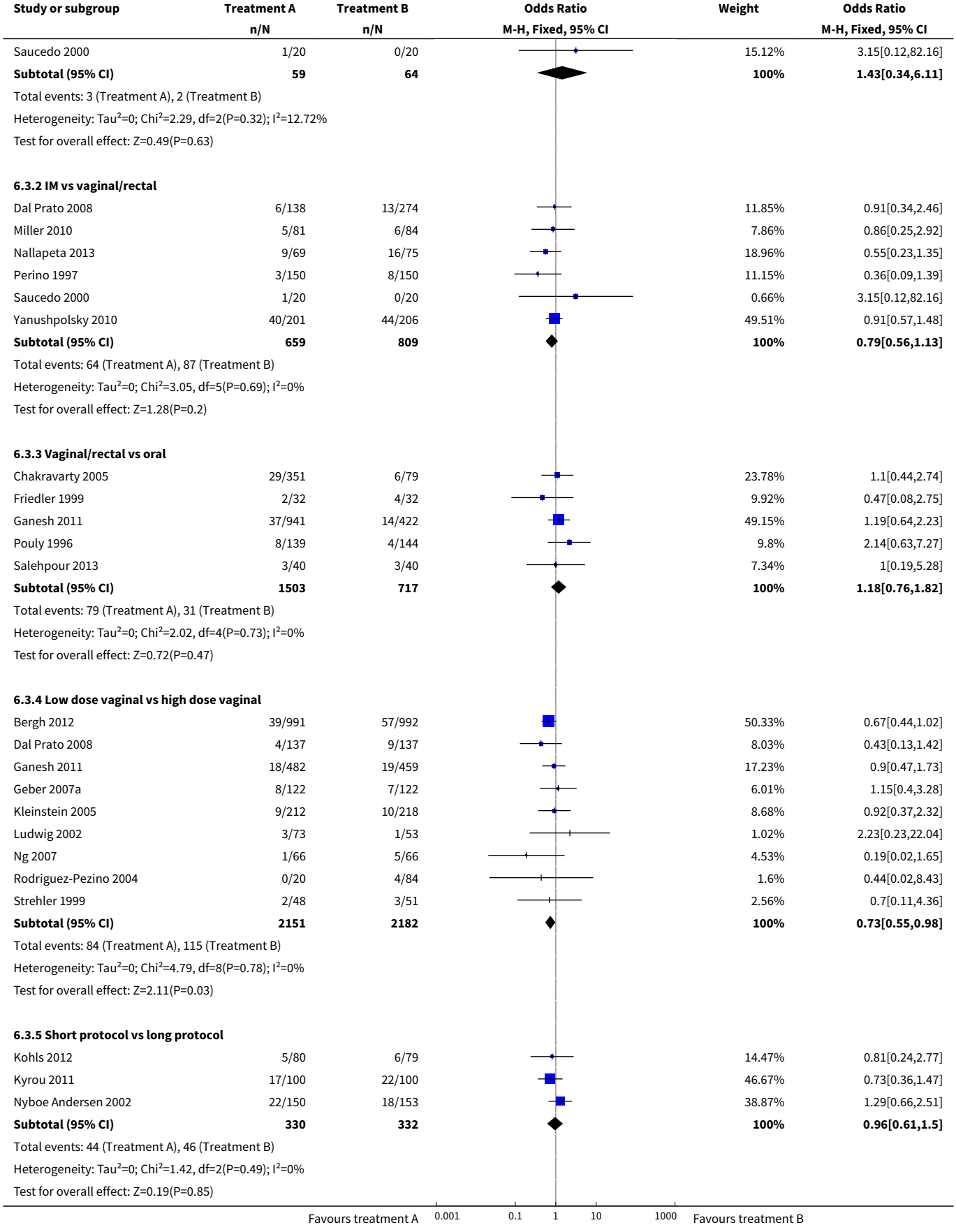


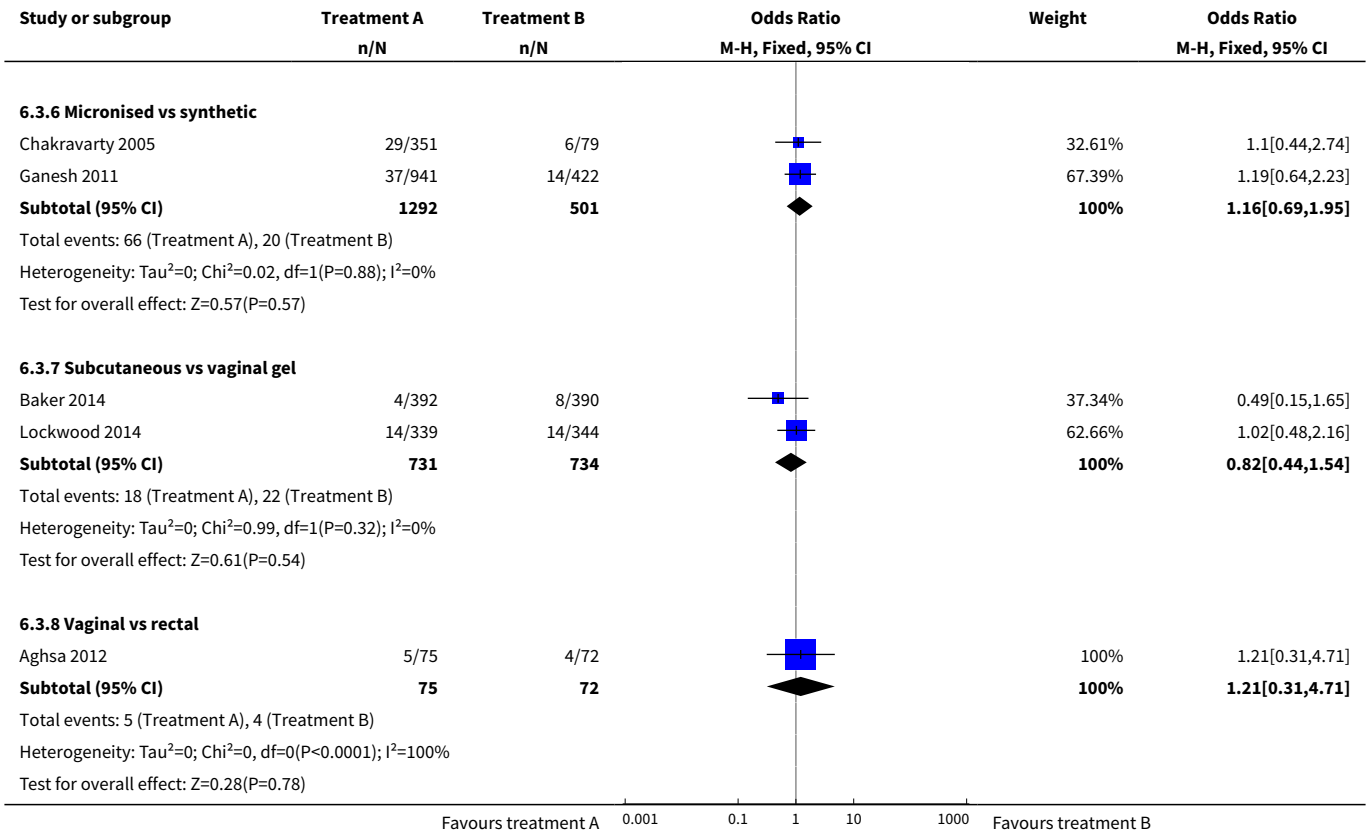
Study or subgroup	Treatment A n/N	Treatment B n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Abate 1999a	18/52	10/52		2.19%	2.22[0.91,5.44]
Artini 1995	6/44	7/44		2.03%	0.83[0.26,2.72]
Dal Prato 2008	45/138	87/274		13.16%	1.04[0.67,1.61]
Geusa 2001	42/150	40/150		9.65%	1.07[0.64,1.78]
Miller 2010	38/81	37/84		6.46%	1.12[0.61,2.07]
Perino 1997	69/150	41/150		7.42%	2.26[1.4,3.67]
Porcu 2003	27/112	30/112		7.63%	0.87[0.48,1.59]
Propst 2001	48/99	31/102		5.27%	2.16[1.21,3.84]
Saucedo 2000	8/20	7/20		1.41%	1.24[0.34,4.46]
Saucedo 2003	13/42	17/44		3.84%	0.71[0.29,1.74]
Sumita 2003	13/50	17/50		4.21%	0.68[0.29,1.61]
Yanushpolsky 2010	125/201	137/206		17.14%	0.83[0.55,1.24]
Zegers-Hochschild 2000	96/262	89/243		19.6%	1[0.7,1.44]
Subtotal (95% CI)	**1401**	**1531**		**100%**	**1.14[0.97,1.33]**
Total events: 548 (Treatment A), 550 (Treatment B)					
Heterogeneity: Tau²=0; Chi²=21.22, df=12(P=0.05); I²=43.45%					
Test for overall effect: Z=1.63(P=0.1)					
6.2.3 Vaginal/rectal vs oral					
Chakravarty 2005	109/351	25/79		10.46%	0.97[0.58,1.65]
Friedler 1999	16/32	10/32		1.86%	2.2[0.79,6.1]
Ganesh 2011	242/941	121/422		46.15%	0.86[0.67,1.11]
Patki 2007	70/247	122/308		28.93%	0.6[0.42,0.86]
Pouly 1996	40/139	36/144		9.37%	1.21[0.72,2.05]
Salehpour 2013	13/40	10/40		2.51%	1.44[0.55,3.83]
Saucedo 2000	7/20	3/20		0.73%	3.05[0.66,14.14]
Subtotal (95% CI)	**1770**	**1045**		**100%**	**0.89[0.75,1.05]**
Total events: 497 (Treatment A), 327 (Treatment B)					
Heterogeneity: Tau²=0; Chi²=12.47, df=6(P=0.05); I²=51.9%					
Test for overall effect: Z=1.36(P=0.17)					
6.2.4 Low dose vaginal vs high dose vaginal					
Bergh 2012	320/991	359/992		39.93%	0.84[0.7,1.01]
Dal Prato 2008	36/137	51/137		6.18%	0.6[0.36,1.01]
Doody 2009	174/403	346/808		21.51%	1.01[0.8,1.29]
Dunstone 1999	2/15	3/23		0.34%	1.03[0.15,7]
Ganesh 2011	138/482	104/459		12.5%	1.37[1.02,1.84]
Geber 2007a	54/122	44/122		4.03%	1.41[0.84,2.35]
Kleinstein 2005	47/212	55/218		6.94%	0.84[0.54,1.32]
Ludwig 2002	21/73	10/53		1.36%	1.74[0.74,4.08]
Ng 2003	7/30	9/30		1.13%	0.71[0.22,2.25]
Ng 2007	18/66	19/66		2.27%	0.93[0.43,1.98]
Rodriguez-Pezino 2004	18/40	37/84		2.16%	1.04[0.49,2.22]
Strehler 1999	18/45	18/51		1.66%	1.22[0.53,2.8]
Subtotal (95% CI)	**2616**	**3043**		**100%**	**0.98[0.87,1.09]**
Total events: 853 (Treatment A), 1055 (Treatment B)					
Heterogeneity: Tau²=0; Chi²=15.79, df=11(P=0.15); I²=30.32%					
Test for overall effect: Z=0.41(P=0.68)					
6.2.5 Short protocol vs long protocol					
Goudge 2010	32/51	29/46		11.69%	0.99[0.43,2.25]
Kohls 2012	80/110	79/110		22.17%	1.05[0.58,1.89]
		Treatment B	0.2 0.5 1 2 5	Treatment A	



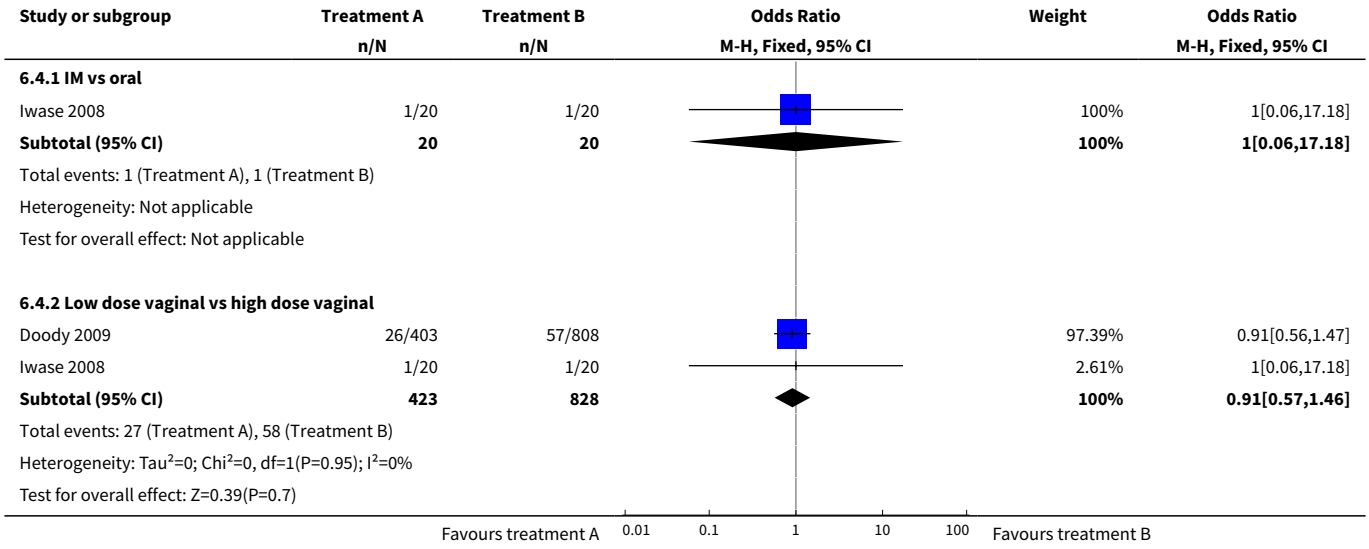
Analysis 6.3. Comparison 6 Progesterone regimens, Outcome 3 Miscarriage rate.



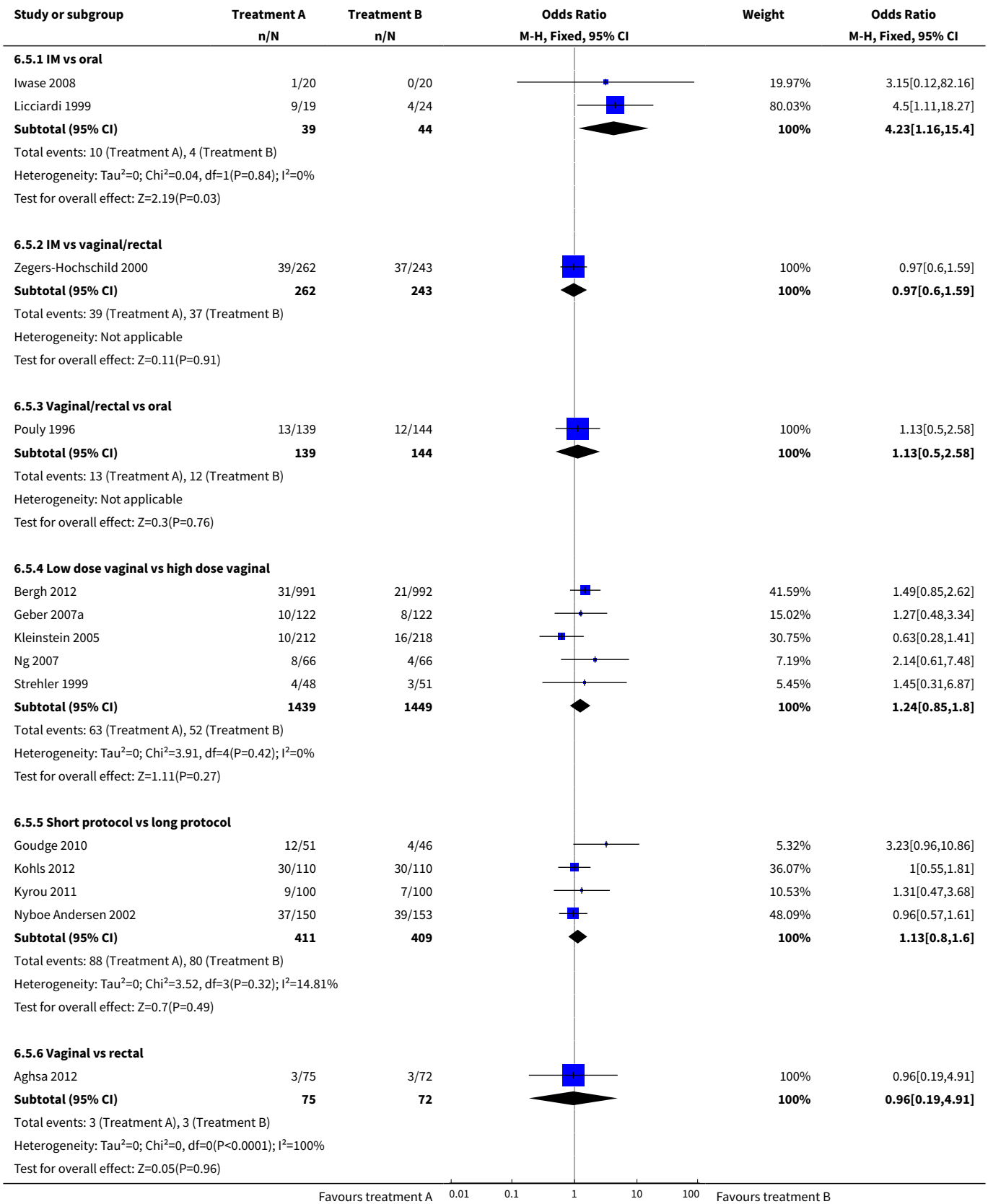




Analysis 6.4. Comparison 6 Progesterone regimens, Outcome 4 OHSS.

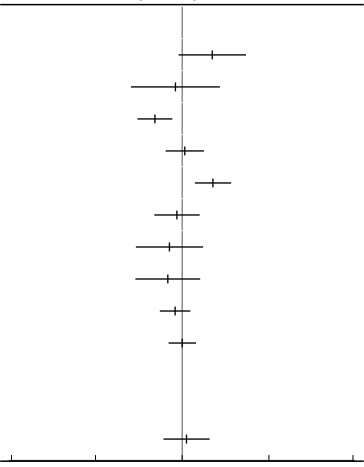


Analysis 6.5. Comparison 6 Progesterone regimens, Outcome 5 Multiple pregnancy.



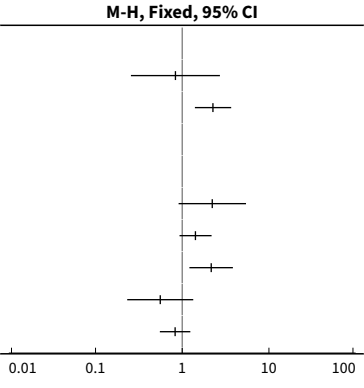
Analysis 6.6. Comparison 6 Progesterone regimens, Outcome 6 Clinical pregnancy: IM vs vaginal/rectal: subgroup analysis by COH method.

Study or subgroup	IM progesterone n/N	Vaginal/rectal progesterone n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.6.1 Human gonadotropins with or without GnRH agonists				
Abate 1999a	18/52	10/52		2.22[0.91,5.44]
Artini 1995	6/44	7/44		0.83[0.26,2.72]
Dal Prato 2008	45/138	87/174		0.48[0.3,0.77]
Geusa 2001	42/150	40/150		1.07[0.64,1.78]
Perino 1997	69/150	41/150		2.26[1.4,3.67]
Porcu 2003	27/112	30/112		0.87[0.48,1.59]
Saucedo 2003	13/42	17/44		0.71[0.29,1.74]
Sumita 2003	13/50	17/50		0.68[0.29,1.61]
Yanushpolsky 2010	125/201	137/206		0.83[0.55,1.24]
Zegers-Hochschild 2000	96/262	89/243		1[0.7,1.44]
6.6.2 Human gonadotropins with or without GnRH antagonists				
Miller 2010	38/81	37/84		1.12[0.61,2.07]



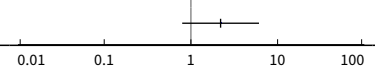
Analysis 6.7. Comparison 6 Progesterone regimens, Outcome 7 Clinical pregnancy: IM vs vaginal/rectal: subgroup analysis by treatment duration.

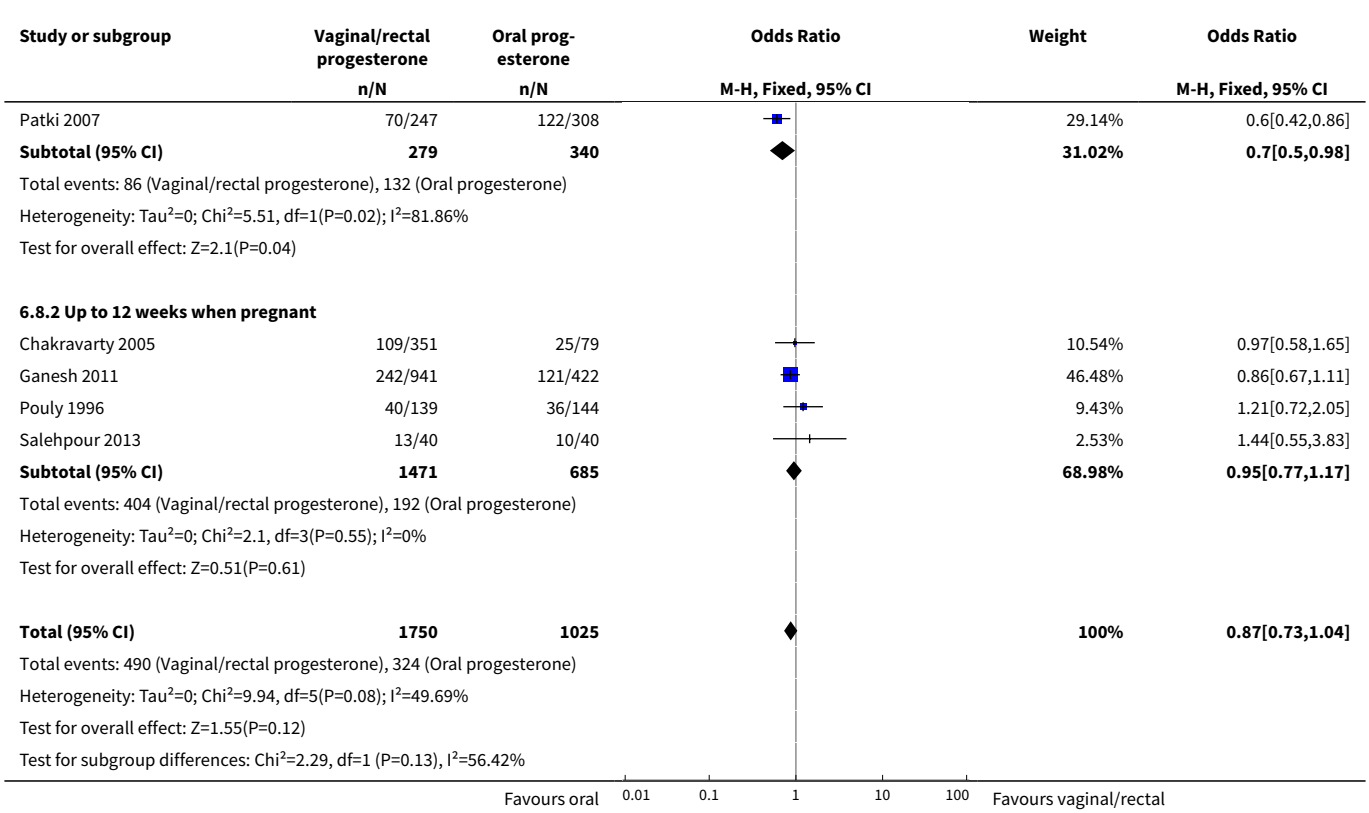
Study or subgroup	IM progesterone n/N	Vaginal/rectal progesterone n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.7.1 Stop at pregnancy test				
Artini 1995	6/44	7/44		0.83[0.26,2.72]
Perino 1997	69/150	41/150		2.26[1.4,3.67]
6.7.2 Up to 12 weeks when pregnant				
Abate 1999a	18/52	10/52		2.22[0.91,5.44]
Dal Prato 2008	55/138	87/274		1.42[0.93,2.18]
Propst 2001	48/99	31/102		2.16[1.21,3.84]
Sumita 2003	13/50	17/44		0.56[0.23,1.34]
Yanushpolsky 2010	125/201	137/206		0.83[0.55,1.24]



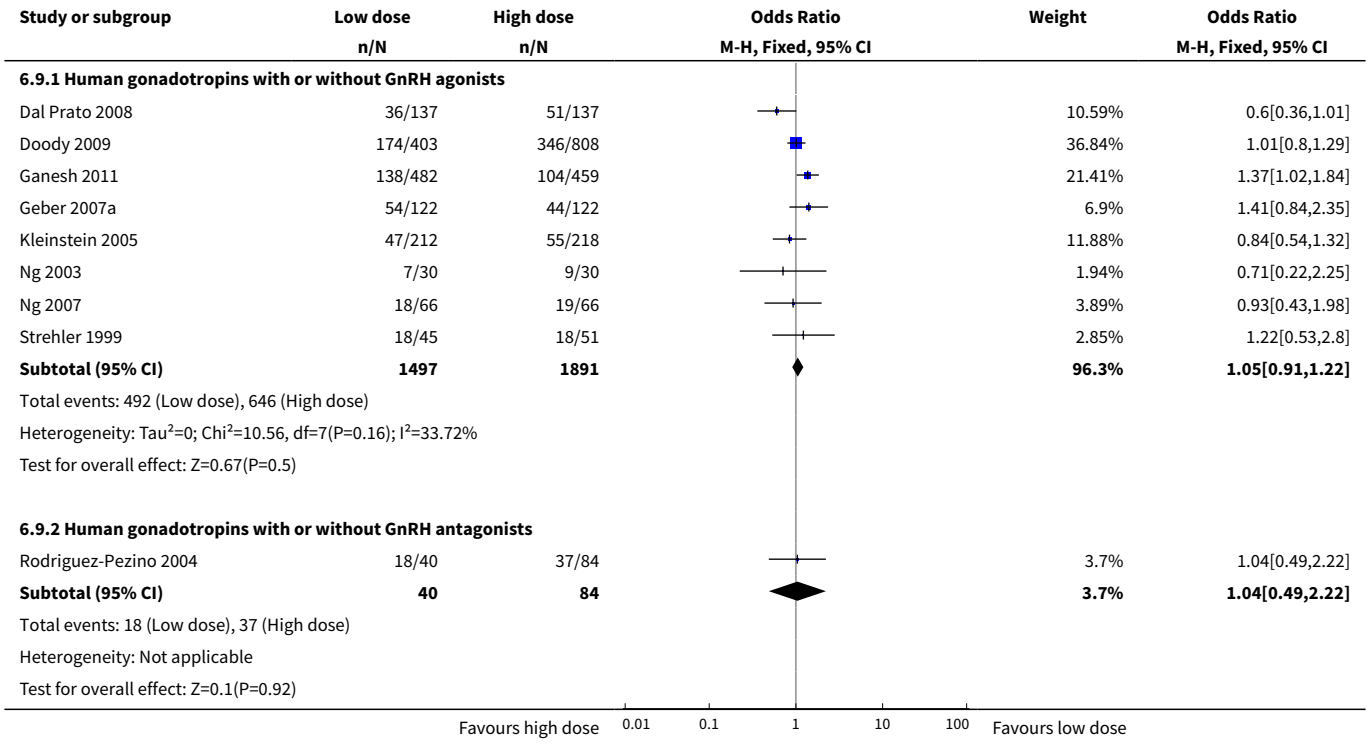
Analysis 6.8. Comparison 6 Progesterone regimens, Outcome 8 Clinical pregnancy: vaginal/rectal vs oral: subgroup analysis by treatment duration.

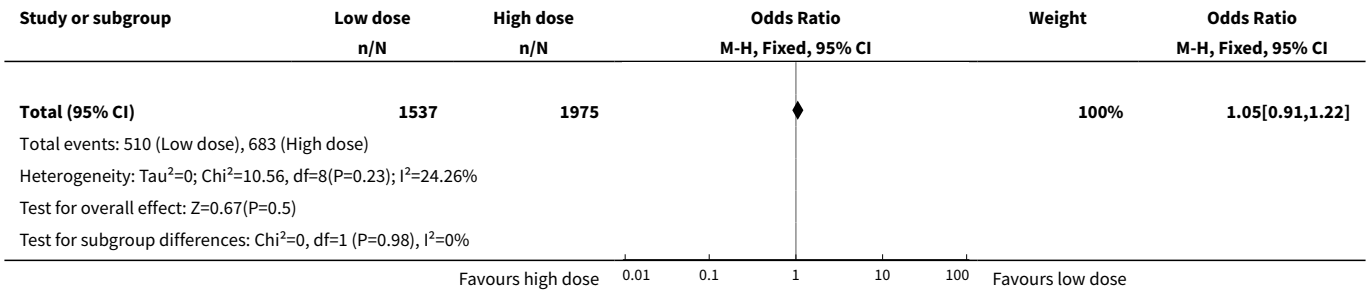
Study or subgroup	Vaginal/rectal progesterone n/N	Oral prog-esterone n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
6.8.1 Stop at pregnancy test					
Friedler 1999	16/32	10/32		1.87%	2.2[0.79,6.1]



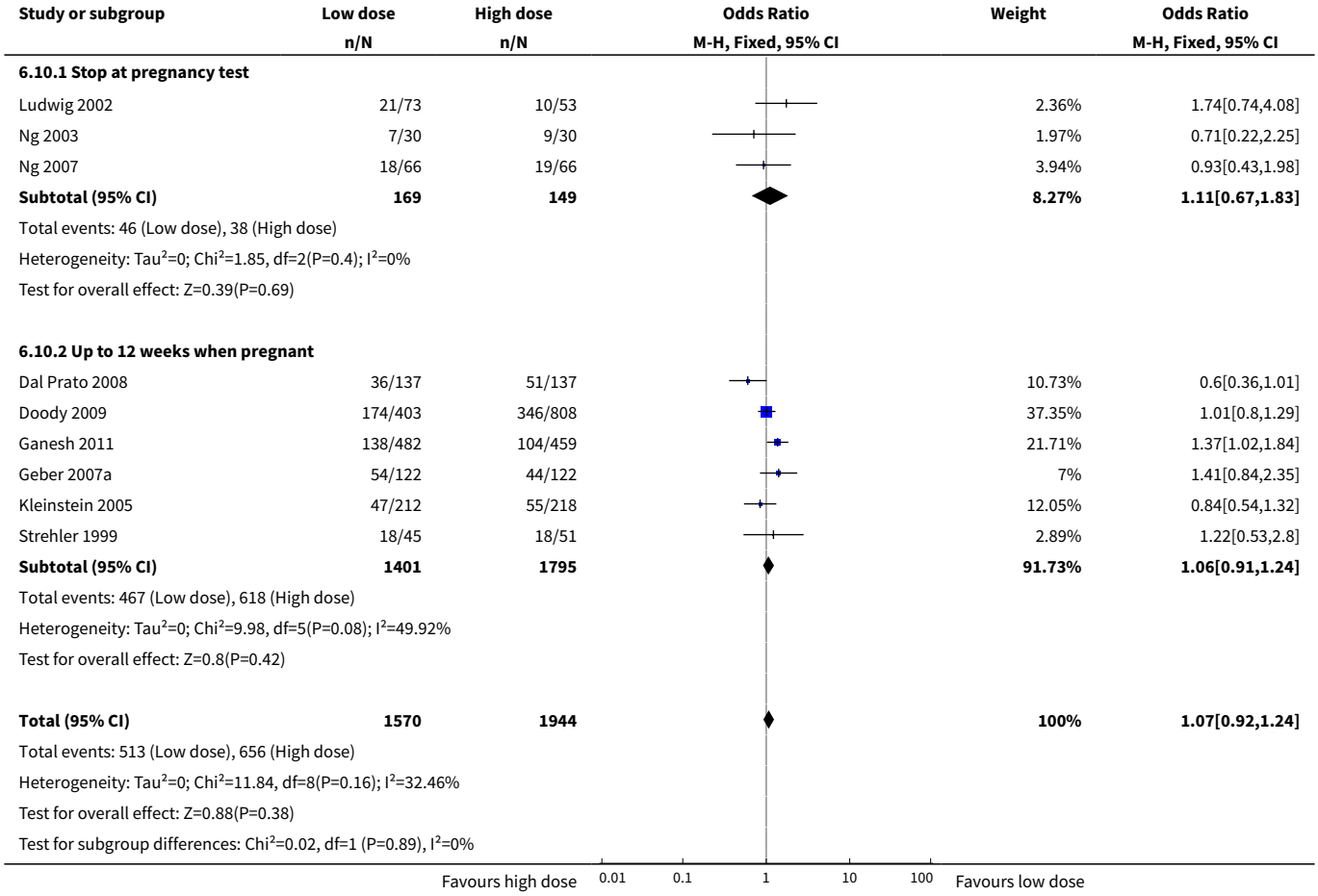


Analysis 6.9. Comparison 6 Progesterone regimens, Outcome 9 Clinical pregnancy: low vs high dose vaginal: subgroup analysis by COH method.

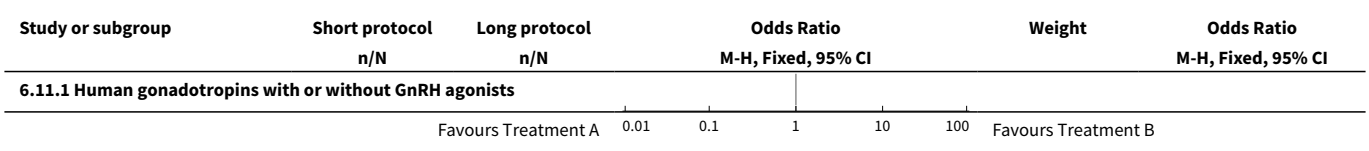


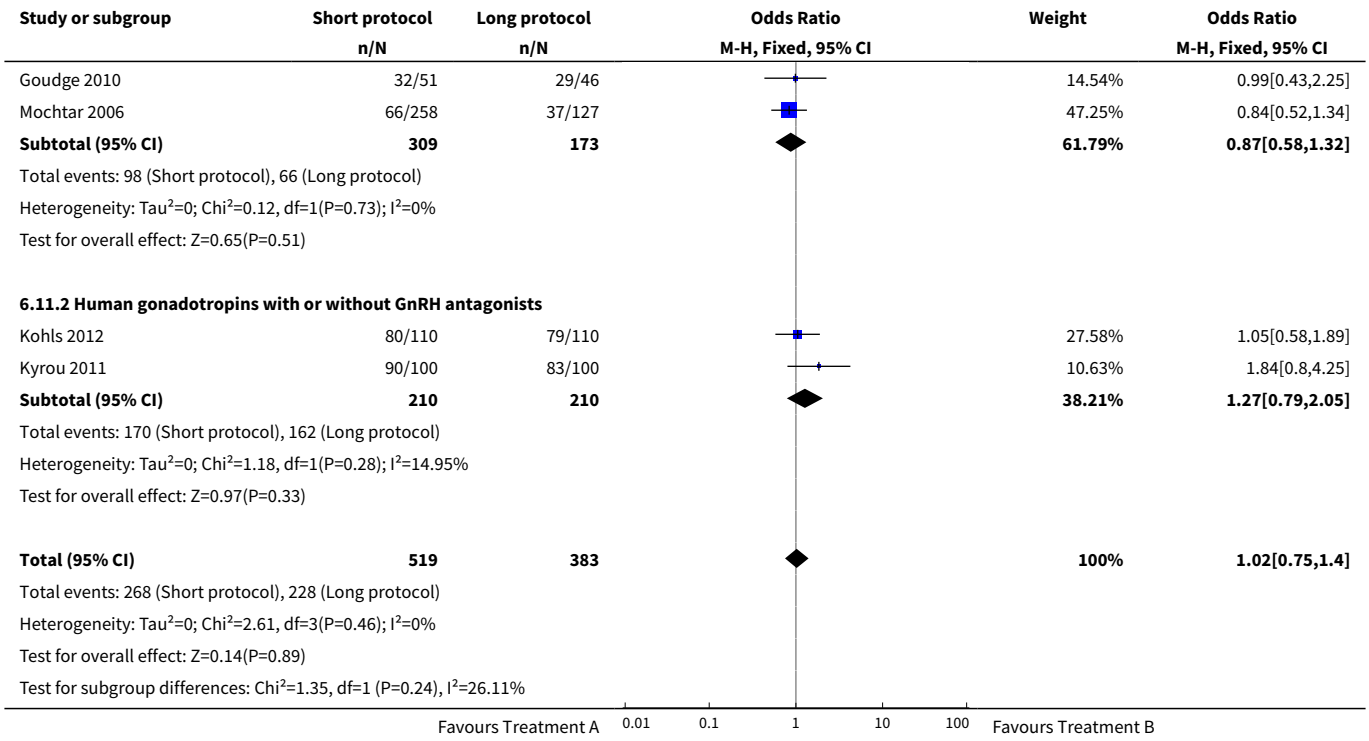


Analysis 6.10. Comparison 6 Progesterone regimens, Outcome 10 Clinical pregnancy: low vs high dose vaginal: subgroup analysis by duration of treatment.



Analysis 6.11. Comparison 6 Progesterone regimens, Outcome 11 Clinical pregnancy: short vs long protocol: subgroup analysis by COH method.





Comparison 7. Progesterone + oestrogen regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancy rate	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Short protocol vs long protocol	1	910	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.81, 1.43]
1.2 Low dosage vs high dosage	1	285	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.37, 1.13]
2 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low dosage vs high dosage	1	285	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.48, 1.37]
3 Miscarriage rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Low dosage vs high dosage	1	285	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [0.86, 11.39]
4 Multiple pregnancy	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Low dosage vs high dosage	1	285	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.12]

Analysis 7.1. Comparison 7 Progesterone + oestrogen regimens, Outcome 1 Live birth/ongoing pregnancy rate.

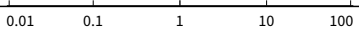
Study or subgroup	Treatment A n/N	Treatment B n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
7.1.1 Short protocol vs long protocol					
Feichtinger 2011	138/446	136/464		100%	1.08[0.81,1.43]
Subtotal (95% CI)	**446**	**464**		**100%**	**1.08[0.81,1.43]**
Total events: 138 (Treatment A), 136 (Treatment B)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
7.1.2 Low dosage vs high dosage					
Tonguc 2011	24/95	65/190		100%	0.65[0.37,1.13]
Subtotal (95% CI)	**95**	**190**		**100%**	**0.65[0.37,1.13]**
Total events: 24 (Treatment A), 65 (Treatment B)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.13)					

Analysis 7.2. Comparison 7 Progesterone + oestrogen regimens, Outcome 2 Clinical pregnancy rate.

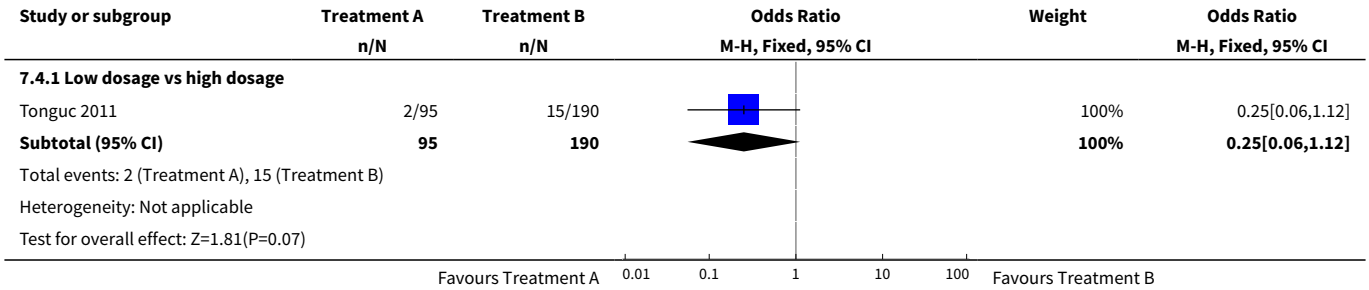
Study or subgroup	Treatment A n/N	Treatment B n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
7.2.1 Low dosage vs high dosage					
Tonguc 2011	30/95	69/190		100%	0.81[0.48,1.37]
Subtotal (95% CI)	**95**	**190**		**100%**	**0.81[0.48,1.37]**
Total events: 30 (Treatment A), 69 (Treatment B)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					

Analysis 7.3. Comparison 7 Progesterone + oestrogen regimens, Outcome 3 Miscarriage rate.

Study or subgroup	Treatment A n/N	Treatment B n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
7.3.1 Low dosage vs high dosage					
Tonguc 2011	6/95	4/190		100%	3.13[0.86,11.39]
Subtotal (95% CI)	**95**	**190**		**100%**	**3.13[0.86,11.39]**
Total events: 6 (Treatment A), 4 (Treatment B)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					



Analysis 7.4. Comparison 7 Progesterone + oestrogen regimens, Outcome 4 Multiple pregnancy.



APPENDICES

Appendix 1. Gynaecology and Fertility search strategy

From inception until 05.08.15

Keywords CONTAINS "luteal phase" or "luteal phase support" or "luteal phase support timing" or "luteal phase supprt" or "luteal support" or Title CONTAINS "luteal phase" or "luteal phase support" or "luteal phase support timing" or "luteal phase supprt" or "luteal support"

AND

Keywords CONTAINS "Progesterone" or "progesterone capsule" or "progesterone gel" or "progesterone, micronized" or "progesterone receptor agonist" or "HCG" or "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "dydrogesterone" or "dydrogestrone" or "utrogestan" or "vaginal micronised progesterone" or "vaginal micronized progesterone capsules" or "vaginal micronized progesterone gel" or "vaginal progesterone" or "17-alpha hydroxyprogesterone" or"GnRH a"or "GnRH agonist"or "Gonadotrophin releasing agonist"or "gonadotropin releasing hormone agonist"or "triptorelin"or"leuprolide"or"leuprolide acetate"or"leuprolide depot"or "Goserelin"or "Zoladex"or "nafarelin"or"buserelin"or"Buserelin Acetate"or "crinone"or "Crinone 8"or Title CONTAINS "Progesterone" or "progesterone capsule" or "progesterone gel" or "progesterone, micronized" or "progesterone receptor agonist" or "HCG" or "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "dydrogesterone" or "dydrogestrone" or "utrogestan" or "vaginal micronised progesterone" or "vaginal micronized progesterone capsules" or "vaginal micronized progesterone gel" or "vaginal progesterone" or "17-alpha hydroxyprogesterone" or "GnRH a"or "GnRH agonist"or "Gonadotrophin releasing agonist"or "gonadotropin releasing hormone agonist"or "triptorelin"or"leuprolide"or"leuprolide acetate"or"leuprolide depot"or "Goserelin"or "Zoladex"or "nafarelin"or"buserelin"or"Buserelin Acetate"or "crinone"or "Crinone 8" (361 hits)

Appendix 2. CENTRAL search strategy

From inception until 05.08.15

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (1756)
2 embryo transfer$.tw. (1200)
3 in vitro fertili?ation.tw. (1610)
4 ivf-et.tw. (324)
5 (ivf or et).tw. (13581)
6 icsi.tw. (992)
7 intracytoplasmic sperm injection$.tw. (538)
8 (blastocyst adj2 transfer$).tw. (130)
9 exp Insemination, Artificial/ (296)
10 Insemination$.tw. (820)
11 iui.tw. (398)
12 or/1-11 (15755)
13 exp Luteal Phase/ (455)
14 (luteal adj5 support$).tw. (285)
15 (luteal adj5 phase).tw. (1041)
16 (ischemic adj5 phase).tw. (158)
17 post ovulat$.tw. (20)
18 (post adj5 transfer$).tw. (76)
19 (after adj5 transfer$).tw. (8297)

20 (post adj5 trigger$).tw. (19)
21 (after adj5 trigger$).tw. (3284)
22 or/13-21 (12631)
23 12 and 22 (2186)
24 exp Progesterone/ (2262)
25 Progesterone$.tw. (2894)
26 dydrogesterone.tw. (167)
27 utrogest.tw. (7)
28 17 alpha-hydroxyprogesterone.tw. (93)
29 Prontogest.tw. (5)
30 exp chorionic gonadotropin/ or exp chorionic gonadotropin, beta subunit, human/ (632)
31 HCG.tw. (1313)
32 crinone.tw. (46)
33 chorionic gonadotropin$.tw. (515)
34 chorionic gonadotrophin$.tw. (287)
35 exp Gonadotropin-Releasing Hormone/ (1892)
36 gnrha.tw. (246)
37 gnrh agonist$.tw. (821)
38 gnrh a.tw. (1441)
39 Gonadotrop?in-Releasing Hormone agonist$.tw. (514)
40 buserelin/ or goserelin/ or leuprolide/ or nafarelin/ or triptorelin pamoate/ (1268)
41 leuprolide.tw. (460)
42 triptorelin.tw. (205)
43 (goserelin or Zoladex).tw. (550)
44 (nafarelin or buserelin).tw. (360)
45 or/24-44 (8084)
46 23 and 45 (925)

Appendix 3. MEDLINE search strategy

From inception until 05.08.15

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (34795)
2 embryo transfer$.tw. (8997)
3 in vitro fertili?ation.tw. (18351)
4 ivf-et.tw. (1956)
5 (ivf or et).tw. (199930)
6 icsi.tw. (6126)
7 intracytoplasmic sperm injection$.tw. (5452)
8 (blastocyst adj2 transfer$).tw. (634)
9 exp Insemination, Artificial/ (10415)
10 Insemination$.tw. (13455)
11 iui.tw. (1330)
12 or/1-11 (239597)
13 exp Luteal Phase/ (4707)
14 (luteal adj5 support$).tw. (609)
15 (luteal adj5 phase).tw. (9066)
16 (ischemic adj5 phase).tw. (1010)
17 post ovulat$.tw. (722)
18 (post adj5 transfer$).tw. (1196)
19 (after adj5 transfer$).tw. (18597)
20 (post adj5 trigger$).tw. (423)
21 (after adj5 trigger$).tw. (2718)
22 or/13-21 (34992)
23 12 and 22 (4736)
24 exp Progesterone/ (65145)
25 Progesterone$.tw. (71879)
26 dydrogesterone.tw. (386)
27 utrogest.tw. (4)
28 17 alpha-hydroxyprogesterone.tw. (1233)
29 Prontogest.tw. (5)
30 exp chorionic gonadotropin/ or exp chorionic gonadotropin, beta subunit, human/ (29789)

31 HCG.tw. (21949)
32 crinone.tw. (55)
33 chorionic gonadotropin$.tw. (14208)
34 chorionic gonadotrophin$.tw. (4428)
35 exp Gonadotropin-Releasing Hormone/ (29797)
36 gnrha.tw. (1216)
37 gnrh agonist$.tw. (3674)
38 gnrh a.tw. (962)
39 Gonadotrop?in-Releasing Hormone agonist$.tw. (2279)
40 buserelin/ or goserelin/ or leuprolide/ or nafarelin/ or triptorelin pamoate/ (7400)
41 leuprolide.tw. (1648)
42 triptorelin.tw. (591)
43 (goserelin or Zoladex).tw. (1060)
44 (nafarelin or buserelin).tw. (1508)
45 or/24-44 (158445)
46 23 and 45 (1880)
47 randomized controlled trial.pt. (415276)
48 controlled clinical trial.pt. (92000)
49 randomized.ab. (337080)
50 randomised.ab. (68774)
51 placebo.tw. (173943)
52 clinical trials as topic.sh. (179581)
53 randomly.ab. (243225)
54 trial.ti. (148605)
55 (crossover or cross-over or cross over).tw. (66344)
56 or/47-55 (1052850)
57 exp animals/ not humans.sh. (4138378)
58 56 not 57 (970697)
59 46 and 58 (413)

Appendix 4. EMBASE search strategy

From inception until 05.08.15

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (58478)
2 embryo$ transfer$.tw. (14723)
3 in vitro fertili?ation.tw. (22782)
4 ivf-et.tw. (2613)
5 icsi.tw. (11295)
6 intracytoplasmic sperm injection$.tw. (7090)
7 (blastocyst adj2 transfer$).tw. (1405)
8 (ivf or et).tw. (562334)
9 exp artificial insemination/ (13046)
10 Insemination$.tw. (14515)
11 iui.tw. (2291)
12 or/1-11 (613465)
13 exp luteal phase/ (8055)
14 (luteal adj5 support$).tw. (935)
15 (luteal adj5 phase).tw. (9877)
16 (ischemic adj5 phase).tw. (1407)
17 post ovulat$.tw. (724)
18 (post adj5 transfer$).tw. (1828)
19 (after adj5 transfer$).tw. (21870)
20 (post adj5 trigger$).tw. (617)
21 (after adj5 trigger$).tw. (3522)
22 or/13-21 (41810)
23 12 and 22 (7785)
24 exp PROGESTERONE/ (74004)
25 Progesterone$.tw. (76866)
26 dydrogesterone.tw. (481)
27 utrogest.tw. (39)
28 17 alpha-hydroxyprogesterone.tw. (544)

29 Prontogest.tw. (69)
30 exp chorionic gonadotropin/ (39901)
31 HCG.tw. (26131)
32 crinone.tw. (342)
33 chorionic gonadotropin$.tw. (14449)
34 chorionic gonadotrophin$.tw. (4514)
35 exp gonadorelin/ (29277)
36 gnrha.tw. (1660)
37 gonadorelin.tw. (265)
38 gnrh agonist$.tw. (5201)
39 gnrh a.tw. (1168)
40 Gonadotrop?in-Releasing Hormone agonist$.tw. (2638)
41 exp triptorelin/ (4310)
42 exp leuprorelin/ (9237)
43 (leuprolide or leuprorelin).tw. (2810)
44 (triptorelin or nafarelin).tw. (1207)
45 nafarelin acetate/ or nafarelin/ (1355)
46 exp goserelin/ (6081)
47 buserelin acetate/ or buserelin/ (4709)
48 (goserelin or Zoladex).tw. (2780)
49 (nafarelin or buserelin).tw. (1792)
50 or/24-49 (187454)
51 23 and 50 (3417)
52 Clinical Trial/ (852394)
53 Randomized Controlled Trial/ (387382)
54 exp randomization/ (68604)
55 Single Blind Procedure/ (21212)
56 Double Blind Procedure/ (124532)
57 Crossover Procedure/ (44903)
58 Placebo/ (265208)
59 Randomi?ed controlled trial$.tw. (125918)
60 Rct.tw. (18621)
61 random allocation.tw. (1464)
62 randomly.tw. (303665)
63 randomly allocated.tw. (23537)
64 allocated randomly.tw. (2071)
65 (allocated adj2 random).tw. (741)
66 Single blind$.tw. (16522)
67 Double blind$.tw. (155916)
68 ((treble or triple) adj blind$).tw. (497)
69 placebo$.tw. (222683)
70 prospective study/ (312235)
71 or/52-70 (1692110)
72 case study/ (34359)
73 case report.tw. (293151)
74 abstract report/ or letter/ (942602)
75 or/72-74 (1263530)
76 71 not 75 (1651662)
77 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5399612)
78 76 not 77 (1535561)
79 51 and 78 (837)

Appendix 5. PsycINFO search strategy

From inception until 05.08.15

1 exp Reproductive Technology/ (1519)
2 embryo transfer$.tw. (103)
3 in vitro fertili?ation.tw. (603)
4 ivf-et.tw. (17)
5 (ivf or et).tw. (105955)
6 icsi.tw. (58)

7 intracytoplasmic sperm injection$.tw. (44)
8 (blastocyst adj2 transfer$).tw. (4)
9 Insemination$.tw. (644)
10 iui.tw. (27)
11 or/1-10 (107656)
12 (luteal adj5 support$).tw. (1)
13 (luteal adj5 phase).tw. (901)
14 (ischemic adj5 phase).tw. (69)
15 post ovulat$.tw. (16)
16 (post adj5 transfer$).tw. (170)
17 (after adj5 transfer$).tw. (1133)
18 (post adj5 trigger$).tw. (46)
19 (after adj5 trigger$).tw. (224)
20 or/12-19 (2539)
21 11 and 20 (88)
22 exp Progesterone/ (1933)
23 Progesterone$.tw. (3631)
24 dydrogesterone.tw. (9)
25 utrogest.tw. (0)
26 17 alpha-hydroxyprogesterone.tw. (6)
27 Prontogest.tw. (0)
28 exp Gonadotropic Hormones/ (3880)
29 HCG.tw. (81)
30 crinone.tw. (0)
31 chorionic gonadotropin$.tw. (87)
32 chorionic gonadotrophin$.tw. (12)
33 exp Gonadotropic Hormones/ (3880)
34 gnrha.tw. (29)
35 gnrh agonist$.tw. (58)
36 gnrh a.tw. (9)
37 Gonadotrop?in-Releasing Hormone agonist$.tw. (61)
38 (leuprolide or leuprorelin).tw. (85)
39 (triptorelin or nafarelin).tw. (24)
40 gonadorelin.tw. (3)
41 (goserelin or Zoladex).tw. (28)
42 buserelin.tw. (6)
43 or/22-42 (7576)
44 21 and 43 (4)

Appendix 6. CINAHL search strategy

From 1982 to 05.08.15

#	Query	Results
S29	S20 AND S28	58
S28	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	856
S27	TX after N5 trigger*	214
S26	TX post N3 transfer*	81
S25	TX post ovulat*	11

(Continued)

S24	TX ischemic N5 phase	105
S23	TX luteal N5 phase	446
S22	TX luteal N5 support*	29
S21	(MM "Luteal Phase")	54
S20	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	5,745
S19	TX intra-uterine insemination	9
S18	TX (ovari* N2 induction)	12
S17	TX COH	61
S16	TX ovarian hyperstimulation	317
S15	TX superovulat*	22
S14	TX intrauterine insemination	142
S13	TX IUI	75
S12	TX artificial insemination	443
S11	TX assisted reproduct*	1,250
S10	(MM "Insemination, Artificial")	236
S9	(MM "Reproduction Techniques+")	3,791
S8	TX intracytoplasmic sperm injection*	223
S7	TX embryo* N3 transfer*	729
S6	TX ovar* N3 hyperstimulat*	319
S5	TX ovari* N3 stimulat*	236
S4	TX IVF or TX ICSI	1,196
S3	(MM "Fertilization in Vitro")	1,388
S2	TX vitro fertilization	2,750
S1	TX vitro fertilisation	259

Appendix 7. *The Cochrane Library* - DARE search strategy

ID	Search

(Continued)

#1	utrogestan in Other Reviews
#2	vaginal micronised progesterone in Other Reviews
#3	dydrogestrone in Other Reviews
#4	Progesterone in Other Reviews
#5	human chorionic gonadotrophin in Other Reviews
#6	human chorionic gonadotropin in Other Reviews
#7	luteal phase in Other Reviews
#8	luteal phase support in Other Reviews
#9	luteal phase support in Other Reviews
#10	((#1 OR #2 OR #3 OR #4 OR #5 OR #6) AND (#7 OR #8 OR #9))

Appendix 8. WHO ICTRP and clinicaltrials.gov

Searched from inception until 05.08.15

ICTRP

"Agonist and luteal phase" (39 hits)

"Progesterone and luteal phase support" (14 hits)

"Estradiol and luteal phase support" (4 hits)

"Estrogen and luteal phase support" (1 hit)

"Progesterone and luteal phase" (10 hits)

" HCG and luteal phase" (14 hits)

Clinicaltrials.gov

"Agonist and luteal phase" (55 hits)

"GNRH and luteal phase" (67 hits)

"Progesterone and luteal phase support" (60)

"Estrogen and luteal phase support" (16 hits)

Appendix 9. Web of Science search strategy

Set	Results	
#7	323	#5 AND #6 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years*
#6	55,927	TS=(embryo transfer) OR TS=(ivf) OR TS=(in vitro fertilisation) OR TS=(in vitro infertilization) OR TS=(iui) OR TS=(icsi)

(Continued)

		Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years
#5	740	#1 AND #4 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years*
#4	4,153	#3 AND #2 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years*
#3	28,229	TS=(hcg) OR TS=(chorionic gonadotropin) OR TS=(chorionic gonadotrophin) OR TS=(human chorionic gonadotropin) OR TS=(human chorionic gonadotrophin) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years*
#2	74,620	TS=(progesterone) OR TS=(progesteron) OR TS=(dydrogesterone) OR TS=(utrogest) OR TS=(prontogest) OR TS=(17 alpha-hydroxyprogesterone) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years*
#1	9,045	TS=(Luteal phase) OR TS=(luteal support) OR TS=(Luteal phase support) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years*

Appendix 10. Study eligibility form

Study ID	
Report ID	
ID review author	
Date form completed	
Report authors	
Complete reference	
Publication type	
Report author contact details	

Study characteristics	Review inclusion criteria	Assessment			Quotation
		Yes	No	Unclear	
Type of study	RCT or cross-over?				
Participants	Women undergoing ART?				

(Continued)

	When used: GIFT or ZIFT < 20%?
Interventions	**No** frozen ET?
	No other substances than progesterone/hCG/oestrogen?
	No ET from donated oocytes?
	No ET from frozen oocytes/frozen ovarian tissue?
	No in vivo maturation (IVM)?
	Include progesterone administration (any route/type/duration) and/or hCG administration (any route/type/duration)?
	Progesterone administration for at least 5 days in luteal phase?
	At least 2 times hCG administration in luteal phase?

Final decision
o Include (if all 'yes')
o Exclude (if any 'no')
Reason for exclusion:
If Unclear, action undertaken:

Appendix 11. Data extraction form

General information

Study ID	
ID review author	
Date form completed	
Complete reference	
Published?	o Yes

(Continued)

	o No
Publication type	Journal/Abstract/Other (specify)
Report author contact details	
Notes:	

Study eligibility	
Confirm eligibility	o Included
	o Excluded
	Reason for exclusion:
	o Unclear
	Reason:
	Action undertaken:

Study details

Study intention	**Description as stated in report**	**Reference**
Aim of study		
Setting	o Multi-centre o Single centre o Unclear	
Type of study	o RCT o Cross-over	
Country		
Power calculation done	o Yes o No o Unclear	

Methods	Description as stated in report	Reference
Inclusion/Exclusion criteria for participation in study		
Total number of intervention groups (specify)		
Allocation concealment?		
Moment of randomisation		
Method randomisation sequence		
Blinding	Clinician o Yes o No o Unclear Researcher o Yes o No o Unclear Participant o Yes o No o Unclear	
Method of blinding		
Reporting bias		

Participants	Description	Reference
Total number randomly assigned		
Total number analysed		
Reason why not analysed		
Number of cycles per woman		
Number allocated to each intervention group		
Numbers and reasons for exclusion for each intervention group		
Age (median, mean, range, if available)		

(Continued)

Number of IVF
Number of ICSI
Number of previous cycles
Number of transferred embryo's

Intervention group		
Group name		
Intervention	**Description**	**Reference**
Type		
Dosage		
Number of doses		
Route		
Duration		
Duration of follow-up		
Protocol for ovulation induction		
Scheme for trigger		
GnRH	o Agonist o Antagonist	
GnRH scheme	o Duration o Dose o Route of administration	

Comparison group		
Group name		
Comparison	**Description**	**Reference**
Type		
Dosage		

(Continued)

Number of doses	
Route	
Duration	
Duration of follow-up	
Protocol for ovulation induction	
Scheme for trigger	
GnRH	o Agonist o Antagonist
GnRH scheme	o Duration o Dose o Route of administration

Outcomes	**Yes**	**No**	**Definition?**	**References**
LBR				
CPR				
OPR				
MR				
OHSS				
MPR				
Other (specify)				

Results	Copy table for each comparison.	
Comparison		
ITT?		
Results	**Intervention**	**Comparison**

(Continued)

	Events	Number of participants	Events	Number of participants
ET				
CPR				
OPR				
LBR				
OHSS				
MR				
MultiP				
Number of missing participants				
Reasons for missing participants				
Any other results reported				

Other relevant information

Information	Description	References
Funding source and possible conflict of interest		
Notes review author		
Correspondence required (specify)	o No o Yes o E-mail sent on o Letter sent on o Fax sent on ***Reaction received: Yes/No***	

(Continued)

USE NEW FORM WITH COMPLETE INFO

Appendix 12. Risk of Bias

Entry	Judgement	Description	Reference
Adequate sequence generation?	High risk Unclear risk Low risk	*Method used to produce comparable groups*	
Adequate allocation concealment?	High risk Unclear risk Low risk	*Method used in detail*	
Adequate blinding?	High risk Unclear risk Low risk	*All measures used*	
Incomplete outcome data addressed?	High risk Unclear risk Low risk	*Completeness of data primary outcome (LBR) incl attrition and exclusions from analysis*	
Free of selective reporting?	High risk Unclear risk Low risk	*State how possibility of selective outcome reporting is examined*	
Free of other bias?	High risk Unclear risk Low risk	*State any important concerns*	

WHAT'S NEW

Date	Event	Description
20 October 2016	Amended	Conclusions reworded to clarify that the evidence for hCG is very similar to the evidence for progesterone, with respect to their effect on live birth and pregnancy.

HISTORY

Protocol first published: Issue 6, 2011
Review first published: Issue 10, 2011

Date	Event	Description
28 October 2015	Amended	Response to feedback, opportunity taken to add two new studies (Aboulghar 2015;Yildiz 2014). Corrected analyses 1.1 and 3.5, corrected median values in summary of findings table.
29 April 2015	New citation required but conclusions have not changed	The addition of 24 new studies has not led to a change in the conclusions of the review
29 April 2015	New search has been performed	This is an update of a previously published review (van der Linden 2011). We have included 24 new studies in the review (Aghahosseini 2011; Aghsa 2012; Ata 2010; Baker 2014; Beltsos 2011; Bergh 2012; Brigante 2013; Colakoglu 2011; Erdem 2013; Feichtinger 2011; Humaidan 2006; Inamdar 2012; Kably Ambe 2005; Kyrou 2011; Lin 2013; Lockwood 2014; Mochtar 2006; Moini 2011; Nallapeta 2013; Nyboe Andersen 2002; Salehpour 2013; Serour 2012; Tonguc 2011; Williams 2001). Kohls 2012 and Stadtmauer 2013 replace the abstracts previously published in 2010 New comparisons added: progesterone + oestrogen regimens, vaginal suppositories vs vaginal gel, vaginal progesterone vs rectal progesterone, subcutaneous progesterone vs vaginal gel, vaginal ring vs vaginal gel Correction to analyses: all now set to record "event" rather than "non-event" Primary outcome: changed from live birth to live birth or ongoing pregnancy No major change to conclusions (although advantage for synthetic progesterone is no longer evident)
4 June 2012	Amended	Correction to summary of main results: progesterone and oestrogen for luteal phase support
11 May 2012	Amended	Correction of erroneous data for Elgindy 2010 (Analyses 4.2.1 and 4.2.3)
16 March 2011	New search has been performed	This is an update of a previously published review with the same title and has been prepared by a new review author team

CONTRIBUTIONS OF AUTHORS

MvdL, MM and KB extracted data. MvdL entered data and wrote the review and the update. CF acted as a third review author in cases of disagreement, helped draft the review, acted as a clinical expert and commented on the review and the update. JK acted as a clinical expert and commented on the review and the update.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- MDSG, Other.

External sources

- Stichting Nijmeegs Universiteitsfonds, Netherlands.

  Scholarship to support students from the Radboud University Nijmegen to study, do an internship or conduct research abroad.
- Commissie Voorzieningen Studenten Budget (CVSB), Netherlands.

  Grant to subsidise activities of (medical) student organisation and foreign internships of individual students from the medical faculty of the Radboud University Nijmegen.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Objective.

We changed the objective from "To determine the effectiveness and safety of luteal phase support in subfertile women undergoing assisted reproductive technology" to "To determine the relative effectiveness and safety of methods of luteal phase support provided to subfertile women undergoing assisted reproduction". We made this change because we investigated not only the use of luteal phase support but also the different ways by which luteal phase support is delivered.

2. Inclusion criteria.

In the protocol, we stated that we would exclude studies using any other substance in the luteal phase than progesterone, hCG or GnRH agonists. We found one study investigating LH instead of hCG (Geber 2007). Because LH is very similar to hCG, we decided to include this study in the comparison of progesterone versus progesterone + hCG. We also decided to delete the exclusion criterion "use of other substances for luteal phase support than progesterone, hCG or oestrogen". This means that in the future we will be able to include new agents.

3. Exclusion criteria.

In the 2015 update, we have added luteal phase support after intrauterine insemination cycles as an exclusion criterion, as we believe this is based on a different physiological process.

4. Effect estimate.

In the 2015 update, we used Mantel-Haenszel odds ratios rather than Peto odds ratios for the main analysis, as this is recommended (in the *Cochrane Handbook for Systematic Reviews of Interventions*) as an option for default unless events are very rare.

5. Outcomes.

In the 2015 update, we combined live birth and ongoing pregnancy as our primary outcomes to improve the power of this analysis. We conducted a sensitivity analysis that included only studies that reported live birth to determine how use of a combined outcome influenced review findings. Sensitivity analyses limited to studies reporting live birth yielded findings very similar to the combined outcome, suggesting that ongoing pregnancy was a reasonable surrogate for live birth in this review.

6. Comparisons.

We stated 10 comparisons in the protocol, namely:

1. progesterone versus placebo or no treatment;
2. progesterone versus hCG;
3. progesterone versus progesterone and hCG;
4. progesterone versus progesterone and oestrogen;
5. progesterone versus progesterone and GnRH agonist;
6. different methods of administration of progesterone: IM versus vaginal versus rectal versus oral;
7. micronised versus synthetic progesterone;
8. hCG versus placebo or no treatment;
9. urinary versus recombinant hCG; and
10. single-dose GnRH agonist versus placebo.

We changed these to:

1. hCG versus placebo or no treatment;
2. progesterone versus placebo or no treatment;
3. progesterone versus hCG regimens:
   a. Progesterone versus hCG.
   b. Progesterone versus progesterone and hCG.
4. progesterone versus progesterone and oestrogen.
   a. Oral oestrogen.
   b. Transdermal oestrogen.
   c. Vaginal oestrogen.
   d. Oral and transdermal oestrogen.
5. progesterone versus progesterone and GnRH agonist.
   a. Single dose.
   b. Multiple doses.
6. progesterone regimens.
   a. IM progesterone versus oral progesterone.
   b. IM progesterone versus vaginal or rectal progesterone.
   c. Vaginal or rectal progesterone versus oral progesterone.
   d. Low-dose vaginal progesterone (≤ 100 mg) versus high-dose vaginal progesterone (> 100 mg).
   e. Short protocol versus long protocol.
   f. Micronised progesterone versus synthetic progesterone.
   g. Vaginal ring versus vaginal gel.
   h. Subcutaneous versus vaginal gel.
   i. Vaginal progesterone versus rectal progesterone.
7. progesterone + oestrogen regimens.
   a. Short protocol versus long protocol.
   b. Low dose oestrogen (≤ 2 mg) versus high dose oestrogen (> 2 mg).

To keep things clear, we split comparison six in the protocol into three different subgroups but combined vaginal and rectal administration of progesterone. After our search, we found a large number of studies that researched different types and dosages of vaginal progesterone administration. Therefore we added comparison 6d: low-dose vaginal progesterone versus high-dose vaginal progesterone. We also found some studies that compared different durations of progesterone administration, which we included in comparison 6e: short protocol progesterone versus long protocol progesterone.

In the update of van der Linden 2011, we found studies comparing a new vaginal progesterone ring versus vaginal gel, subcutaneous progesterone versus vaginal gel and vaginal versus rectal progesterone. So we added comparisons 6g, 6h and 6i.

We found no studies comparing urinary hCG and recombinant hCG, and no studies comparing only single-dose GnRH agonist versus placebo, but we did come across some studies that used multiple doses of a GnRH agonist. Therefore we included these in comparison five, changing 'single-dose GnRH agonist' to 'GnRH agonist'. It is unlikely that comparisons for urinary hCG versus recombinant hCG and GnRH agonist versus placebo will be made in the future, as hCG is an older method of providing luteal phase support and is known for its high risk of OHSS; we do not expect new trials will be conducted to investigate differences between urinary and recombinant hCG. Nowadays, progesterone is an accepted method of providing luteal phase support, and it is considered unethical to not provide any form of luteal phase support. Therefore we do not expect that new trials will investigate the effects of GnRH agonists in providing luteal phase support versus placebo. For these reasons, we chose to remove these comparisons.

We believe that these changes in the comparisons enabled us to present an overview of luteal phase support in assisted reproduction cycles that is as complete as possible.

7. Sensitivity analyses.

In the 2015 update, we added sensitivity analyses for choice of effect estimate and statistical model to determine whether these choices influenced our findings. We discontinued the sensitivity analysis that excluded outliers, as this is a data-driven approach that is not recommended best practice.

INDEX TERMS

Medical Subject Headings (MeSH)

*Reproductive Techniques, Assisted; Chorionic Gonadotropin [adverse effects] [*therapeutic use]; Drug Therapy, Combination; Estrogens [*therapeutic use]; Gonadotropin-Releasing Hormone [*agonists]; Live Birth [epidemiology]; Luteal Phase [*drug effects] [physiology]; Ovarian Hyperstimulation Syndrome [chemically induced]; Pregnancy Maintenance [drug effects]; Progesterone [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy