Luteal phase support for assisted reproduction cycles (Review)

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M

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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), which is produced by the corpus luteum. This occurs in the luteal phase of the menstrual cycle. In assisted reproduction techniques (ART) the progesterone or hCG levels, or both, are low and the natural process is insufficient, so the luteal phase is supported with either progesterone, hCG or gonadotropin releasing hormone (GnRH) agonists. Luteal phase support improves implantation rate and thus pregnancy rates but the ideal method is still unclear. This is an update of a Cochrane Review published in 2004 (Daya 2004).

Objectives

To determine the relative effectiveness and safety of methods of luteal phase support in subfertile women undergoing assisted reproductive technology.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL, Database of Abstracts of Reviews of Effects (DARE), LILACS, conference abstracts on the ISI Web of Knowledge, OpenSigle for grey literature from Europe, and ongoing clinical trials registered online. The final search was in February 2011.

Selection criteria

Randomised controlled trials of luteal phase support in ART investigating progesterone, hCG or GnRH agonist supplementation in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles. Quasi-randomised trials and trials using frozen transfers or donor oocyte cycles were excluded.

Data collection and analysis

We extracted data per women and three review authors independently assessed risk of bias. We contacted the original authors when data were missing or the risk of bias was unclear. We entered all data in six different comparisons. We calculated the Peto odds ratio (Peto OR) for each comparison.

Main results

Sixty-nine studies with a total of 16,327 women were included. We assessed most of the studies as having an unclear risk of bias, which we interpreted as a high risk of bias. Because of the great number of different comparisons, the average number of included studies in a single comparison was only 1.5 for live birth and 6.1 for clinical pregnancy.

Five studies (746 women) compared hCG versus placebo or no treatment. There was no evidence of a difference between hCG and placebo or no treatment except for ongoing pregnancy: Peto OR 1.75 (95% CI 1.09 to 2.81), suggesting a benefit from hCG. There was a significantly higher risk of ovarian hyperstimulation syndrome (OHSS) when hCG was used (Peto OR 3.62, 95% CI 1.85 to 7.06).

There were eight studies (875 women) in the second comparison, progesterone versus placebo or no treatment. The results suggested a significant effect in favour of progesterone for the live birth rate (Peto OR 2.95, 95% CI 1.02 to 8.56) based on one study. For clinical pregnancy (CPR) the results also suggested a significant result in favour of progesterone (Peto OR 1.83, 95% CI 1.29 to 2.61) based on seven studies. For the other outcomes the results indicated no difference in effect.

The third comparison (15 studies, 2117 women) investigated progesterone versus hCG regimens. The hCG regimens were subgrouped into comparisons of progesterone versus hCG and progesterone versus progesterone + hCG. The results did not indicate a difference of effect between the interventions, except for OHSS. Subgroup analysis of progesterone versus progesterone + hCG showed a significant benefit from progesterone (Peto OR 0.45, 95% CI 0.26 to 0.79).

The fourth comparison (nine studies, 1571 women) compared progesterone versus progesterone + oestrogen. Outcomes were subgrouped by route of administration. The results for clinical pregnancy rate in the subgroup progesterone versus progesterone + transdermal oestrogen suggested a significant benefit from progesterone + oestrogen. There was no evidence of a difference in effect for other outcomes.

Six studies (1646 women) investigated progesterone versus progesterone + GnRH agonist. We subgrouped the studies for single-dose GnRH agonist and multiple-dose GnRH agonist. For live birth, clinical pregnancy and ongoing pregnancy rate the results suggested a benefit from progesterone + GnRH agonist, with significantly lower rates in the progesterone group. The Peto OR for the live birth rate was 0.40 (95% CI 0.26 to 0.61), for the clinical pregnancy rate was 0.74 (95% CI 0.60 to 0.90) and for the ongoing pregnancy rate was 0.76 (95% CI 0.60 to 0.97). The results for miscarriage and multiple pregnancy did not indicate a difference of effect.

The last comparison (32 studies, 9839 women) investigated different progesterone regimens: intramuscular (IM) versus oral administration, IM versus vaginal or rectal administration, vaginal or rectal versus oral administration, low-dose vaginal versus high-dose vaginal progesterone administration, short protocol versus long protocol and micronized progesterone versus synthetic progesterone. The main results of this comparison did not indicate a difference of effect except in some subgroup analyses. For the outcome clinical pregnancy, subgroup analysis of micronized progesterone versus synthetic progesterone showed a benefit from synthetic progesterone, with a significantly lower rate in the micronized progesterone group (Peto OR 0.79, 95% CI 0.65 to 0.96). For the outcome multiple pregnancy, the subgroup analysis of IM progesterone versus oral progesterone suggested a benefit from oral progesterone, with a significantly higher rate in the IM progesterone group (Peto OR 4.39, 95% CI 1.28 to 15.01).

Authors' conclusions

This review showed a significant effect in favour of progesterone for luteal phase support, favouring synthetic progesterone over micronized progesterone. Overall, the addition of other substances such as estrogen or hCG did not seem to improve outcomes. We also found no evidence favouring a specific route or duration of administration of progesterone. We found that hCG, or hCG plus progesterone, was associated with a higher risk of OHSS. The use of hCG should therefore be avoided. There were significant results showing a benefit from addition of GnRH agonist to progesterone for the outcomes of live birth, clinical pregnancy and ongoing pregnancy. For now, progesterone seems to be the best option as luteal phase support, with better pregnancy results when synthetic progesterone is used.

PLAIN LANGUAGE SUMMARY

Luteal phase support for assisted reproduction

Luteal phase support for assisted reproduction cycles (Review)

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A woman's menstrual cycle consists of different phases. After ovulation the luteal phase starts and lasts until the next menstruation. It is named after the corpus luteum, the yellow body. This consists of the remnants of the ovulated egg in the ovary and produces different hormones, including progesterone. Progesterone stimulates proliferation of the lining of the uterus, preparing for implantation.

When in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), are used for subfertility treatment, fertilisation takes place outside the human body. It is standard protocol to obtain as many eggs as possible. The woman's pituitary gland is desensitised, making it possible to stimulate the ovaries. This process is called controlled ovarian hyperstimulation. In this way more mature eggs are produced, increasing the chance of successful fertilisation. This hyperstimulation causes a luteal phase defect, meaning that the multiple yellow bodies are 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 luteinizing hormone (LH) which triggers ovulation and develops the yellow body. GnRH agonists are thought to restore LH levels and support the luteal phase naturally.

Many different interventions, dosages and administration routes of luteal phase support have been investigated. We made six different comparisons, with an average of six studies for each comparison. We found six statistically significant results. Progesterone was more effective than placebo for live birth and clinical pregnancy. There are two different forms of progesterone, micronized (natural) and synthetic. When we compared these the results favoured synthetic progesterone. When we compared progesterone with progesterone + a single dose of GnRH agonist, the results favoured GnRH agonist supplementation for live birth and clinical pregnancy. In the comparison of progesterone with progesterone + multiple-dose GnRH agonist the results again favoured GnRH agonist supplementation. We also found that the use of hCG was linked to a significantly higher risk of ovarian hyperstimulation syndrome (OHSS), a side effect.

Because the number of studies in each comparison was small, we cannot be too certain about the results. This uncertainty is enhanced by the unclear methodology and high risk of bias of most included studies.

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

hCG versus placebo/no treatment for assisted reproduction cycles						
Patient or population: patients with assisted reproduction cycles Settings: Intervention: hCG versus placebo/no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	hCG versus placebo/no treatment				
Live Birth Rate Follow-up: 9 months	120 per 1000	235 per 1000 (48 to 653)	OR 2.25 (0.37 to 13.8)	38 (1 study)	⊕⊕○○ low ^{1,2,3}	
Clinical Pregnancy Rate Follow-up: 6 weeks	169 per 1000	209 per 1000 (155 to 277)	OR 1.3 (0.9 to 1.88)	746 (5 studies)	⊕⊕○○ low ^{1,2,3}	
OHSS	41 per 1000	134 per 1000 (73 to 232)	OR 3.62 (1.85 to 7.06)	387 (1 study)	⊕⊕○○ low ^{1,2,3}	
*The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Risk of bias was 'unclear' therefore there might be limitations

² Total number of events is less than 300

³ Number of studies is not sufficient to assess publication bias

BACKGROUND

Description of the condition

Assisted reproductive technology (ART), such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are increasingly used to assist couples to have a family. Of the cases where one or more embryos are transferred, less than one third result in a live birth (CDC 2009; de Mouzon 2010; Wang 2009a). 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 luteinizing hormone (LH) surge which causes the 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 'luteinization'. Under the influence of LH specific cells called granulosa cells produce progesterone, which in turn induces the secretory transformation of the endometrium preparing it for implantation by thickening and increasing vascularisation in order 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. It maintains and stimulates the corpus luteum, the remnant of the follicle, to produce estradiol and progesterone (Pabuccu 2005). This is important for 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 deficient, 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 the aspirated follicles under the influence of LH and produces progesterone and estradiol (Messinis 2009). Initially it was thought that oocyte retrieval caused a luteal phase defect and, in particular, steroid secretion but this 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 a prolonged pituitary recovery which resulted in a lack of LH and thus the corpus luteum did not develop fully (Smitz 1992a). The lack of LH was thought to be caused by a short-loop negative feedback mechanism after hCG administration for the oocyte maturation. This theory was also rejected as long-loop negative feedback by ovarian oestrogens has more effect on LH levels (Miyake 1979) and hCG does not lower the LH secretion in non-stimulated, normal ovulating women (Tavaniotou 2003). Currently it is thought

that LH levels are lowered by high steroid levels (Faremi 2009). These steroid levels are high because of the multiple corpora lutea, which produce more steroids than in a natural cycle. This causes a negative feedback on the pituitary gland and lowers the LH levels. In this way the length of the luteal phase is shortened (known as premature luteolysis) and the chances of pregnancy are reduced. In summary, premature luteolysis results from high concentrations of steroids caused by the 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 way of luteal phase support. GnRH blocks the LH surge and it was assumed GnRH agonists might keep their stimulatory effect throughout the luteal phase and restore LH levels, which would support the luteal phase (Pirard 2005). In 2004, Tesarik reported on the use of GnRH agonist six days after ICSI amongst oocyte donors. This study showed that single-dose agonist administration increased the implantation rate without affecting the 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 to improve 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 for the luteal phase.

1. Progesterone (including micronized progesterone or synthetic progestogens such as dydrogesterone, which have a higher bioavailability (Schindler 2009)), administered using the following routes:

- i) intramuscular (IM);
- ii) oral;

- iii) vaginal, where 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 due to bypassing the first-pass effect through the liver (Geber 2007a);

- iv) rectal.

2. Human chorionic gonadotropin (hCG) is similar to LH in its mode of action and physiological effects. The molecular structure is also similar. However it differs from LH as there are elevated sialic acid residues that 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 using the following routes:

- i) intramuscular (IM);

ii) subcutaneous (sc). It has been suggested that the bioavailability of hCG is lower after sc injections compared to intramuscular injections but this is still unclear (Chan 2003, Saal 1991; Mannaerts 1998; Wikland 1995).

3. Oestrogen: oral administered in combination with progesterone.

4. GnRH agonists:

- i) intranasal;
- ii) intramuscular (IM);
- iii) subcutaneous (sc).

How the intervention might work

In ART the levels of progesterone in the luteal phase are insufficient (see above) and 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 in the form of hCG, which in turn stimulates progesterone secretion.

Why it is important to do this review

Luteal phase support may have a positive effect on the outcome of ART. There are many randomised trials which compare different methods of administration and preparations. 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 in subfertile women undergoing assisted reproductive technology (ART).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing any of the agents used for luteal phase support during the luteal phase of a ART cycle were included. Crossover trials were included in the review for completeness but only the first phase data were used in the analysis. Quasi-RCTs were not included.

Types of participants

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

Types of interventions

Trials were included if they investigated or included:

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

All ovarian stimulation protocols were considered.

Trials were excluded if they investigated or included:

- luteal phase support after frozen embryo transfer;
- luteal phase support after embryo transfer from donated oocytes;
- luteal phase support after embryo transfer from frozen oocytes or frozen ovarian tissue;
- luteal phase support after in vitro maturation (IVM) cycles.

Types of outcome measures

Primary outcomes

Live birth rate (LBR) per woman (defined as the delivery of one or more living infants)

Secondary outcomes

- Clinical pregnancy rate (CPR) per woman (defined as the presence of a gestational sac, with or without a fetal heart beat, on ultrasonography)
- Ongoing pregnancy rate (OPR) per woman (defined as a pregnancy beyond 12 weeks of gestation)
- Miscarriage rate (MR) per woman
- Ovarian hyperstimulation syndrome (OHSS) per woman
- Multiple pregnancy rate per woman (counted as one)

Search methods for identification of studies

This review used the information in the Cochrane Menstrual Disorder and Subfertility Group (MDSG) Module regarding search strategies (www.mrw.interscience.wiley.com/cochrane/about/articles/MENSTR/frame.html). All published and unpublished RCTs that described progesterone or HCG, or both, for luteal support in women undergoing ART were sought. Indexed and free text terms were used. The search strategies were designed in consultation with the MDSG Trials Search Co-ordinator.

Electronic searches

The following databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), see [Appendix 1](#);
- MEDLINE, see [Appendix 2](#);
- EMBASE, see [Appendix 3](#);
- PsycINFO, see [Appendix 4](#);
- MDSG Specialized Register, see [Appendix 5](#);
- CINAHL, see [Appendix 6](#);
- Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library*), see [Appendix 7](#).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the Cochrane Handbook of Systematic Reviews of Interventions Version 5.0.2, chapter 6, 6.4.11 ([Higgins 2011](#)). The EMBASE search was combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random). There were no language restrictions on the searches.

Searching other resources

We searched:

- ClinicalTrials.gov <http://clinicaltrials.gov/ct2/home> for ongoing and registered trials in the USA using the keywords “Luteal phase support”;
- the World Health Organisation International Trials Registry Platform www.who.int/trialsearch/Default.aspx for ongoing and registered trials using the keywords “Luteal phase support”;
- conference abstracts on the ISI Web of Knowledge (<http://isiwebofknowledge.com>) see [Appendix 8](#);
- OpenSige for grey literature from Europe (<http://opensigle.inist.fr>) using the search string “((chorionic gonadotropin) OR (progesterone)) AND (luteal phase)”;
- LILACS (<http://regional.bvsalud.org/php/index.php?lang=en>) with the keywords “luteal phase support”;
- Clinicalstudyresults.org (www.clinicalstudyresults.org) using the terms “In vitro fertilisation”, “Infertility” and “Infertility, female”.

Data collection and analysis

Selection of studies

Titles and abstracts were screened independently by two review authors (MvdL, MM) to exclude studies that were clearly irrelevant. The full texts of potentially eligible studies were retrieved for further independent scrutiny by two review authors (MvdL, MM) and compliance with the inclusion criteria was checked using the study eligibility form, see [Appendix 9](#). The reasons for exclusions are provided in the table ‘Characteristics of excluded trials’. When it was unclear whether a study was eligible the original authors were contacted. Disagreements were resolved by a third review author (CF).

Data extraction and management

Data were extracted using a data extraction form, see [Appendix 10](#), designed and pilot-tested by the review authors. In the case of multiple publications, studies were referenced by their main trial report and the references were linked. The original authors were contacted if further information was required. Three review authors (MvdL, MM, KB) independently extracted data and disagreements were resolved by the other review authors.

Assessment of risk of bias in included studies

Risk of bias was assessed 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. Conclusions were summarised in a ‘Risk of bias’ table, see [Appendix 11](#). Review authors judged all six domains as at ‘Low risk’, ‘High risk’ or ‘Unclear risk’ of bias, and described the methods used in the table. Where information was missing, the authors of the studies were contacted.

- Random sequence generation (selection bias)
 - Proper methods included using a computer random number generator, coin tossing, throwing dice, shuffling cards or envelopes
 - Allocation by judgement of clinician, preference of participant, lab tests, date of birth, record number, and inadequate sequence generation such as day of week were not sufficient
- Allocation concealment (selection bias)
 - Proper methods were sequentially numbered drug containers of identical appearance, numbered opaque sealed envelopes or secure third party randomisation such as telephone or computer allocation
 - Prior knowledge of the allocation because of either an open random allocation schedule or alternation, rotation etc were not sufficient
- Blinding of participants and personnel (performance bias)

- Low risk of bias when blinding of clinicians and participants (where possible) was ensured, or incomplete blinding had no effect on the outcome measurement
- When there was no blinding and it had an influence on the outcome measurement, there was a risk of bias
- Blinding of outcome assessment (detection bias):
 - Low risk of bias when blinding of researchers (where possible) was ensured, or incomplete blinding had no effect on the outcome measurement
 - When there was no blinding and it had an influence on the outcome measurement, there was a risk of bias
- Incomplete outcome data (attrition bias)
 - Low risk of bias when missing outcome data was unlikely to be related to true outcomes or when all outcome data were complete
 - High risk of bias when reasons for missing outcome data were likely to be related to true outcome or when the proportion of missing outcome results compared with observed event risk was enough to induce clinically relevant bias in observed effect size
- Selective reporting (reporting bias)
 - Low risk of bias when all pre-specified outcomes that were of interest or described in the protocol were reported
 - High risk of bias when not all pre-specified outcomes were mentioned, reported outcomes were not pre-specified, or a key outcome which would be expected was not reported
- Free of other bias
 - Risk of other bias e.g. embryo transfer policies different in the different arms of the study, had extreme baseline imbalance

When the risk of bias tables were filled in, a risk of bias summary figure was generated (Higgins 2011).

Measures of treatment effect

We retrieved only dichotomous data for this review and thus Peto odds ratios (OR) were calculated with 95% confidence intervals (CI).

Unit of analysis issues

The primary analysis was per woman randomised. Multiple live births were counted as one live birth. Crossover data from the first phase of the study was included. Where information was missing, the authors of the studies were contacted.

Dealing with missing data

To obtain complete data, as much as possible, the original authors were contacted. In case data were unobtainable, imputation was undertaken for the primary outcome. It was assumed that there was

no live birth when this was not reported. When data for secondary outcomes were missing, only the available data were analysed.

Assessment of heterogeneity

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

Assessment of reporting biases

Publication bias was assessed by a funnel plot if there were more than 10 included studies. An asymmetric funnel plot indicates possible publication bias, though there may be other causes of the asymmetry. Within study reporting bias was assessed if study protocols were available and there was a difference between the outcomes in the protocol and in the subsequent publication.

Data synthesis

The data from primary studies were combined 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:
 - i) progesterone versus hCG,
 - ii) progesterone versus progesterone and hCG;
4. progesterone versus progesterone and estrogen;
5. progesterone versus progesterone and GnRH agonist;
6. progesterone regimens:
 - i) IM progesterone versus oral progesterone,
 - ii) IM progesterone versus vaginal or rectal progesterone,
 - iii) vaginal or rectal progesterone versus oral progesterone,
 - iv) low-dose vaginal progesterone (≤ 100 mg) versus high-dose vaginal progesterone (> 100 mg),
 - v) micronized progesterone versus synthetic progesterone.

Subgroup analysis and investigation of heterogeneity

Data were analysed in the following subgroups as well.

1. Ovarian stimulation protocols including:
 - i) clomiphene citrate alone without GnRH agonists,
 - ii) human gonadotropins with clomiphene citrate without GnRH agonists,
 - iii) human gonadotropins with or without GnRH agonists,
 - iv) human gonadotropins with or without GnRH antagonists.
2. Patients with previously failed cycles:
 - i) ≤ 2 failed ART cycles,
 - ii) > 2 failed ART cycles.

3. Duration of progesterone:
 - i) stop at day of positive pregnancy test,
 - ii) given up to 12 weeks in women who conceive.
4. Number of embryos transferred:
 - i) single embryo transfer,
 - ii) > one embryo transferred.

Sensitivity analysis

A sensitivity analysis was done to determine the difference in results caused by:

- eligibility restricted to studies without high-risk of bias,
- alternative imputation strategies had been adopted,
- studies with outlying results.

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

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

RESULTS

Description of studies

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

Results of the search

Our search was done on February 17, 2011 (using the strings reported in the appendices [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#) and OpenSigle and LILACS). It identified 715 studies, while five studies were found using other methods, like handsearching.

On the website [ClinicalTrials.gov](#) we found 14 ongoing studies after using the keywords “luteal phase support”. Three studies did not have sufficient contact details, the authors of one study (NCT00708539) replied but did not have any data available yet. Two other studies (NCT01007851; NCT01177904) sent us their data, but it turned out they were already published as conference abstracts ([Ata 2008](#); [Kohls 2010](#)) and therefore we combined the received data with the abstracts. The World Health Organization [International Trials Registry Platform](#), searched with the keywords “luteal phase support”, only brought up studies which were already found at ClinicalTrials.gov. [Clinicalstudyresults.org](#) was searched using the terms “in vitro fertilisation”, “infertility” and “infertility, female” but did not show any relevant studies.

After removal of duplicates there were 221 studies left for screening. We excluded 59 clearly irrelevant studies. From the other 162 studies the full-text articles were obtained and fully reviewed. All quasi-randomised trials were excluded, together with the articles which did not meet our inclusion criteria. A total of 69 articles were included (See [Figure 1](#) for a study flow diagram).

Figure 1. Study flow diagram.

Included studies

Sixty-nine studies were included, all randomised controlled trials. We did not find any crossover trials to include. In total 16,327 women were included with a mean age of 32.5 years. The inclusion and exclusion criteria of the studies varied. Some studies included women with polycystic ovarian syndrome (PCOS), which was an exclusion criterion in other studies. A few studies used women undergoing their first cycle while most studies included women who had already undergone ART. Overall a mean of 2.55 embryos per woman were transferred, mostly with a maximum of three or four embryos.

Eight studies investigated down regulation using GnRH antagonists (Ceyhan 2008; Engmann 2008; Fatemi 2006; Geber 2007; Isik 2009; Rodriguez-Pezino 2004; Serna 2008; Tesarik 2006), six studies did not use down regulation with GnRH analogues (Colwell 1991; Hurd 1996; Kupfermink 1990; Lewin 1994; Torode 1987; Wong 1990); clomiphene citrate, human menopausal gonadotropin (hMG) or both were used in most of those studies. Forty-three studies investigated GnRH agonists. The other studies did not define the down regulation protocol used.

For 17 studies only the abstract was published (Albert 1991; Caligara 2007; Dunstone 1999; Geber 2007; Geusa 2001; Kohls 2010; Loh 1996; Macrolin 1993; Miller 2010; Porcu 2003; Rodriguez-Pezino 2004; Saucedo 2000; Saucedo 2003; Stadtmayer 2010; Strehler 1999; Sumita 2003; Ugur 2001), the other studies were full text journal publications. Only eight studies were multi-centre studies (Belaisch-Allart 1990; Doody 2009; Elgindy 2010; Kleinstein 2005; Miller 2010; Pouly 1996; Stadtmayer 2010; Zegers-Hochschild 2000).

Ten of our included studies were carried out in the United States of America (Albert 1991; Doody 2009; Engmann 2008; Goudge 2010; Hurd 1996; Licciardi 1999; Miller 2010; Propst 2001; Stadtmayer 2010; Yanushpolsky 2010). Six studies were from Turkey (Ara 2008; Ceyhan 2008; Gorkemli 2004; Isik 2009; Isikoglu 2007; Ugur 2001) and seven from Italy (Abate 1999; Abate 1999a; Artini 1995; Dal Prato 2008; Geusa 2001; Perino 1997; Porcu 2003). Nineteen studies were done in other European countries: Belgium (Fatemi 2006; Pirard 2006), Fin-

land (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), the Netherlands (Beckers 2000), Spain (Caligara 2007; Kohls 2010; Martinez 2000; Serna 2008; Tesarik 2006) and the UK (Dunstone 1999; Tay 2005). Eleven studies were carried out in Asia: China (Lam 2008; Ng 2003; Ng 2007; Wong 1990), India (Chakravarty 2005; Ganesh 2011; 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), Israel (Friedler 1999; Golan 1993; Kupfermink 1990; Lewin 1994), Jordan (Qublan 2008), Mexico (Rodriguez-Pezino 2004; Saucedo 2000; Saucedo 2003) and a multi-centre, multi-national study from Chile, Colombia and Brazil (Zegers-Hochschild 2000).

Excluded studies

Eighty-five studies did not meet our inclusion criteria and were excluded from the review. 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 were included in the previous review (Daya 2004). All studies including GIFT or ZIFT in more than 20% of the cycles, or which did not mention their percentage of GIFT or ZIFT cycles, were excluded (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 the included studies. There is 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). See also the risk of bias graph (see Figure 2) and 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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abate 1998	Y	Y	Y	Y	Y	Y	
Abate 1999a	Y	Y	Y	Y	Y	Y	
Aboughar 2008	Y	Y	Y	Y	Y	Y	
Albert 1991	Y	Y	Y	Y	Y	Y	
Adini 1995	Y	Y	Y	Y	Y	Y	
Als 2008	Y	Y	Y	Y	Y	Y	
Beckers 2000	Y	Y	Y	Y	Y	Y	
Belesch-Altart 1987	Y	Y	Y	Y	Y	Y	
Belesch-Altart 1998	Y	Y	Y	Y	Y	Y	
Caligara 2007	Y	Y	Y	Y	Y	Y	
Cayhan 2005	Y	Y	Y	Y	Y	Y	
Chakravarty 2005	Y	Y	Y	Y	Y	Y	
Colwell 1991	Y	Y	Y	Y	Y	Y	
Dal Prato 2008	Y	Y	Y	Y	Y	Y	
Doody 2008	Y	Y	Y	Y	Y	Y	
Drakakis 2007	Y	Y	Y	Y	Y	Y	
Dunstone 1999	Y	Y	Y	Y	Y	Y	
Elgindy 2010	Y	Y	Y	Y	Y	Y	
Engmann 2008	Y	Y	Y	Y	Y	Y	
Faloni 2006	Y	Y	Y	Y	Y	Y	
Friedler 1999	Y	Y	Y	Y	Y	Y	
Fujimoto 2002	Y	Y	Y	Y	Y	Y	
Ganesht 2011	Y	Y	Y	Y	Y	Y	
Geber 2007	Y	Y	Y	Y	Y	Y	
Geber 2007a	Y	Y	Y	Y	Y	Y	
Geusa 2007	Y	Y	Y	Y	Y	Y	
Golan 1993	Y	Y	Y	Y	Y	Y	
Gonemli 2004	Y	Y	Y	Y	Y	Y	
Goudge 2010	Y	Y	Y	Y	Y	Y	
Hurd 1996	Y	Y	Y	Y	Y	Y	
Isik 2009	Y	Y	Y	Y	Y	Y	
Isikoglu 2007	Y	Y	Y	Y	Y	Y	
Iwase 2008	Y	Y	Y	Y	Y	Y	
Kleinstein 2005	Y	Y	Y	Y	Y	Y	
Kohls 2010	Y	Y	Y	Y	Y	Y	
Kufterman 1998	Y	Y	Y	Y	Y	Y	
Lam 2008	Y	Y	Y	Y	Y	Y	
Lewin 1994	Y	Y	Y	Y	Y	Y	
Liccardi 1999	Y	Y	Y	Y	Y	Y	
Loh 1996	Y	Y	Y	Y	Y	Y	
Ludwig 2007	Y	Y	Y	Y	Y	Y	
Ludwig 2002	Y	Y	Y	Y	Y	Y	
Macrolin 1993	Y	Y	Y	Y	Y	Y	
Martinez 2006	Y	Y	Y	Y	Y	Y	
Miller 2010	Y	Y	Y	Y	Y	Y	
Nig 2003	Y	Y	Y	Y	Y	Y	
Nig 2007	Y	Y	Y	Y	Y	Y	
Pakli 2007	Y	Y	Y	Y	Y	Y	
Perrin 1997	Y	Y	Y	Y	Y	Y	
Pirard 2008	Y	Y	Y	Y	Y	Y	
Porus 2003	Y	Y	Y	Y	Y	Y	
Pouly 1998	Y	Y	Y	Y	Y	Y	
Probst 2007	Y	Y	Y	Y	Y	Y	
Gubian 2008	Y	Y	Y	Y	Y	Y	
Rodriguez-Pazino 2004	Y	Y	Y	Y	Y	Y	
Saucedo 2006	Y	Y	Y	Y	Y	Y	
Saucedo 2003	Y	Y	Y	Y	Y	Y	
Serna 2008	Y	Y	Y	Y	Y	Y	
Stadtmayer 2010	Y	Y	Y	Y	Y	Y	
Strehler 1999	Y	Y	Y	Y	Y	Y	
Sunika 2003	Y	Y	Y	Y	Y	Y	
Tay 2005	Y	Y	Y	Y	Y	Y	
Tesarik 2006	Y	Y	Y	Y	Y	Y	
Torode 1987	Y	Y	Y	Y	Y	Y	
Ugur 2001	Y	Y	Y	Y	Y	Y	
Vimpali 2001	Y	Y	Y	Y	Y	Y	
Wong 1998	Y	Y	Y	Y	Y	Y	
Yanushpolsky 2010	Y	Y	Y	Y	Y	Y	
Zegers-Hochschild 2000	Y	Y	Y	Y	Y	Y	

Allocation

Thirty-seven studies did not report their method of randomisation. The ones which did report their method mostly used computerized randomisation (Ata 2008; Caligara 2007; Ceyhan 2008; Engmann 2008; Fatemi 2006; Gorkemli 2004; Isik 2009; Isikoglu 2007; Iwase 2008; Kleinstein 2005; Kohls 2010; Lam 2008; Ludwig 2002; Martinez 2000; Ng 2003; Ng 2007; Pirard 2006; Pouly 1996; Serna 2008; Tesarik 2006; Yanushpolsky 2010; Zegers-Hochschild 2000). Randomisation lists or tables were often used (Belaisch-Allart 1987; Belaisch-Allart 1990; Ludwig 2001; Qublan 2008) and a third party or study investigator was also used (Aboulghar 2008; Dal Prato 2008; Ganesh 2011). Doody 2009 used a telephone-based electronic interactive voice response system and Elgindy 2010 and Propst 2001 used permuted block randomisation.

Thirty-nine studies did not report their method of allocation concealment. Numbered, sealed envelopes were used most of the time (Aboulghar 2008; Ata 2008; Beckers 2000; Dal Prato 2008; Elgindy 2010; Engmann 2008; Ganesh 2011; Geber 2007; Geber 2007a; Goudge 2010; Hurd 1996; Kleinstein 2005; Lam 2008; Ng 2003; Ng 2007; Pirard 2006; Propst 2001; Qublan 2008; Serna 2008; Tesarik 2006). Caligara 2007 used a phone call to an unrelated department, Ceyhan 2008 central consultation, Doody 2009 a telephone-based electronic interactive voice response system, Isik 2009 used a third party nurse and Isikoglu 2007, Lam 2008 and Yanushpolsky 2010 concealed allocation via an onsite computer system utilising locked files.

Fatemi 2006 and Ludwig 2002 were the only studies reporting that they used a non-concealed randomisation list.

Blinding

Ten studies mentioned that they used blinding (Ata 2008; Belaisch-Allart 1990; Colwell 1991; Doody 2009; Ganesh 2011; Geber 2007; Geber 2007a; Isik 2009; Isikoglu 2007; Tesarik 2006). The other studies did not blind their personnel, researchers and participants (Aboulghar 2008; Caligara 2007; Ceyhan 2008; Dal Prato 2008; Doody 2009; Engmann 2008; Fatemi 2006; Ganesh 2011; Kleinstein 2005; Kohls 2010; Lam 2008; Miller 2010; Ng 2003; Ng 2007; Pirard 2006; Propst 2001; Serna 2008; Yanushpolsky 2010) or did not mention blinding. The studies of Parki 2007 and Qublan 2008 were placebo controlled but did not specify the use of blinding. The main reasons reported (either in the paper or after contacting the original authors) for not blinding was that the authors felt it was difficult because of the different routes of administration. We feel it is possible to use proper blinding by using a double-dummy design.

Incomplete outcome data

Twenty-eight studies reported the number of and reasons for withdrawal or reported that there were no drop-outs. Some studies included a flow diagram clearly showing the exclusions, inclusions, withdrawals and the reasons (Ata 2008; Beckers 2000; Ceyhan 2008; Colwell 1991; Dal Prato 2008; Doody 2009; Elgindy 2010; Engmann 2008; Fatemi 2006; Ganesh 2011; Geber 2007; Geber 2007a; Golan 1993; Goudge 2010; Isik 2009; Isikoglu 2007; Kleinstein 2005; Kohls 2010; Lam 2008; Ng 2003; Ng 2007; Pirard 2006; Pouly 1996; Propst 2001; Serna 2008; Tesarik 2006; Torode 1987; Yanushpolsky 2010). Qublan 2008 reported that there were more participants recruited than analysed, but did not report the reasons.

Live birth was only reported in 15 studies (Abate 1999; Abate 1999a; Beckers 2000; Chakravarty 2005; Dal Prato 2008; Doody 2009; Golan 1993; Goudge 2010; Isik 2009; Lewin 1994; Ludwig 2001; Pouly 1996; Propst 2001; Qublan 2008; Zegers-Hochschild 2000). All studies reported (clinical) pregnancy except for five studies which used ongoing pregnancy as their main outcome (Colwell 1991; Fatemi 2006; Kohls 2010; Serna 2008; Tay 2005).

Selective reporting

As stated before, there was only an abstract available for 17 studies, which meant there was a high risk of selective reporting. Most studies reported their planned outcomes, except for 17 (Abate 1999; Artini 1995; Beckers 2000; Belaisch-Allart 1987; Belaisch-Allart 1990; Drakakis 2007; Friedler 1999; Golan 1993; Goudge 2010; Hurd 1996; Kupferminc 1990; Lewin 1994; Licciardi 1999; Perino 1997; Tay 2005; Torode 1987; Vimpeli 2001). 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

Four studies were supported by the pharmaceutical companies, which supplied the investigated interventions (Doody 2009; Miller 2010; Propst 2001; Stadtmauer 2010). Two studies were supported by a grant from a pharmaceutical company (Ludwig 2002; Vimpeli 2001), Kleinstein 2005 was supported by a pharmaceutical company but this company does not supply the investigated products.

We looked at the comparisons 3.2 Progesterone versus hCG regimens, outcome clinical pregnancy rate (CPR); 6.2.1 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 three comparisons had more than 10 included studies. We did this by making a funnel plot (see

Figure 4; Figure 5). Figure 4 shows the majority of studies around the pooled estimate, showing 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 and therefore this funnel plot indicated a small risk of publication bias. Figure 5 shows the majority of the studies around the pooled estimate with the studies reasonably equally divided on both sides. There is quite a large space at the lower side of the graph, which means that small studies may not be published. Overall the funnel plot indicated a small risk of publication bias. Figure 6 shows the majority 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 versus hCG, outcome: 2.2 Clinical Pregnancy Rate.

Figure 5. Funnel plot of comparison: 6 Progesterone regimens, outcome: 6.2 Clinical Pregnancy Rate.

Effects of interventions

See: [Summary of findings for the main comparison](#) Human chorionic gonadotropin (hCG) versus placebo or no treatment for assisted reproduction cycles; [Summary of findings 2](#) Progesterone versus placebo or no treatment for assisted reproduction cycles; [Summary of findings 3](#) Progesterone versus hCG regimens for assisted reproduction cycles; [Summary of findings 4](#) Progesterone versus progesterone + estrogen for assisted reproduction cycles; [Summary of findings 5](#) Progesterone versus progesterone + GnRH agonist for assisted reproduction cycles; [Summary of findings 6](#) Progesterone regimens for luteal phase support

All data were entered into six comparisons, separated into the six previously stated different outcomes. We also analysed data in the

previously stated subgroups with the CPR as outcome, as all studies except five ([Colwell 1991](#); [Fatemi 2006](#); [Kohls 2010](#); [Serna 2008](#); [Tay 2005](#)) reported this outcome.

1. hCG versus placebo or no treatment

1.1 Live birth rate

One study ([Beckers 2000](#)) with 6 events (3 in hCG group, 3 in placebo group) in 38 participants: Peto OR of 2.25 (95% CI 0.37 to 13.80).

This showed no evidence of effect for this outcome. See [Figure 6](#) for details of this comparison.

Figure 6. Forest plot of comparison: I hCG versus placebo or no treatment, outcome: I.1 Live Birth Rate.

1.2 Clinical pregnancy rate(CPR)

Five studies (Artini 1995; Beckers 2000; Belaisch-Allart 1990; Kupfermink 1990; Torode 1987) with 140 events (75 in hCG group, 65 in placebo group) in 746 participants: Peto OR of 1.30 (95% CI 0.90 to 1.88).

This showed no evidence of effect for this outcome. See Analysis 1.2 for details of this comparison.

1.3 Ongoing pregnancy rate

Three studies (Beckers 2000; Belaisch-Allart 1990; Kupfermink 1990) with 81 events (49 in hCG group, 32 in placebo group) in 527 participants: Peto OR of 1.75 (95% CI 1.09 to 2.81).

This suggested a significant effect in favour of hCG. See Analysis 1.3 for details of this comparison.

1.4 Miscarriage rate

Two studies (Beckers 2000; Kupfermink 1990) with 7 events (4 in hCG group, 3 in placebo group) in 140 participants: Peto OR of 1.49 (95% CI 0.32 to 6.85).

This showed no evidence of effect for this outcome. See Analysis 1.4 for details of this comparison.

1.5 Ovarian hyperstimulation syndrome (OHSS)

One study (Belaisch-Allart 1990) with 38 events (30 in hCG group, 8 in placebo group) in 387 participants: Peto OR of 3.62 (95% CI 1.85 to 7.06).

This result showed a significant effect in favour of placebo. As this result was based on one study only it should be interpreted with caution. See Analysis 1.5 for details of this comparison.

1.6 Multiple pregnancy

None of the studies reported this outcome.

1.7 Subgroup analysis 1: ovarian stimulation protocols (clinical pregnancy rate)

Five studies were included (Artini 1995; Beckers 2000; Belaisch-Allart 1990; Kupfermink 1990; Torode 1987): Peto OR of 1.30 (95% 0.90 to 1.88).

This comparison showed no evidence of effect for the different subgroups. See Analysis 1.7 for details of this comparison.

1.8 Subgroup analysis 2: patients with previously failed cycles (clinical pregnancy rate)

No data were available for this subgroup analysis.

1.9 Subgroup analysis 3: duration of progesterone (clinical pregnancy rate)

Not applicable.

1.10 Subgroup analysis 4: number of embryos transferred (clinical pregnancy rate)

No data were available for this subgroup analysis.

2. Progesterone versus placebo or no treatment

2.1 Live birth rate

One study (Abate 1999a) with 17 events (15 in progesterone group, 2 in placebo or no treatment group) in 156 participants: Peto OR of 2.95 (95% CI 1.02 to 8.56).

This suggested a significant effect in favour of progesterone. See Figure 7 for details of this comparison.

Figure 7. Forest plot of comparison: I Progesterone versus placebo or no treatment, outcome: I.I Live Birth Rate.

2.2 Clinical pregnancy rate

Seven studies (Abate 1999; Abate 1999a; Artini 1995; Belaisch-Allart 1987; Hurd 1996; Kupfermenc 1990; Wong 1990) with 158 events (106 in progesterone group, 52 in placebo or no treatment group) in 841 participants: Peto OR of 1.83 (95% CI 1.29 to 2.61).

This suggested a significant effect favouring progesterone. See Analysis 2.2 for details of this comparison.

2.3 Ongoing pregnancy rate

Five studies (Abate 1999a; Belaisch-Allart 1987; Colwell 1991; Hurd 1996; Kupfermenc 1990) with 91 events (61 in progesterone group, 30 in placebo or no treatment group) in 642 participants: Peto OR of 1.87 (95% CI 1.19 to 2.94).

This suggested a significant effect favouring progesterone. See Analysis 2.3 for details of this comparison.

2.4 Miscarriage rate

Three studies (Belaisch-Allart 1987; Colwell 1991; Kupfermenc 1990) with 19 events (10 in progesterone group, 9 in placebo or no treatment group) in 425 participants: Peto OR of 1.19 (95% CI 0.47 to 2.99).

This showed no evidence of effect for this outcome. See Analysis 2.4 for details of this comparison.

2.5 Ovarian hyperstimulation syndrome (OHSS)

None of the studies reported this outcome.

2.6 Multiple pregnancy

One study (Colwell 1991) with 1 event (in progesterone group) in 34 participants: Peto OR of 17.00 (95% CI 0.28 to 1027.28] This showed no evidence of effect for this outcome. See Analysis 2.6 for details of this comparison.

2.7 Subgroup analysis 1: ovarian stimulation protocols (clinical pregnancy rate)

Seven studies were included (Abate 1999; Abate 1999a; Artini 1995; Belaisch-Allart 1987; Hurd 1996; Kupfermenc 1990; Wong 1990): Peto OR of 1.83 (95% CI 1.29 to 2.61).

Subgroup 2.7.3 human gonadotropins with or without GnRH agonists showed a significant effect in favour of progesterone: Peto OR of 1.90 (95% CI 1.21 to 2.99), which was strengthened when we did not take the study without GnRH agonists (Kupfermenc 1990) into account: Peto OR of 2.37 (95% CI 1.38 to 4.07). See Analysis 2.7 for details of this comparison.

2.8 Subgroup analysis 2: patients with previously failed cycles (clinical pregnancy rate)

No data were available for this subgroup analysis.

2.9 Subgroup analysis 3: duration of progesterone (clinical pregnancy rate)

Seven studies were included (Abate 1999; Abate 1999a; Artini 1995; Belaisch-Allart 1987; Hurd 1996; Kupfermenc 1990; Wong 1990): Peto OR of 1.83 (95% CI 1.29 to 2.61).

Subgroup 1.9.2 up to 12 weeks when pregnant showed a significant effect in favour of progesterone: Peto OR of 2.07 (95% CI 1.35 to 3.17). See Analysis 2.9 for details of this comparison.

2.10 Subgroup analysis 4: number of embryos transferred (clinical pregnancy rate)

No data were available for this subgroup analysis.

3. Progesterone versus hCG regimens

3.1 Live birth rate

Studies comparing progesterone with hCG regimens showed no evidence of a difference between the groups for this outcome. See Figure 8 for details of this comparison.

Figure 8. Forest plot of comparison: 3 Progesterone versus hCG regimens, outcome: 3.1 Live Birth Rate.

3.1.1 versus hCG

Two studies (Golan 1993; Ludwig 2001) with 15 events (4 in progesterone group, 11 in hCG group) in 203 participants: Peto OR of 0.41 (95% CI 0.14 to 1.18).

This showed no evidence of a difference between the groups.

3.1.2 versus progesterone + hCG

One study (Ludwig 2001) with 8 events (3 in progesterone group, 5 in progesterone + hCG group) in 132 participants: Peto OR of

0.52 (95% CI 0.12 to 2.16).

This showed no evidence of a difference between the groups.

3.2 Clinical pregnancy rate

Studies comparing progesterone with hCG regimens showed no evidence of a difference between the groups for this outcome. See Analysis 3.2 for details of this comparison.

3.2.1 versus hCG

Ten studies (Albert 1991; Artini 1995; Golan 1993; Kupfermanc 1990; Lam 2008; Loh 1996; Ludwig 2001; Martinez 2000; Ugur 2001; Vimpeli 2001) with 391 events (218 in progesterone group, 173 in hCG group) in 1448 participants: Peto OR of 1.14 (95% CI 0.90 to 1.45).

This showed no evidence of a difference between the groups. See Figure 16 for details of this comparison.

Because this comparison included 10 studies, we made a funnel plot to determine the risk of publication bias (see Figure 4). This is assessed in the section [Selective reporting \(reporting bias\)](#). We concluded it showed a small risk of publication bias.

We did a sensitivity analysis for studies with an outlying result (Golan 1993), see Table 1. This did not show a significant difference: Peto OR of 1.19 (95% CI 0.94 to 1.52).

3.2.2 versus progesterone + hCG

Seven studies (Caligara 2007; Fujimoto 2002; Geber 2007; Ludwig 2001; Macrolin 1993; Ugur 2001; Wong 1990) with 342 events (169 in progesterone group, 173 in progesterone + hCG group) in 1080 participants: Peto OR of 0.96 (95% CI 0.74 to 1.25).

This showed no evidence of a difference between the groups

3.3 Ongoing pregnancy rate

Studies comparing progesterone with hCG regimens showed no evidence of a difference between the groups for this outcome. See [Analysis 3.3](#) for details of this comparison.

3.3.1 versus hCG

Three studies (Kupfermanc 1990; Ludwig 2001; Tay 2005) with 100 events (67 in progesterone group, 33 in hCG group) in 413 participants: Peto OR of 1.09 (95% CI 0.66 to 1.80).

This showed no evidence of a difference between the groups.

3.3.2 versus progesterone + hCG

Two studies (Ludwig 2001; Macrolin 1993) with 85 events (44 in progesterone group, 41 in progesterone + hCG group) in 434 participants: Peto OR of 1.04 (95% CI 0.65 to 1.68).

This showed no evidence of a difference between the groups.

3.4 Miscarriage rate

Studies comparing progesterone with hCG regimens showed no evidence of effect for this outcome. See [Analysis 3.4](#) for details of this comparison.

3.4.1 versus hCG

Five studies (Golan 1993; Kupfermanc 1990; Lam 2008; Ludwig 2001; Martinez 2000) with 37 events (21 in progesterone group, 16 in hCG group) in 770 participants: Peto OR of 1.34 (95% CI 0.69 to 2.60).

This showed no evidence of a difference between the groups.

3.4.2 versus progesterone + hCG

One study (Ludwig 2001) with 8 events (4 in progesterone group, 4 in progesterone + hCG group) in 132 participants: Peto OR of 0.88 (95% CI 0.21 to 3.66).

This showed no evidence of a difference between the groups. We felt that this study had a very high number of miscarriages. Therefore the results between live birth and the clinical pregnancy and ongoing pregnancy rates were not consistent.

3.5 Ovarian hyperstimulation syndrome (OHSS)

Studies comparing progesterone with hCG regimens showed some evidence of effect for this outcome but should be interpreted with caution as there was a disagreement between the studies. See [Analysis 3.5](#) for details of this comparison.

3.5.1 versus hCG

Four studies (Albert 1991; Ludwig 2001; Martinez 2000; Ugur 2001) with 94 events (30 in progesterone group, 42 in hCG group) in 706 participants: Peto OR of 0.63 (95% CI 0.38 to 1.03).

This showed no evidence of a difference between the groups.

3.5.2 versus progesterone + hCG

Three studies (Ludwig 2001; Macrolin 1993; Ugur 2001) with 55 events (18 in progesterone group, 37 in progesterone + hCG group) in 713 participants: Peto OR of 0.45 (95% CI 0.26 to 0.79).

This suggested a significant effect in favour of progesterone.

Heterogeneity was detected, $I^2 = 76\%$. Ugur 2001 was the largest study in this comparison with the most weight. We only had an abstract for this study so it had a high risk of bias. All three studies separated their participants into a high risk of OHSS and low risk of OHSS group. Study results differed in their direction of effect. Therefore this result, although it is significant, should be interpreted very cautiously.

We did a sensitivity analysis for studies with outlying results, which in this case were Ludwig 2001 and Ugur 2001, see Table 2. When we deleted Ludwig 2001 the outcome became more significant:

Peto OR of 0.26 (95% 0.13 to 0.51) and there was no heterogeneity, but without [Ugur 2001](#) the outcome was no longer significant. Therefore this result should be interpreted very cautiously.

3.6 Multiple pregnancy

Studies comparing progesterone with hCG regimens showed no evidence of a difference between the groups for this outcome. See [Analysis 3.6](#) for details of this comparison.

3.6.1 versus hCG

One study ([Ludwig 2001](#)) with 4 events (1 in progesterone group, 3 in hCG group) in 268 participants: Peto OR of 0.40 (95% CI 0.05 to 2.88).

This showed no evidence of a difference between the groups.

3.6.2 versus progesterone + hCG

One study ([Ludwig 2001](#)) with 4 events (1 in progesterone group, 3 in progesterone + hCG group) in 132 participants: Peto OR of 0.32 (95% CI 0.04 to 2.30).

This showed no evidence of a difference between the groups.

3.7 Subgroup analysis 1: ovarian stimulation protocols, progesterone versus hCG (clinical pregnancy rate)

No data were available for this subgroup analysis.

3.8 Subgroup analysis 1: ovarian stimulation protocols, progesterone versus progesterone + hCG (clinical pregnancy rate)

Four studies were included ([Fujimoto 2002](#); [Ludwig 2001](#); [Macrolin 1993](#); [Wong 1990](#)): Peto OR of 0.91 (95% CI 0.65 to 1.29).

This comparison showed no evidence of a difference between the subgroups. See [Analysis 3.8](#) for details of this comparison.

3.9 Subgroup analysis 2: patients with previously failed cycles, progesterone versus hCG (clinical pregnancy rate)

No data were available for this subgroup analysis.

3.10 Subgroup analysis 2: patients with previously failed cycles, progesterone versus progesterone + hCG (clinical pregnancy rate)

No data were available for this subgroup analysis.

3.11 Subgroup analysis 3: duration of progesterone, progesterone versus hCG (clinical pregnancy rate)

Six studies were included ([Artini 1995](#); [Golan 1993](#); [Kupferminc 1990](#); [Ludwig 2001](#); [Martinez 2000](#); [Vimpeli 2001](#)): Peto OR of 1.10 (95% CI 0.81 to 1.51).

This comparison showed no evidence of a difference between the subgroups. See [Analysis 3.11](#) for details of this comparison.

3.12 Subgroup analysis 3: duration of progesterone, progesterone versus progesterone + hCG (clinical pregnancy rate)

No data were available for this subgroup analysis.

3.13 Subgroup analysis 4: number of embryos transferred, progesterone versus hCG (clinical pregnancy rate)

No data were available for this subgroup analysis.

3.14 Subgroup analysis 4: number of embryos transferred, progesterone versus progesterone + hCG (clinical pregnancy rate)

No data were available for this subgroup analysis.

4. Progesterone versus progesterone + estrogen

After data extraction we found that different routes of estrogen administration were used, with different dosages of estrogen. Therefore we decided to use subgroups based on route of administration.

4.1 Live birth rate

One study ([Lewin 1994](#)) with 21 events (11 in progesterone group, 10 in progesterone + estrogen group) in 100 participants: Peto OR of 1.13 (95% CI 0.43 to 2.94).

This showed no evidence of effect. See [Figure 9](#) for details of this comparison.

Figure 9. Forest plot of comparison: 4 Progesterone versus progesterone + estrogen, outcome: 4.1 Live Birth Rate.

4.2 Clinical pregnancy rate

Seven studies (Ceyhan 2008; Drakakis 2007; Elgindy 2010; Engmann 2008; Gorkemli 2004; Lewin 1994; Yanushpolsky 2010) with 596 events (326 in progesterone group, 270 in progesterone + estrogen group) in 1345 participants: Peto OR of 0.80 (95% CI 0.63 to 1.01).

This showed no evidence of effect. See Analysis 4.2 for details of this comparison.

Subgroup 4.2.2: transdermal supplementation suggested a benefit from progesterone + estrogen, with a significantly lower rate in the progesterone-only group Peto OR of 0.50 (95% CI 0.31 to 0.82).

Subgroup 4.2.4: transdermal and oral also suggested a benefit from progesterone + estrogen, with a significantly lower rate in the progesterone-only group; but it was based on only one study: Peto OR of 0.33 (95% CI 0.12 to 0.94)

Elgindy 2010 was a three-arm study comparing progesterone, progesterone + oral estrogen and progesterone + vaginal estrogen. To make sure we did not duplicate any data, we divided the data of 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'.

Heterogeneity was detected in the subgroups 4.2.2: transdermal, $I^2 = 63\%$; and 4.2.3: vaginal, $I^2 = 82\%$. This resulted in heterogeneity between the subgroups ($I^2 = 65.9\%$). The main difference between studies was the route of administration and the dose, but the 95% CIs still overlapped. This result should be interpreted very cautiously.

Gorkemli 2004 has an outlying result, which might be caused by the higher dose and frequency of estrogen supplementation (100 µg daily versus 2 µg twice weekly or 50 µg every 4 days in the other studies using the transdermal route). We did a sensitivity analysis for studies with outlying results, see Table 3. This did not change the result into a significant result.

4.3 Ongoing pregnancy rate

Five studies (Ceyhan 2008; Engmann 2008; Fatemi 2006; Serna 2008; Yanushpolsky 2010) with 408 events (247 in progesterone group, 161 in progesterone + estrogen group) in 993 participants: Peto OR of 1.00 (95% CI 0.77 to 1.31).

This showed no evidence of a difference between the groups.. See Analysis 4.3 for details of this comparison.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment, see Table 4 for details.

4.4 Miscarriage rate

Six studies (Drakakis 2007; Elgindy 2010; Engmann 2008; Fatemi 2006; Yanushpolsky 2010) with 157 events (98 in progesterone group, 59 in progesterone + estrogen group) in 1281 participants: Peto OR of 1.01 (95% CI 0.70 to 1.45).

This showed no evidence of a difference between the groups. See Analysis 4.4 for details of this comparison.

We found high heterogeneity in the subgroup 4.4.3: vaginal, $I^2 = 75\%$. Overall heterogeneity was $I^2 = 43\%$.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See Table 5 for details of the sensitivity analysis without Fatemi 2006.

4.5 Ovarian hyperstimulation syndrome (OHSS)

One study (Ceyhan 2008) with 2 events (both in progesterone + estrogen group) in 59 participants: Peto OR of 0.14 (95% CI 0.01 to 2.21).

This showed no evidence of a difference between the groups. See Analysis 4.5 for details of this comparison.

4.6 Multiple pregnancy

None of the studies reported this outcome.

4.7 Subgroup analysis 1: ovarian stimulation protocols

Seven studies were initially included (Ceyhan 2008; Drakakis 2007; Elgindy 2010; Engmann 2008; Gorkemli 2004; Lewin 1994; Yanushpolsky 2010). See Analysis 4.7. When these studies were pooled there was marked heterogeneity ($I^2=69\%$) among studies using human gonadotrophins with or without GnRH agonists (analysis 4.7.3). Gorkemli 2004 had an outlying result, possibly due to a difference in dose. Exclusion of Gorkemli 2004 reduced the I^2 value in analysis 4.7.3 from 69% to 52% and the overall I^2 value in this subgroup analysis from 58% to 30%. There was no evidence of effect (Peto OR 1.00, 95% CI 0.76 to 1.31). No heterogeneity was detected between subgroups (i.e. analyses 4.7.1. to 4.7.4).

4.8 Subgroup analysis 2: patients with previously failed cycles

No data were available for this subgroup analysis.

4.9 Subgroup analysis 3: duration of progesterone

Seven studies were included (Ceyhan 2008; Drakakis 2007; Elgindy 2010; Engmann 2008; Gorkemli 2004; Lewin 1994;

Yanushpolsky 2010). They were not pooled due to marked heterogeneity ($I^2=68\%$). See Analysis 4.9 .

4.10 Subgroup analysis 4: number of embryos transferred

No data were available for this subgroup analysis.

5. Progesterone versus progesterone + GnRH agonist

5.1 Live birth rate

Three studies (Isik 2009; Isikoglu 2007; Qublan 2008) with 140 events (50 in progesterone group, 90 in progesterone + GnRH agonist group) in 455 participants: Peto OR of 0.40 (95% CI 0.26 to 0.61).

This showed a benefit for progesterone + GnRH agonist, with significantly fewer events in the progesterone group. However there was marked heterogeneity for this analysis ($I^2=66\%$) and the result should be interpreted with caution. See Figure 10 for details of this comparison.

Figure 10. Forest plot of comparison: 5 Progesterone versus progesterone + GnRH agonist, outcome: 5.1 Live Birth Rate.

Subgroup 5.1.1: single dose includes one study (Isik 2009) with 39 events (13 in progesterone group, 26 in progesterone + GnRH agonist group) in 154 participants: Peto OR of 0.36 (95% CI 0.17 to 0.77).

This showed a significant result in favour of progesterone + GnRH agonist.

Subgroup 5.1.2: multiple dose included two studies (Isikoglu 2007; Qublan 2008) with 101 events (37 in progesterone group,

64 in progesterone + GnRH agonist group) in 301 participants: Peto OR of 0.42 (95% CI 0.2 to 0.70)..

This showed a significant result in favour of progesterone + GnRH agonist. However there was marked heterogeneity for this analysis ($I^2=82\%$) and the result should be interpreted with caution.

5.2 Clinical pregnancy rate

Six studies (Ata 2008; Isik 2009; Isikoglu 2007; Pirard 2006; Qublan 2008; Tesarik 2006) with 664 events (302 in progesterone group, 362 in progesterone + GnRH agonist group) in 1646 participants: Peto OR of 0.74 [0.60, 0.90]

This suggested a significant result in favour of progesterone + GnRH agonist. See Analysis 5.2 for details of this comparison.

We did a sensitivity analysis for studies with outlying results, see Table 6 for results without Pirard 2006.

Subgroup 5.2.1: single dose included three studies with 542 events (249 in progesterone group, 293 in progesterone + GnRH agonist group) in 1324 participants: Peto OR of 0.75 (95% CI 0.60 to 0.93).

This showed a significant result in favour of progesterone + GnRH agonist. Heterogeneity was detected in this subgroup ($I^2 = 69\%$). All 95% confidence intervals overlapped but the result should be interpreted with caution.

Subgroup 5.2.2: multiple dose included three studies with 122 events (53 in progesterone group, 69 in progesterone + GnRH agonist group) in 322 participants: Peto OR of 0.67 (95% CI 0.42 to 1.07).

This showed a significant result in favour of progesterone + GnRH agonist. Heterogeneity was detected in this subgroup ($I^2 = 67\%$). All 95% confidence intervals overlapped but the results should be interpreted with caution.

5.3 Ongoing pregnancy rate

Two studies (Ata 2008; Tesarik 2006) with 404 events (184 in progesterone group, 220 in progesterone + GnRH agonist group) in 1170 participants: Peto OR of 0.76 (95% CI 0.60 to 0.97). . This suggested a significant effect in favour of progesterone + GnRH agonists. See Analysis 5.3 for details of this comparison. Heterogeneity was detected, $I^2 = 51\%$. However the 95% confidence intervals for the two studies overlapped.

5.4 Miscarriage rate

One study (Qublan 2008) with 8 events (5 in progesterone group, 3 in progesterone + GnRH agonist group) in 120 participants: Peto OR of 1.70 (95% CI 0.41 to 7.10).

This showed no evidence of a difference between the groups. See Analysis 5.4 for details of this comparison.

5.5 Ovarian hyperstimulation syndrome (OHSS)

None of the studies reported this outcome.

5.6 Multiple pregnancy

Two studies (Ata 2008; Isik 2009) with 107 events (50 in progesterone group, 57 in progesterone + GnRH agonist group) in 724 participants: Peto OR of 0.84 (95% CI 0.55 to 1.26).

This showed no evidence of effect. See Analysis 5.6 for details of this comparison.

5.7 Subgroup analysis 1: ovarian stimulation protocols (clinical pregnancy rate)

Six studies were included (Ata 2008; Isik 2009; Isikoglu 2007; Pirard 2006; Qublan 2008; Tesarik 2006): Peto OR of 1.36 (95% CI 1.11 to 1.66).

Subgroup 5.7.4: human gonadotropins with or without GnRH antagonists suggested a significant effect in favour of GnRH agonists: Peto OR of 0.74 (95% CI 0.60 to 0.90). See Analysis 5.7 for details of comparison.

As discussed before, this analysis seemed to indicate some heterogeneity, but all 95% confidence intervals overlapped.

5.8 Subgroup analysis 2: patients with previously failed cycles (clinical pregnancy rate)

No data were available for this subgroup analysis.

5.9 Subgroup analysis 3: duration of progesterone (clinical pregnancy rate)

Five studies were included (Ata 2008; Isik 2009; Isikoglu 2007; Pirard 2006; Tesarik 2006): Peto OR of 0.78 (95% CI 0.63 to 0.96).

This suggested a significant result in favour of progesterone + GnRH agonists. See Analysis 5.9 for details of this comparison.

5.10 Subgroup analysis 4: number of embryos transferred (clinical pregnancy rate)

No data were available for this subgroup analysis.

6. Progesterone regimens

6.1 Live birth rate

See Figure 11 for details of this comparison.

Figure 11. Forest plot of comparison: 6 Progesterone regimens, outcome: 6.1 Live Birth Rate.

6.1.1 Intramuscular (IM) versus oral

One study (Iwase 2008) with 7 events (3 in IM progesterone group, 4 in oral progesterone group) in 40 participants: Peto OR of 0.71 (95% CI 0.14 to 3.57).

This showed no evidence of a difference between the groups.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See Table 7 for details of the comparison without Iwase 2008.

6.1.2 IM versus vaginal or rectal

Four studies (Abate 1999a; Dal Prato 2008; Propst 2001; Zegers-Hochschild 2000) with 346 events (167 in IM progesterone group, 179 in vaginal or rectal progesterone group) in 1222 participants: Peto OR of 1.17 (95% CI 0.91 to 1.51).

This showed no evidence of a difference between the groups.

Heterogeneity was detected, $I^2 = 60\%$. 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. This third arm in the original study had a higher dose of progesterone than in the other studies. This might account for the heterogeneity.

6.1.3 Vaginal or rectal versus oral

Two studies (Chakravarty 2005; Pouly 1996) with 163 events (112 in vaginal or rectal progesterone group, 51 in oral progesterone group) in 713 participants: Peto OR of 0.99 (95% CI 0.66 to 1.48).

This showed no evidence of a difference between the groups.

6.1.4 Low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg)

Two studies (Dal Prato 2008; Doody 2009) with 528 events (185 in low dose group, 336 in high dose group) in 999 participants: Peto OR of 0.99 (95% CI 0.79 to 1.24).

This showed no evidence of a difference between the groups.

Doody 2009 was a three-arm study comparing micronized 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.

6.1.5 Short protocol versus long protocol

One study (Goudge 2010) with 49 events (25 in short protocol group, 24 in long protocol group) in 97 participants: Peto OR of 0.88 (95% CI 0.40 to 1.95).

This showed no evidence of a difference between the groups.

6.1.6 Micronized progesterone versus synthetic progesterone

Two studies (Chakravarty 2005; Iwase 2008) with 106 events (83 in micronized progesterone group, 23 in synthetic progesterone group) in 470 participants: Peto OR of 0.90 (95% CI 0.52 to 1.56).

This showed no evidence of a difference between the groups.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See Table 8 for details of this comparison without Iwase 2008.

6.2 Clinical pregnancy rate

See Analysis 6.2 for details of this comparison.

6.2.1 IM versus oral

Three studies (Iwase 2008; Licciardi 1999; Saucedo 2000) with 42 events (24 in IM progesterone group, 18 in oral progesterone group) in 123 participants: Peto OR of 1.92 (95% CI 0.89 to 4.14).

This showed no evidence of a difference between the groups.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See Table 9 for details of the comparison without Iwase 2008.

6.2.2 IM versus vaginal or rectal

Thirteen studies (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) with 1098 events (548 in IM progesterone group, 550 in vaginal or rectal progesterone group) in 2932 participants: Peto OR of 1.14 (95% CI 0.97 to 1.33).

This showed no evidence of a difference between the groups.

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.

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

We did a sensitivity analysis for studies with outlying results, see Table 10 for details of this comparison without Perino 1997.

6.2.3 Vaginal or rectal versus oral

Six studies (Chakravarty 2005; Friedler 1999; Ganesh 2011; Patki 2007; Pouly 1996; Saucedo 2000) with 801 events (484 in vaginal or rectal progesterone group, 317 in oral progesterone group) in 2735 participants: Peto OR of 0.87 (95% CI 0.73 to 1.04).

This showed no evidence of a difference between the groups.

Heterogeneity was detected, $I^2 = 57\%$, which might have been caused by Patki 2007 as it compared vaginal progesterone versus vaginal progesterone + oral progesterone, although we did not find a significant result in favour of high-dose vaginal progesterone supplementation (see comparison 6.2.4: low dose vaginal versus high dose vaginal). The two different routes may have played a role in this outlying result. Therefore this result should be interpreted with caution.

6.2.4 Low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg)

Twelve studies (Dal Prato 2008; Doody 2009; Dunstone 1999; Ganesh 2011; Geber 2007a; Kleinstein 2005; Ludwig 2002; Ng 2003; Ng 2007; Rodriguez-Pezino 2004; Stadtmauer 2010; Strehler 1999) with 1846 events (840 in low dose group, 1006 in high dose group) in 4973 participants: Peto OR of 1.04 (95% CI 0.92 to 1.17).

This showed no evidence of effect.

Doody 2009 was a three-arm study comparing micronized 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.

Because this comparison included more than 10 studies, we made a funnel plot to determine the risk of publication bias (see Figure 5). This was assessed in the section [Selective reporting \(reporting bias\)](#); we concluded it showed a small risk of publication bias.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See [Table 11](#) for details about this comparison without Ludwig 2002.

6.2.5 Short protocol versus long protocol

One study (Goudge 2010) with 61 events (32 in short protocol group, 29 in long protocol group) in 97 participants: Peto OR of 0.99 (95% CI 0.43 to 2.24).

This showed no evidence of a difference between the groups.

6.2.6 Micronized progesterone versus synthetic progesterone

Four studies (Chakravarty 2005; Ganesh 2011; Iwase 2008; Patki 2007) with 698 events (426 in micronized progesterone group, 272 in synthetic progesterone group) in 2388 participants: Peto OR of 0.79 (95% CI 0.65 to 0.96).

This suggested a significant result in favour of synthetic progesterone.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See [Table 12](#) for details of this comparison without Iwase 2008.

6.3 Ongoing pregnancy rate

See [Analysis 6.3](#) for details of this comparison. There was marked heterogeneity ($I^2=81\%$) for comparisons of IM versus vaginal/rectal routes and the findings may not be reliable. There was also heterogeneity ($I^2=63\%$) for comparisons of vaginal/rectal versus oral routes, though confidence intervals overlapped.

6.3.1 IM versus oral

None of the studies reported this outcome.

6.3.2 IM versus vaginal or rectal

Four studies (Abate 1999a; Dal Prato 2008; Perino 1997; Yanushpolsky 2010) with 410 events (204 in IM progesterone group, 206 in vaginal or rectal progesterone group) in 1223 participants: Peto OR of 1.34 (95% CI 1.05 to 1.61).

This suggested a significant result in favour of IM progesterone. As noted above, marked heterogeneity was detected ($I^2 = 81\%$).

We did a sensitivity analysis for studies with outlying results, see [Table 13](#) for details of this comparison without Perino 1997.

6.3.3 Vaginal or rectal versus oral

Two studies (Friedler 1999; Pouly 1996) with 89 events (50 in vaginal or rectal progesterone group, 39 in oral progesterone group) in 346 participants: Peto OR of 1.45 (95% CI 0.89 to 2.34).

This showed no evidence of effect. As noted above, heterogeneity was detected, $I^2 = 63\%$. The result was not significant and the comparison included only two studies whose 95% confidence intervals overlapped.

6.3.4 Low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg)

Five studies (Dal Prato 2008; Doody 2009; Ludwig 2002; Stadtmauer 2010; Tay 2005) with 1236 events (527 in low dose group, 709 in high dose group) in 3034 participants: Peto OR of 0.99 (95% CI 0.85 to 1.15).

This showed no evidence of a difference between the groups.

Doody 2009 was a three-arm study comparing micronized 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. We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See [Table 14](#) for details about this comparison without [Ludwig 2002](#).

6.3.5 Short protocol versus long protocol

One study ([Goudge 2010](#)) with 53 events (26 in short protocol group, 27 in long protocol group) in 97 participants: Peto OR of 0.73 (95% CI 0.33 to 1.63). This showed no evidence of effect.

6.3.6 Micronized progesterone versus synthetic progesterone

None of the studies reported this outcome.

6.4 Miscarriage rate

See [Analysis 6.4](#) for details of this comparison.

6.4.1 IM versus oral

Three studies ([Iwase 2008](#); [Licciardi 1999](#); [Saucedo 2000](#)) with 5 events (3 in IM progesterone group, 2 in oral progesterone group) in 123 participants: Peto OR of 0.60 (95% CI 0.10 to 3.56). This showed no evidence of a difference between the groups. Heterogeneity was detected ($I^2 = 54\%$), though all 95% confidence intervals overlapped. All studies were small and Saucedo 2000 was an abstract only, with a high risk of bias. Therefore this result should be interpreted with caution. We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See [Table 15](#) for details of the comparison without [Iwase 2008](#). We did a sensitivity analysis for studies with outlying results, see [Table 16](#) for details of the comparison without [Licciardi 1999](#). In both sensitivity analyses the results remained insignificant.

6.4.2 IM versus vaginal or rectal

Five studies ([Dal Prato 2008](#); [Miller 2010](#); [Perino 1997](#); [Saucedo 2000](#); [Yanushpolsky 2010](#)) with 126 events (55 in IM progesterone group, 71 in vaginal or rectal progesterone group) in 1324 participants: Peto OR of 0.85 [0.58, 1.25]. This showed no evidence of a difference between the groups. We did a sensitivity analysis for studies with outlying results, see [Table 17](#) for details of this comparison without [Saucedo 2000](#).

6.4.3 Vaginal or rectal versus oral

Four studies ([Chakravarty 2005](#); [Friedler 1999](#); [Ganesh 2011](#); [Pouly 1996](#)) with 109 events (76 in vaginal or rectal progesterone group, 28 in oral progesterone group) in 2140 participants: Peto OR of 1.18 [0.76, 1.85].

This showed no evidence of a difference between the groups.

[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.

We did a sensitivity analysis for studies with outlying results, see [Table 18](#) for details of this comparison without [Friedler 1999](#).

6.4.4 Low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg)

Eight studies ([Dal Prato 2008](#); [Ganesh 2011](#); [Geber 2007a](#); [Kleinstein 2005](#); [Ludwig 2002](#); [Ng 2007](#); [Rodriguez-Pezino 2004](#); [Strehler 1999](#)) with 103 events (45 in low dose group, 58 in high dose group) in 2370 participants: Peto OR of 0.79 [0.53, 1.17]. This showed no evidence of a difference between the groups. We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See [Table 19](#) for details about this comparison without [Ludwig 2002](#).

6.4.5 Short protocol versus long protocol

None of the studies reported this outcome.

6.4.6 Micronized progesterone versus synthetic progesterone

Two studies ([Chakravarty 2005](#); [Ganesh 2011](#)) with 86 events (66 in micronized progesterone group, 20 in synthetic progesterone group) in 1793 participants: Peto OR of 1.16 [0.70, 1.91]. None of the studies reported this outcome.

6.5 Ovarian hyperstimulation syndrome (OHSS)

See [Analysis 6.5](#) for details of this comparison.

6.5.1 IM versus oral

One study ([Iwase 2008](#)) with 2 events (1 in IM progesterone group, 1 in oral progesterone group) in 40 participants: Peto OR of 1.00 (95% CI 0.06 to 16.58).

This showed no evidence of a difference between the groups.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See [Table 20](#) for details.

6.5.2 IM versus vaginal or rectal

None of the studies reported this outcome.

6.5.3 Vaginal or rectal versus oral

None of the studies reported this outcome.

6.5.4 Low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg)

One study (Doody 2009) with 83 events (26 in low dose group, 57 in high dose group) in 1211 participants: Peto OR of 0.91 (95% CI 0.57 to 1.46).

This showed no evidence of a difference between the groups.

Doody 2009 was a three-arm study comparing micronized 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.

6.5.5 Short protocol versus long protocol

None of the studies reported this outcome.

6.5.6 Micronized progesterone versus synthetic progesterone

One study (Iwase 2008) with 2 events (1 in micronized progesterone group, 1 in synthetic progesterone group) in 40 participants: Peto OR of 1.00 (95% CI 0.06 to 16.58).

This showed no evidence of a difference between the groups.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See Table 21 for details of this comparison without Iwase 2008.

6.6 Multiple pregnancy

See Analysis 6.6 for details of this comparison.

6.6.1 IM versus oral

Two studies (Iwase 2008; Licciardi 1999) with 14 events (10 in IM progesterone group, 4 in oral progesterone group) in 83 participants: Peto OR of 4.39 (95% CI 1.28 to 15.01).

This analysis favoured oral progesterone, with a significantly higher rate of multiple pregnancies occurring in the IM proges-

terone group, but it included only two small studies so this result should be interpreted with caution.

We did a sensitivity analysis for studies with high risk of bias, based on allocation concealment. See Table 22 for details of the comparison without Iwase 2008.

6.6.2 IM versus vaginal or rectal

One study (Zegers-Hochschild 2000) with 76 events (39 in IM group, 37 in vaginal/rectal group) in 505 participants: Peto OR of 0.97 (95% CI 0.60 to 1.59).

This showed no evidence of a difference between the groups.

6.6.3 Vaginal or rectal versus oral

One study (Pouly 1996) with 25 events (13 in vaginal or rectal progesterone group, 12 in oral progesterone group) in 283 participants: Peto OR of 1.13 (95% CI 0.50 to 2.58).

This showed no evidence of a difference between the groups.

6.6.4 Low -dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg)

Four studies (Geber 2007a; Kleinstein 2005; Ng 2007; Strehler 1999) with 63 events (32 in low dose group, 31 in high dose group) in 905 participants: Peto OR of 0.95 (95% CI 0.57 to 1.58).

This showed no evidence of a difference between the groups.

6.6.5 Short protocol versus long protocol

Two studies (Goudge 2010; Kohls 2010) with 29 events (18 in short protocol group, 11 in long protocol group) in 317 participants: Peto OR of 1.06 (95% CI 0.63 to 1.76).

This showed no evidence of a difference between the groups.

6.6.6 Micronized progesterone versus synthetic progesterone

None of the studies reported this outcome.

6.7 Subgroup analysis 1: ovarian stimulation protocols, IM versus vaginal or rectal (clinical pregnancy rate)

Eleven studies were included (Abate 1999a; Artini 1995; Geusa 2001; Miller 2010; Perino 1997; Porcu 2003; Saucedo 2003; Sumita 2003; Yanushpolsky 2010; Zegers-Hochschild 2000).

These studies were not pooled, as the forest plot showed differing directions of effect and confidence intervals did not overlap. See Analysis 6.7 for details of this comparison.

6.8 Subgroup analysis 1: ovarian stimulation protocols, low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg) (clinical pregnancy rate)

Nine studies were included (Dal Prato 2008; Doody 2009; Ganesh 2011; Geber 2007a; Kleinstein 2005; Ng 2003; Ng 2007; Strehler 1999): Peto OR of 1.05 (95% CI 0.91 to 1.22).

This showed no evidence of a difference between these different subgroups. See Analysis 6.8 for details of this comparison.

6.9 Subgroup analysis 2: patients with previously failed cycles (clinical pregnancy rate)

No data were available for this subgroup analysis.

6.10 Subgroup analysis 3: duration of progesterone, IM versus vaginal or rectal (clinical pregnancy rate)

Seven studies were included (Abate 1999a; Artini 1995; Dal Prato 2008; Perino 1997; Propst 2001; Sumita 2003; Yanushpolsky 2010). They were unsuitable for pooling, due to heterogeneity was in both subgroups: $I^2 = 62\%$ in the low-dose group, $I^2 = 87\%$ in the high-dose group, and also between subgroups ($I^2 = 72.2\%$). See Analysis 6.10 for details of this comparison.

6.11 Subgroup analysis 3: duration of progesterone, vaginal

versus oral (clinical pregnancy rate)

Five studies were included (Chakravarty 2005; Friedler 1999; Ganesh 2011; Parki 2007; Pouly 1996): Peto OR of 0.85 (95% CI 0.71 to 1.02). This showed no evidence of a difference between the subgroups.

See Analysis 6.11 for details of this comparison.

6.12 Subgroup analysis 3: duration of progesterone, low-dose vaginal (≤ 100 mg) versus high-dose vaginal (> 100 mg) (clinical pregnancy rate)

Ten studies were included (Dal Prato 2008; Doody 2009; Ganesh 2011; Geber 2007a; Kleinstein 2005; Ludwig 2002; Ng 2003; Ng 2007; Stadtmayer 2010; Strehler 1999): Peto OR of 1.04 (95% CI 0.92 to 1.17).

This showed no evidence of a difference between the subgroups. See Analysis 6.12 for details of this comparison.

6.13 Subgroup analysis 4: number of embryos transferred (clinical pregnancy rate)

No data were available for this subgroup analysis.

7. Funnel plots

For the comparisons with more than 10 included studies we constructed a funnel plot. Neither of the funnel plots (Figure 4; Figure 5) suggested publication bias.

ADDITIONAL SUMMARY OF FINDINGS [\[Explanation\]](#)

Progesterone versus placebo/no treatment for assisted reproduction cycles						
Patient or population: patients with assisted reproduction cycles Settings: Intervention: Progesterone versus placebo/no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Progesterone versus placebo/no treatment				
Live Birth Rate Follow-up: 9 months	38 per 1000	104 per 1000 (39 to 253)	OR 2.95 (1.02 to 8.56)	156 (1 study)	⊕⊕○○ low ^{1,2,3}	
Clinical Pregnancy Rate Follow-up: 6 weeks	140 per 1000	230 per 1000 (174 to 298)	OR 1.83 (1.29 to 2.61)	841 (7 studies)	⊕⊕○○ low ^{1,2,3}	
OHSS	See comment	See comment	Not estimable	0 (0)	See comment	
<p>*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).</p> <p>CI: Confidence interval; OR: Odds ratio;</p>						
GRADE Working Group grades of evidence						
High quality: Further research is very unlikely to change our confidence in the estimate of effect.						
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.						
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.						
Very low quality: We are very uncertain about the estimate.						

¹ Risk of bias was 'unclear' therefore there might be limitations

² Total number of events is less than 300

³ Number of studies is not sufficient to assess publication bias

Progesterone versus hCG regimens for assisted reproduction cycles						
Patient or population: patients with assisted reproduction cycles						
Settings:						
Intervention: Progesterone versus hCG regimens						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Progesterone hCG regimens versus				
Live Birth Rate - versus hCG Follow-up: 9 months	103 per 1000	45 per 1000 (16 to 119)	OR 0.41 (0.14 to 1.18)	203 (2 studies)	⊕⊕○○ low ^{1,2,3}	
Live Birth Rate - versus progesterone + hCG Follow-up: 9 months	81 per 1000	44 per 1000 (10 to 160)	OR 0.52 (0.12 to 2.16)	132 (1 study)	⊕⊕○○ low ^{1,2,3}	
Clinical Pregnancy Rate - versus hCG Follow-up: 6 weeks	256 per 1000	282 per 1000 (236 to 333)	OR 1.14 (0.9 to 1.45)	1448 (10 studies)	⊕⊕⊕○ moderate ¹	
Clinical Pregnancy Rate - versus progesterone + hCG Follow-up: 6 weeks	320 per 1000	311 per 1000 (258 to 370)	OR 0.96 (0.74 to 1.25)	1080 (7 studies)	⊕⊕⊕○ moderate ^{3,4}	
OHSS - versus hCG	126 per 1000	83 per 1000 (52 to 129)	OR 0.63 (0.38 to 1.03)	706 (4 studies)	⊕⊕⊕○ moderate ^{1,2}	
OHSS - versus proges- terone + hCG	105 per 1000	50 per 1000 (30 to 85)	OR 0.45 (0.26 to 0.79)	713 (3 studies)	⊕○○○ very low ^{1,2,5}	

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

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

GRADE Working Group grades of evidence

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

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

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

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

¹ Risk of bias was 'unclear' therefore there might be limitations

² Total number of events is less than 300

³ Number of studies is not sufficient to assess publication bias

⁴ Risk of bias was unclear or both high risk and low risk, there might be limitations

⁵ Heterogeneity = 71%

Progesterone versus progesterone + estrogen for assisted reproduction cycles						
Patient or population: patients with assisted reproduction cycles						
Settings:						
Intervention: Progesterone versus progesterone + estrogen						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Progesterone versus progesterone + estrogen				
Live Birth Rate Follow-up: 9 months	200 per 1000	220 per 1000 (97 to 424)	OR 1.13 (0.43 to 2.94)	100 (1 study)	⊕⊕○○ low ^{1,2,3}	
Clinical Pregnancy Rate Follow-up: 6 weeks	425 per 1000	372 per 1000 (318 to 430)	OR 0.8 (0.63 to 1.02)	1345 (7 studies)	⊕⊕○○ low ^{3,4}	
OHSS	67 per 1000	10 per 1000 (1 to 137)	OR 0.14 (0.01 to 2.21)	59 (1 study)	⊕⊕○○ low ^{2,3,5}	
*The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Risk of bias was 'unclear' therefore there might be limitations

² Total number of events is less than 300

³ Number of studies is not sufficient to assess publication bias

- ⁴ Although 95%CI overlap, heterogeneity is detected
- ⁵ Risk of bias was unclear or both high risk and low risk, there might be limitations

Progesterone versus progesterone + GnRH agonist for assisted reproduction cycles						
Patient or population: patients with assisted reproduction cycles						
Settings:						
Intervention: Progesterone versus progesterone + GnRH agonist						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Progesterone versus progesterone + GnRH agonist				
Live Birth Rate Follow-up: 9 months	400 per 1000	215 per 1000 (153 to 292)	OR 0.41 (0.26 to 0.61)	455 (3 studies)	⊕⊕⊕○ moderate ^{1,2}	
Clinical Pregnancy Rate Follow-up: 6 weeks	438 per 1000	366 per 1000 (319 to 412)	OR 0.74 (0.6 to 0.9)	1646 (6 studies)	⊕⊕⊕○ moderate ^{2,3}	
OHSS	See comment	See comment	Not estimable	0 (0)	See comment	
*The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Total number of events is less than 300

² Number of studies is not sufficient to assess publication bias

³ Although 95%CI overlap, heterogeneity is detected

Progesterone regimens for luteal phase support						
Patient or population: Settings: Intervention: Progesterone regimens						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Progesterone regimens				
Live Birth Rate - IM versus Oral Follow-up: 9 months	200 per 1000	151 per 1000 (34 to 472)	OR 0.71 (0.14 to 3.57)	40 (1 study)	⊕⊕○○ low ^{1,2,3}	
Live Birth Rate - IM versus Vaginal/rectal Follow-up: 9 months	267 per 1000	299 per 1000 (249 to 355)	OR 1.17 (0.91 to 1.51)	1222 (4 studies)	⊕○○○ very low ^{1,2,3,4}	
Live Birth Rate - Vaginal/rectal versus Oral Follow-up: 9 months	229 per 1000	227 per 1000 (164 to 305)	OR 0.99 (0.66 to 1.48)	713 (2 studies)	⊕⊕○○ low ^{2,3,5}	
Live Birth Rate - Low dose vaginal versus high dose vaginal Follow-up: 9 months	356 per 1000	354 per 1000 (304 to 407)	OR 0.99 (0.79 to 1.24)	1485 (2 studies)	⊕⊕⊕○ moderate ^{1,3}	
Live Birth Rate - Short protocol versus long protocol Follow-up: 9 months	522 per 1000	490 per 1000 (304 to 680)	OR 0.88 (0.4 to 1.95)	97 (1 study)	⊕⊕○○ low ^{2,3,5}	

Live Birth Rate - Micronized versus synthetic Follow-up: 9 months	232 per 1000	214 per 1000 (136 to 320)	OR 0.9 (0.52 to 1.56)	470 (2 studies)	⊕⊕○○ low ^{2,3,5}
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*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence

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

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

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

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

¹ Risk of bias was unclear or both high risk and low risk, there might be limitations

² Total number of events is less than 300

³ Number of studies is not sufficient to assess publication bias

⁴ Although 95%CI overlap, heterogeneity is detected

⁵ Risk of bias was 'unclear' therefore there might be limitations

DISCUSSION

Summary of main results

This systematic review of all randomised controlled trials of luteal phase support, from 1987 to 2011, had a broad range of subjects. We therefore came up with six comparisons to make sure 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 less evidence regarding the current standard luteal phase protocols. For a complete overview 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](#)).

We can summarize the following results from our review.

Human chorionic gonadotropin (hCG) for luteal phase support

Human chorionic gonadotropin (hCG) compared to placebo suggested a significant result in favour of hCG for the ongoing pregnancy rate. The hCG is known to have a higher risk of OHSS. We found this in two comparisons (1.5: hCG versus placebo or no treatment; and 3.5.2: progesterone versus progesterone + hCG) where the results showed a significant difference. Addition of hCG to progesterone did not show any significant advantages or differences, except for the outcome OHSS. In that comparison progesterone was significantly favoured over progesterone + hCG; hCG compared to progesterone showed no difference in effect.

Progesterone for luteal phase support

Progesterone had a significant positive effect on clinical pregnancy, ongoing pregnancy and live birth rates. There were no significant results when we compared progesterone with hCG.

Progesterone and estrogen for luteal phase support

Findings for progesterone and estrogen were inconsistent. Progesterone + oral estrogen did not have a significant effect on live birth and pregnancy rates compared to progesterone alone, but both transdermal and oral+transdermal estrogen supplementation suggested a significant benefit from progesterone plus estrogen compared to progesterone alone. Results for progesterone plus vaginal estrogen versus progesterone alone were not statistically significant but require very cautious interpretation as there was high heterogeneity ($I^2 = 82\%$). There was no significant difference between the groups for miscarriage or OHSS.

Progesterone and GnRH agonists for luteal phase support

A relatively new method of luteal phase support is GnRH agonists. The pregnancy and live birth results were all significantly in favour of progesterone + GnRH agonists. There were no significant results for miscarriage and multiple pregnancy.

Different progesterone regimens

When we compared routes of progesterone administration, there were no outstanding results. We found IM progesterone to have more effect on the clinical pregnancy rate than oral and vaginal or rectal progesterone, but none of these results were significant. Vaginal progesterone is the most used formulation in Europe according to a survey of 21 centres in Europe ([Aboulghar 2008](#)). Sixteen centres used vaginal progesterone, three centres used IM progesterone, one centre used oral progesterone and one hCG.

We found a lot of studies investigating Crinone 8% vaginal micronized progesterone gel. Therefore we conducted a comparison investigating low-dose (≤ 100 mg) versus high-dose (> 100 mg) vaginal progesterone. There was no evidence in favour of low or high-dose vaginal progesterone.

The comparison and subgroup analysis regarding the duration of progesterone administration gave differing results. In two comparisons (2.9: progesterone versus placebo or no treatment, and 6.10: IM progesterone versus vaginal or rectal progesterone) the results were significantly in favour of the short progesterone protocol, but in subgroup analysis 5.9: progesterone versus progesterone + GnRH agonist the results were significantly in favour of a long progesterone protocol.

The results suggested a significant effect in favour of synthetic progesterone compared to micronized progesterone. The only synthetic progesterone used was oral dydrogesterone.

The only significant result found regarding multiple pregnancy was for the comparison of IM progesterone with oral progesterone. It showed that IM progesterone causes more multiple pregnancies than oral progesterone.

Pituitary desensitisation with GnRH agonists enhanced the significant positive effect of progesterone compared to placebo or no treatment. Comparing progesterone with progesterone + GnRH, there was a significant result in favour of progesterone + GnRH agonists when the cycle was down regulated with GnRH antagonists.

Overall completeness and applicability of evidence

Most studies provided 'implantation rate' as an outcome. For clinicians this result is not interesting as they would rather know the pregnancy rate or live birth rate. For women the most important result is live birth, which was only reported in a small number of studies. Therefore it was difficult to find reassuring results for this outcome. The outcome clinical pregnancy was reported in most

of the reviews and did come up with 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 and therefore this review might not give an accurate representation of these important factors in luteal phase support.

Some of the studies we found investigated procedures or interventions influencing the luteal phase but did not investigate an intervention used as luteal phase support. These studies are all reported in the [Characteristics of excluded studies](#). We also found a few studies investigating luteal phase support which we could not include in one of our comparisons. We therefore filed them under [Studies awaiting classification](#). [Ding 2005](#) investigated IM progesterone + IM estrogen versus IM progesterone + transdermal estrogen. They concluded that the IM estrogen protocol had better results, which might have been due to the higher dose of estrogen. In our comparison of progesterone versus progesterone + estrogen we did not find a better overall result with a higher dose of estrogen. [Esra 2010](#) investigated IM progesterone + estrogen in three different doses. They concluded that addition of different doses of estrogen did not affect pregnancy rates. Our comparison of clinical pregnancy rates in progesterone versus progesterone + estrogen showed a small effect in favour of estrogen supplementation although this was not significant. [Mochtar 2006](#) investigated the best moment to start luteal phase support, starting at the hCG trigger, oocyte retrieval or embryo transfer. They concluded that there might be a small clinically meaningful difference in pregnancy rates in favour of the group starting at embryo transfer although the live birth rate was quite similar.

We only included first cycle data and four studies reported more cycles than women ([Erman Akar 2005](#); [Lukaszuk 2005](#); [Unfer 2004](#); [Unfer 2004a](#)). We contacted the authors but we have not yet 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 did not find any studies investigating these comparisons. It is unlikely that these comparisons will be made in the future as hCG is an older method for 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 not to provide any form of luteal phase support. Therefore we do not expect any new trials investigating the effect of GnRH agonists for luteal phase support versus a placebo. For these reasons we chose to remove these comparisons. To make sure we were as thorough as possible, we came up with low-dose vaginal progesterone versus high-dose vaginal progesterone, short protocol progesterone versus long protocol progesterone and progesterone versus progesterone + multiple dose GnRH agonist.

The included studies used different 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 our search to ensure we covered as much as possible. Most studies reported pregnancy and implantation rates, but live birth and the negative side effects of luteal phase support were poorly reported.

Quality of the evidence

This review has a huge number of included studies, 69 studies, which investigated a lot of different interventions for luteal phase support. Therefore our results are based on smaller numbers of studies. The total number of included participants was 16,327 but, because of the variety of included studies per comparison, the total number per comparison ranged from 30 to well over 5000 participants.

We found a high overall risk of bias because most studies did not report their method of randomisation and allocation concealment and were therefore judged to have an unclear assessment. We found allocation concealment the most important and we did sensitivity analyses for those studies with a high risk of bias for allocation concealment, namely [Fatemi 2006](#), [Iwase 2008](#) and [Ludwig 2002](#). These sensitivity analysis did not have a significant effect on the results. In only 10 studies the study authors reported that they had used blinding, as it was found difficult by authors to conduct blinding with the differences in dose, routes or intervention.

Only 16 studies reported live birth as an outcome. We feel this outcome is more valuable than short-term outcomes like the clinical pregnancy rate.

We also found heterogeneity in a number of comparisons and we did a sensitivity analysis of these comparisons as well. In most cases we were not able to find a clear reason and in almost all we found that the confidence intervals overlapped. For those results, especially the significant results with detected heterogeneity, the findings should be interpreted with caution. Overall it is likely that there might be some limitations in the evidence. We tried to discover those limitations by doing sensitivity analyses but we were not able to find valid reasons. This can also be seen in the 'Summary of findings tables', where the overall quality is 'Low', sometimes even 'Very low'. 'Moderate' is the best result of the quality assessment in these tables.

Potential biases in the review process

All data were extracted by two review authors. MvdL extracted data from all studies and MM and KB divided all studies between them and thus each extracted data from half of the studies. These results were compared by MvdL, who wrote the review. In case of a disagreement CF acted as a third review author and determined the final verdict. Usually this happened after consulting with MvdL. This means MvdL had a big influence on these decisions, which might have introduced bias.

Due to the large number of topics within the review, we might not have discussed all topics in depth.

We are quite sure we found all relevant studies but there might be studies which were not yet 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 included more cycles than women (Erman Akar 2005; Lukaszuk 2005; Unfer 2004; Unfer 2004a). We contacted these authors but we did not receive a reply, so these studies are not included.

Agreements and disagreements with other studies or reviews

When we compared this review with the previous version (Daya 2004), we find a lot of similarities regarding the quality of included studies. Although the previous review included quasi-randomised trials, the overall quality of the present review is still poor. The implications for research section in Daya 2004 stated that the quality of studies, especially blinding, is important for further research. In the more recent (after 2004) studies that we have included, the quality of studies does indeed seem to be better, although most of these studies 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 is in most cases still not the main outcome.

Regarding the results of Daya 2004, there are some agreements and some disagreements between their findings and the results of this review. As there are no new studies investigating hCG versus placebo, we found the same results. In all comparisons investigating hCG we found that hCG has a higher risk of OHSS. This was significant for hCG versus placebo and progesterone versus progesterone + hCG.

In the previous review, and in this review, there was no significant evidence found in favour of a particular route of administration. Both versions of the review found no difference in effect between different doses of vaginal progesterone.

This review suggests a significant result in favour of progesterone + estrogen, but this is based on only one study. Without this study (Gorkemli 2004) the results do not show a difference between progesterone and progesterone + estrogen. Daya 2004 also failed to show a difference in effect between progesterone and progesterone + estrogen.

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

The main difference between the previous version and this review seems to be the inclusion of the comparisons of micronized and synthetic progesterone and progesterone + GnRH agonists for luteal phase support.

Implications for practice

This review shows a significant effect in favour of progesterone for luteal phase support, favouring synthetic progesterone over micronized progesterone. Overall, the addition of other substances such as estrogen or hCG do not seem to improve outcomes. Additionally, we found that hCG is associated with a significantly higher risk of OHSS.

The route of progesterone administration does not seem to matter, although synthetic progesterone seems to give better results, which in most cases was oral dydrogesterone. The dose of vaginal micronized progesterone does not seem to improve the outcomes. There is no agreement between the results for short or long protocol progesterone. The effect of progesterone in the luteal phase after pituitary desensitisation with GnRH agonists seems to be bigger. The only other significant results were found in the comparison of progesterone versus progesterone plus GnRH agonists. These showed a result significantly favouring progesterone plus GnRH agonists, with either single or multiple doses of GnRH agonists. This means that the addition of GnRH agonist to progesterone has a bigger effect than progesterone alone. However these results are based on a limited number of studies as this is a new method for luteal phase support.

Overall, progesterone has a positive effect on pregnancy rates when used as luteal phase support, with no difference in effect between the different progesterone regimens; hCG should be avoided as it gives a higher risk of OHSS. Addition of estrogen to progesterone does not show, in general, a better effect than progesterone alone, but addition of GnRH agonist to progesterone does show a better effect than progesterone alone.

For now, progesterone is found to be the best method of luteal phase support, favouring synthetic progesterone over micronized progesterone with a small benefit. GnRH agonist addition is a promising new method but the power of the evidence is not strong.

Implications for research

Out of the 69 included studies, only 10 used blinding. The method of blinding and specification of who was blinded were poorly reported. To gain more high quality evidence, studies should be properly blinded using a double-dummy design.

Only 15 studies reported live birth as an outcome. We feel 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. Since research has shown that luteal phase support has a positive effect on pregnancy outcomes, it is unethical not to 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 for luteal phase support but it

AUTHORS' CONCLUSIONS

shows promising results. Therefore, high quality randomised double blind controlled trials should be conducted comparing GnRH agonist support with 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	Randomized placebo controlled trial.
Participants	Women undergoing first time IVF/ET for tubal factor infertility, age <38 (n=86)
Interventions	Pituitary desensitization (PD) and controlled ovarian hyperstimulation (COH): GnRH agonist, 400µg sc twice daily and FSH ET: day +2, max 4 embryos transferred. LPS: 17 alpha-hydroxyprogesterone 341mg 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 randomization 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.

Abate 1999a

Methods	Randomized placebo controlled trial.
Participants	Women undergoing IVF/ET for tubal occlusion, age 25-35y (n=156)

Abate 1999a (Continued)

Interventions	PD/COH: GnRH agonist im and FSH. ET: day +2, max 4 embryos transferred. LPS: progesterone 50mg im daily vs progesterone 90mg 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 gestational), live birth
Notes	No reply from author in 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly treated" Method of randomization 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.

Aboulghar 2008

Methods	Randomized 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 aginal progesterone 600 mg or progesterone 50 mg IM until 3 weeks after first US
Outcomes	Miscarriage (up to 20 weeks gestation)
Notes	

<i>Risk of bias</i>		
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.
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.

Albert 1991

Methods	Randomized controlled trial.	
Participants	Women undergoing IVF/ET (n=57).	
Interventions	PD/COH: GnRH agonist and hMG. LPS: hCG 2,500 IU 4 times vs progesterone 50mg im at day of ET, then 12.5mg im daily	
Outcomes	Clinical pregnancy (not defined), OHSS.	
Notes	Only abstract available.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Patients were treated in a prospective, randomized fashion” Method of randomization not reported.

Albert 1991 (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)	High risk	Only abstract available. Planned outcomes not reported.

Artini 1995

Methods	Randomized 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 50mg im daily vs progesterone 100mg daily in vaginal cream vs hCG 2000IU im every 3 days vs no supplementation
Outcomes	Viable 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 divided" Method of randomization 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.

Artini 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal not reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Ata 2008

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

Selective reporting (reporting bias)	Low risk	Planned outcomes reported.
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Beckers 2000

Methods	Randomized controlled trial, 3 different pituitary desensitization 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 (estradiol >8000 pmol/l) were excluded from analysis
Interventions	PD/COH: GnRH agonist 0.1mg sc from cycle day 1 until trigger vs GnRH agonist 0.1mg sc from cycle day 1 until 3rd day of hMG stimulation vs GnRH agonist 0.1mg 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 not defined per group
Notes	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 randomization 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	Number and reason withdrawals reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Belaisch-Allart 1987

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

Belaisch-Allart 1990

Methods	Multi-centre (12), randomized placebo controlled trial.
Participants	Women undergoing IVF for tubal sterility (50%), serum estradiol on day of ET <2,500 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.

Belaisch-Allart 1990 (Continued)

Notes	2 Authors employed by Organon. Author contacted in 2004, unable to provide any information	
<i>Risk of bias</i>		
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.

Caligara 2007

Methods	Randomized controlled trial.	
Participants	Women undergoing IVF with 10 or less oocytes retrieved and a max estradiol level of 2500 pg/ml at hCG trigger	
Interventions	LPS: vaginal progesterone 200 mg two times daily vs vaginal progesterone 200 mg two times daily plus hCG 1000 IU sc on day +4, +7 and +10. Progesterone from day after oocyte retrieval	
Outcomes	Pregnancy rate (not defined).	
Notes	Only abstract available. Author contacted	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization.

Caligara 2007 (Continued)

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.

Ceyhan 2008

Methods	Randomized 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 0.25mg 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 + estrogen transdermal 100ug/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 fetal heartbeat after 13th week amenorrhoea), OHSS
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"

Ceyhan 2008 (Continued)

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	Number and reason withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Chakravarty 2005

Methods	Randomized 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 25-42 (n=430)
Interventions	PD/COH: GnRH agonist 1 mg sc + r-FSH 150-200 IU sc. ET: day 2, average of 3 embryos transferred. LPS: micronized vaginal progesterone 200 mg 3x 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 author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“The patients were randomly selected” Method of randomization 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.

Colwell 1991

Methods	Randomized 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 100mg oral from day 5 until 9+ hMG ET: day +2, mean 2.6 embryos transferred, ET in only 55% of women LPS: progesterone 200mg oral 4 times daily vs no supplementation
Outcomes	Ongoing pregnancy (not defined), multiple pregnancy.
Notes	No reply from 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 randomization 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	Number and reasons for withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Dal Prato 2008

Methods	Randomized controlled trial.
Participants	Women undergoing IVF for idiopathic, tubal or male factor, grade I-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 (one or more live babies), clinical pregnancy (one or more gestational sacs) , ongoing pregnancy, miscarriage (pregnancy loss after US confirmation of embryo im-plantation and before 12 weeks)	
Notes	Author contacted.	
<i>Risk of bias</i>		
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 in-vestigator 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 alloca-tion 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	Number and reason withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Doody 2009

Methods	Multi-centre (25) randomized controlled trial.
Participants	Women undergoing IVE, excluding women who had a history of recurrent (≥ 3 spontaneous abortions) pregnancy loss, abnormal uterine bleeding of undetermined origin, or a history of either poor response to gonadotrophin or two previous cancelled cycles, mean age 33 (n=1211)
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 2x daily vs progesterone vaginal capsules 100

Doody 2009 (Continued)

	mg 3x daily vs progesterone vaginal gel
Outcomes	Ongoing pregnancy (fetal heart movement at 6 weeks), clinical pregnancy (gestational sac), live birth
Notes	2 Authors are employees of Ferring Pharmaceuticals, one 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	Number and reasons withdrawals reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Drakakis 2007

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ICSI for tubal factor, male infertility, anovulation, endometriosis and unexplained infertility, mean age 35 (n=76)

Drakakis 2007 (Continued)

Interventions	PD/COH: GnRH agonist 100 µg intranasal 5 times daily from day 21 preceeding cycle for 15-24 days + r-FSH LPS: progesterone 100 µg oral 3x daily + vaginal progesterone capsules 200 mg 3x daily until pregnancy test + estradiol valerate oral 2mg + 0.5 mg norgesterel 3x daily for 15 days + estradiol hemihydrate 50 µg transdermal patch every 4 days vs progesterone 100 µg oral 3x daily + vaginal progesterone capsules 200 mg 3x daily until pregnancy test
Outcomes	Clinical pregnancy, miscarriage.
Notes	No reply from 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 randomization 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.

Dunstone 1999

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

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Women undergoing IVF-ET treatment were randomly assigned" Method of randomization 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	"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.

Elgindy 2010

Methods	Randomized 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 the pretreatment cycle + r-FSH + 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 3x daily vs progesterone 100 mg im daily + E2 valerate 2 mg vaginally 3x daily	
Outcomes	Clinical pregnancy (not defined).	
Notes	No reply from author.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Elgindy 2010 (Continued)

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) 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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcome reported.

Engmann 2008

Methods	Randomized 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 + estradiol 2 mg vaginally 2x daily. Both from oocyte retrieval until pregnancy test or fetal 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

Engmann 2008 (Continued)

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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Fatemi 2006

Methods	Randomized controlled trial.
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 micronized progesterone vaginal capsules 200mg 3x daily vs natural micronized progesterone vaginal capsules 200mg 3x daily + oral E2 valerate 2mg twice daily. From day after oocyte retrieval until 7 weeks of gestation
Outcomes	Ongoing pregnancy (beyond 12 weeks), early pregnancy loss (initially positive hCG test, failed to develop beyond 12 weeks)
Notes	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	Not concealed randomization 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	Number and reason of withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.
Other bias	High risk	Only abstract available.

Friedler 1999

Methods	Randomized controlled trial.
Participants	Women undergoing ICSI/ET for male factor infertility with >1 embryo available and a 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 yrs) or in cases of recurrent failures of implantation LPS: micronized progesterone 200mg oral 4 times daily vs micronized progesterone 100 mg vaginal 2 times daily. Both from day +1 after ET until serum test (+14)
Outcomes	Pregnancy (not defined), ongoing pregnancy, miscarriage.
Notes	No reply from author in 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"The patients included in this study were prospectively randomized by order of embryo transfer" Method of randomization not reported.

Friedler 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	Withdrawal not reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Fujimoto 2002

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ET, including only women with low mid-luteal serum estradiol in a previous cycle, mean age 35 (n=114)
Interventions	PD/COH: long protocol GnRH agonist 300µg intranasal 3x 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 randomized to receive either 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 randomization not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.

Fujimoto 2002 (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)	Low risk	Planned outcome reported.

Ganesh 2011

Methods	Randomized 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 + r-FSH. ET: day 2, average of 3 embryos transferred. LPS: dydrogesterone 10 mg oral daily vs micronized progesterone vaginal gel 90 mg daily vs micronized progesterone vaginal capsules 200mg 3x daily. All from ET until 12 weeks gestation
Outcomes	Clinical pregnancy (viable fetus on US), ongoing pregnancy (viable fetus 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"

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawal reported.
Selective reporting (reporting bias)	High risk	Ongoing pregnancy results are not reported, but are reported in the protocol

Geber 2007

Methods	Randomized controlled trial.
Participants	Women undergoing ART (n=150).
Interventions	PD/COH: GnRH agonist or antagonist + r-FSH. 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. 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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	High risk	Only abstract available. Planned outcomes not reported. Dose progesterone not reported.

Geber 2007a

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

Geusa 2001

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ET, excluding women with systemic or endocrine pathologies, age <42 yrs (n=300)
Interventions	PD/COH: GnRH agonist + rFSH. LPS: progesterone 90mg vaginal gel daily vs progesterone 50mg im daily. Both starting at oocyte retrieval

Geusa 2001 (Continued)

Outcomes	Clinical pregnancy (not defined).	
Notes	Only abstract available. No reply from author.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“All 318 patients were randomized” Method of randomization 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.

Golan 1993

Methods	Randomized 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 times vs progesterone 100mg im daily. Both from day of ET	
Outcomes	Clinical pregnancy (gestational sac), miscarriage, OHSS.	
Notes	Author contacted in 2004.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Golan 1993 (Continued)

Random sequence generation (selection bias)	Unclear risk	Patients were prospectively randomized” Method of randomization 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	Number and reason withdrawal reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Gorkemli 2004

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

Risk of bias

Bias	Authors' judgement	Support for judgement
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.

Gorkemli 2004 (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)	Low risk	Planned outcome reported.

Goudge 2010

Methods	Randomized 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 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 randomization not reported.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, 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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Hurd 1996

Methods	Randomized cross-over study.
Participants	Women undergoing IVF-ET, excluding women with a history of anovulation, unresponsive to CC or when their ovaries were 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 versus vaginal progesterone suppositories 100 mg 2x daily from embryo transfer + E2 2 mg oral 3x 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 randomization 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.

Isik 2009

Methods	Randomized controlled trial.
Participants	Women undergoing ICSI/ET, excluding donor, freeze/thaw and/or TESA cycles, mean age 35 (n=154)

Isik 2009 (Continued)

Interventions	PD/COH: GnRH antagonist + FSH. LPS: Micronized progesterone 600 mg 3x 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 micronized progesterone 600 mg 3x daily vaginal capsules from oocyte retrieval for 17 days + single-dose hCG 1500 IU sc on day +8	
Outcomes	Live birth, clinical pregnancy (fetal heartbeat), multiple pregnancy	
Notes		
<i>Risk of bias</i>		
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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Isikoglu 2007

Methods	Randomized 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 (fetal cardiac activity).	
Notes	Author contacted.	

<i>Risk of bias</i>		
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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Iwase 2008

Methods	Randomized 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 2x 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 (fetal heart activity) and OHSS	
Notes	No reply from 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"

Iwase 2008 (Continued)

Allocation concealment (selection bias)	High risk	"The random allocation sequence was concealed until the interventions were assigned."
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.

Kleinstein 2005

Methods	Multicenter (17) randomized 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 3x 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 of gestation, with fetal 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"

Kleinstein 2005 (Continued)

		group only after successful transfer.”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open, phase III RCT.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open, phase III 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.

Kohls 2010

Methods	Randomized controlled trial.
Participants	Women with gestational sac at first ultrasound, mean age 35 (n=220)
Interventions	PD/COH: GnRH analogue. LPS: vaginal progesterone 200 mg 2x daily until first ultrasound vs vaginal progesterone 200 mg 2x daily until 3 weeks after ultrasound
Outcomes	Miscarriage rate (not defined).
Notes	Author contacted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization list.
Allocation concealment (selection bias)	Low risk	Computerized 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) All outcomes	Low risk	No withdrawal reported.

Kohls 2010 (Continued)

Selective reporting (reporting bias)	Low risk	Results directly obtained from author.
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Kupferminc 1990

Methods	Randomized 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. LPS: dydrogesterone 10mg oral 3 times daily from ET for 14 days vs oral placebo vs hCG 2,500 IU im on day 3, 6 and 10
Outcomes	Clinical pregnancy (gestational sac), ongoing pregnancy (beyond 1st trimester) and miscarriage
Notes	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 randomization 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.

Lam 2008

Methods	Randomized 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 600µg intranasal for at least 14 days + hMG or r-FSH IVF/ET: day 3, mean 2.2 embryos transferred. LPS: micronized progesterone 200 mg 3x 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."
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	Number and reason withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Lewin 1994

Methods	Randomized 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/day sc. ET: max 4 embryos transferred. LPS: progesterone 50 mg im from ET vs progesterone 50 mg im + estradiol valerate 2 mg oral daily

Lewin 1994 (Continued)

Outcomes	Clinical pregnancy (not defined), live birth.	
Notes	No reply from author.	
<i>Risk of bias</i>		
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) All outcomes	Unclear risk	Withdrawal not reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Licciardi 1999

Methods	Randomized controlled trial, allocation by randomization table	
Participants	Women undergoing IVF/ET, age <40 years, mean 35 yrs (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 50mg im daily vs micronized progesterone 200mg 3 times daily. Both from day after oocyte retrieval	
Outcomes	Clinical pregnancy (gestational sac), multiple pregnancy, miscarriage	
Notes	No reply from author in 2004, study is terminated early for ethical reasons: differences in implantation rates were highly statistically significant	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Licciardi 1999 (Continued)

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.

Loh 1996

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ET (n=156). 8% of randomized 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 author.

Risk of bias

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

Loh 1996 (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)	High risk	Only abstract available. Planned outcomes not reported.

Ludwig 2001

Methods	Randomized controlled trial.
Participants	Women undergoing IVF or ICSI, excluding women with abdominal discomfort on day of ET and estradiol levels >5000 pg/ml, mean age 32 (n=413)
Interventions	PD/COH: long protocol GnRH agonist + r-FSH or hMG. ET: mean 2.7 embryos transferred. LPS: Low risk category (<12 oocytes retrieved and estradiol 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 3x daily vs progesterone vaginal capsules 200 mg 3x daily High risk category (≥12 oocytes retrieved and estradiol on day of ovulation induction ≥2.500 pg/ml); hCG 5000 IU on day of ET + progesterone vaginal capsules 200 mg 3x daily vs progesterone vaginal capsules 200 mg 3x daily
Outcomes	Clinical pregnancy (positive fetal heart beat), 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-randomized, the data of these arms is not included in the meta analysis. Author contacted in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
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.

Ludwig 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)	Low risk	Planned outcomes reported.

Ludwig 2002

Methods	Randomized 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 <2000pg/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 200mg 3 times daily vaginally vs progesterone in gel 90mg daily. Both from evening before ET until menses or pregnancy test
Outcomes	Clinical pregnancy (positive fetal 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 randomization list.
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.

Ludwig 2002 (Continued)

Selective reporting (reporting bias)	Low risk	Planned outcomes reported.
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Macrolin 1993

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ET, excluding women with OHSS, repeated implantation failure, or estradiol >2700 pg/mL, age <38 yrs (n=302)
Interventions	PD/COH: GnRHa in a long or short protocol + hMG. ET: max 3 (41%) or 2 embryos transferred. LPS: vaginal micronized progesterone 400 mg daily from the day after oocyte retrieval vs vaginal micronized progesterone 400 mg daily from the day after oocyte retrieval + hCG 1500 IU every other day 3 time 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 randomization 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.

Martinez 2000

Methods	Randomized 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 times daily vaginally for 10 days from ET vs hCG 2,500 IU im on days +2, +4 and +6 after oocyte retrieval
Outcomes	Clinical pregnancy (gestational sac), miscarriage, multiple pregnancy, OHSS
Notes	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.

Miller 2010

Methods	Multicenter randomized controlled trial, number of centres not reported
Participants	Women undergoing IVF with GnRH antagonist downregulation, mean age 33 (n=165)
Interventions	PD/COH: GnRH antagonist + Menopur or r-FSH. ET: mean 2.3 embryos transferred. LPS: progesterone vaginal capsules (Endometrin) vs progesterone IM
Outcomes	Ongoing pregnancy, miscarriage.

Miller 2010 (Continued)

Notes	Only abstract available. No reply from author. Support from Ferring Pharmaceuticals Inc.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“With randomization prior to stimulation” Method of randomization 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.

Ng 2003

Methods	Randomized 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) 400mg 2 times daily vaginally vs progesterone gel (Crinone 8%) 90mg once daily vaginally. Both for 14 days from day of ET	
Outcomes	Clinical pregnancy (not defined).	
Notes	Author contacted.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Ng 2003 (Continued)

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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Ng 2007

Methods	Randomized 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 4x daily from mid-luteal phase preceeding cycle + hMG ET: max 3 embryos, mostly 2 embryos transferred. LPS: progesterone vaginal suppositories 400 mg 2x daily vs progesterone vaginal capsules 100 mg 2x daily. Both from ET for 14 days
Outcomes	Clinical pregnancy (1 or more gestational sacs), ongoing pregnancy (beyond 10-12 weeks gestation), miscarriage, multiple pregnancy
Notes	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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Patki 2007

Methods	Randomized 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: micronized progesterone vaginal capsules 600 mg daily + dydrogesterone 20 mg daily oral vs micronized progesterone vaginal capsules 600 mg daily from day of oocyte retrieval + placebo Phase 2: PD/COH: long protocol GnRH agonist. LPS: micronized 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 all until pregnancy test or continued when pregnant
Outcomes	Pregnancy (intrauterine viable pregnancy).
Notes	Phase 1 investigates vaginal progesterone + oral dydrogesterone versus vaginal progesterone + placebo. This does not fit in any of our comparisons and therefore phase 1 is excluded. Both phases included an extra group, which both examined patients in a donor oocyte program and were therefore not included in our data analysis Author contacted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized" Method of randomization not reported.

Patki 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patient receives either 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.

Perino 1997

Methods	Randomized 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. LPS: micronized progesterone 50mg im daily vs natural progesterone 200mg 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 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 randomization 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.

Pirard 2006

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ICSI-ET with indications for ART, median age between 29 and 37 (n=23)
Interventions	PD/COH: hMG/FSH IVF/ICSI-ET: day 3, 1 or 2 embryos transferred. LPS: Group A: trigger 10,000 IU hCG followed by vaginal micronized progesterone 200 mg 3x daily vs Group B: 200 µg GnRH agonist (buserelin) intranasal (IN) followed by 100 µg IN every 2 days vs Group C: 200 µg GnRH agonist (buserelin) IN followed by 100 µg IN daily vs Group D: 200 µg GnRH agonist (buserelin) IN followed by 100 µg IN twice daily vs Group E: 200 µg GnRH agonist (buserelin) IN followed by 100 µg IN 3x daily
Outcomes	Clinical pregnancy (ongoing pregnancy with amniotic sac and a fetal heartbeat)
Notes	Intervention groups B and C were discontinued prematurely as they caused a short luteal phase. Patients in this groups received a further sealed envelope with new allocation instructions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization list was computer-generated by an independent statistician"
Allocation concealment (selection bias)	Low risk	"Treatment allocation instructions were placed in individually sealed envelopes to be opened at the centre in chronological order, on the day of ovulation trigger."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open, parallel group, pilot study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open, parallel group, pilot study"

Pirard 2006 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Porcu 2003

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

Risk of bias

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

Pouly 1996

Methods	Multi-centre (6) randomized 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 90mg vaginal gel daily vs micronized progesterone 100mg oral one in morning, two in evening. Both from day after ET for 14 days or 30 in case of pregnancy
Outcomes	Clinical pregnancy (gestational sac or β -hCG >1000 IU), miscarriage, multiple pregnancy, ongoing pregnancy (13 weeks)
Notes	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.
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 is reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Propst 2001

Methods	Randomized 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 90mg vaginally once daily vs progesterone 50mg im daily. Both

Propst 2001 (Continued)

	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 of gestation), live birth
Notes	Recruitment was 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) All outcomes	High risk	"Open-label study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Qublan 2008

Methods	Randomized 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, 1-3 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 fetal heartbeat), miscarriage, live birth rate

Qublan 2008 (Continued)

Notes	Dosage/frequency of Cyclogest usage not mentioned.	
<i>Risk of bias</i>		
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 Patients recruited, 120 analysed, no reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.
Other bias	High risk	Dosage/frequency of Cyclogest usage not mentioned.

Rodriguez-Pezino 2004

Methods	Randomized 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) 200mg twice daily vs vaginal progesterone suppositories 200mg daily. All from oocyte retrieval
Outcomes	Pregnancy (not defined), miscarriage.
Notes	Only abstract available. No reply from author.

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Were randomised" Method of randomization 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.

Saucedo 2000

Methods	Randomized controlled trial.
Participants	Women undergoing ART (n=60).
Interventions	ET: Day 3, average of 3 embryos transferred. LPS: progesterone 400mg oral daily vs progesterone vaginal gel 90mg daily vs progesterone 50mg im daily
Outcomes	Clinical pregnancy (not defined).
Notes	Only abstract available. No reply from author.

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomized" Method of randomization not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Saucedo 2000 (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)	High risk	Only abstract available. Planned outcomes not reported.

Saucedo 2003

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" Method of randomization 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.
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Serna 2008

Methods	Randomized 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 + r-FSH IVF/ICSI-ET: 2 embryos transferred. LPS: vaginal progesterone 200 mg 2x daily + transdermal E2 10µg daily vs vaginal progesterone 200 mg 2x 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."
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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Stadtmauer 2010

Methods	Multi-centre randomized controlled trial.
Participants	Women undergoing ART aged 18-42 (n=1297).
Interventions	PD/COH: long down regulation protocol GnRH agonist. ET: day 3 or 5. LPS: progesterone weekly vaginal ring vs progesterone vaginal gel 90 mg daily. Borth from ET until 12 weeks when pregnant
Outcomes	Clinical pregnancy (gestational sac and fetal heart beat).
Notes	Only abstract available. No reply from author. Supported by Teva Pharmaceuticals T&D.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After 1:1 randomization" Method of randomization not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Single-blind", not defined.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Single-blind", not defined.
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	Only abstract available.

Strehler 1999

Methods	Randomized 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 90mg daily vs progesterone vaginal suppositories 200mg 3 times daily. Both from oocyte retrieval until 8th week of pregnancy

Strehler 1999 (Continued)

Outcomes	Clinical pregnancy (fetal sac), miscarriage and multiple pregnancy	
Notes	Only abstract available.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Patients were prospectively randomized” Method of randomization 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.

Sumita 2003

Methods	Randomized controlled trial.	
Participants	Women undergoing IVF/ET, mean age 34 (n=100).	
Interventions	PD/COH: GnRH agonist + FSH. IVF/ET: 2 embryos transferred. LPS: progesterone 50 mg im daily vs vaginal micronized 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 author	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Sumita 2003 (Continued)

Random sequence generation (selection bias)	Unclear risk	"A randomized prospective trial" Method of randomization 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.

Tay 2005

Methods	Randomized controlled trial.	
Participants	Women undergoing IVF for tubal disease, male factor, ovulatory dysfunction, endometriosis or unexplained infertility, excluding women with pre-ovulatory estradiol concentration ≥ 15000 pmol/l and/or total oocyte number ≥ 15 . Age is between 21-41, 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 Group 3: natural progesterone vaginal capsules, 200 mg once, twice or 3x daily vs Group 4: hCG 1500 IU sc on day 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 non were given any form of luteal support. These are not included in our data analysis. No reply from author	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Tay 2005 (Continued)

Random sequence generation (selection bias)	Unclear risk	"Subjects were randomised on the day of embryo transfer" Method of randomization 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.

Tesarik 2006

Methods	Randomized placebo controlled trial. Including 2 separate patient groups; patients undergoing a GnRH agonist protocol and patients 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	<p>Agonist:</p> <p>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 + r-FSH and hMG</p> <p>ET: day 3, mean 2.2 embryos transferred.</p> <p>LPS: single-dose GnRH agonist 0.1 mg 6 days after ICSI (3 days after ET) vs placebo</p> <p>Antagonist:</p> <p>PD/COH: r-FSH + hMG from day 2 of menstrual bleeding, followed by withdraw of a contraceptive pill. GnRH antagonist 0.25 mg sc daily from started on day 5 until trigger</p> <p>ET: day 3, mean 2.3 embryos transferred.</p> <p>LPS: single-dose GnRH agonist 0.1 mg 6 days after ICSI (3 days after ET) vs placebo</p> <p>All women received vaginal micronized progesterone 400 mg and E2 valerate 4 mg daily from oocyte retrieval for 17 days and a injection of 250 µg human r-hCG on day of embryo transfer</p>
Outcomes	Live birth, clinical pregnancy (not defined), ongoing pregnancy (not defined)
Notes	
<i>Risk of bias</i>	

Tesarik 2006 (Continued)

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 withdrawal reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Torode 1987

Methods	Randomized 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 author.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Randomly allocated” Method of randomization not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Torode 1987 (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	Number and reasons withdrawal reported.
Selective reporting (reporting bias)	Unclear risk	Planned outcomes not reported.

Ugur 2001

Methods	Randomized controlled trial.
Participants	Women undergoing IVF with high and normal risk developing OHSS (n=375)
Interventions	High risk: PD/COH: GnRH agonist. LPS: vaginal micronized progesterone 400 mg daily vs vaginal micronized progesterone 400 mg daily + hCG 3,000 IU on day 7 Low risk: PD/COH: GnRH agonist. LPS: vaginal micronized progesterone 400 mg daily vs hCG 1500 IU every 3 days vs vaginal micronized progesterone 400 mg daily + hCG 1500 IU every 3 days
Outcomes	Pregnancy (not defined).
Notes	Only abstract available.

Risk of bias

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

Ugur 2001 (Continued)

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.

Vimpeli 2001

Methods	Randomized 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 day 3, 6 and 9 after oocyte retrieval vs vaginal micronize natural progesterone 200 mg 3 times 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 randomization 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.

Wong 1990

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ET for tubal factor (n=30).
Interventions	PD/COH: clomiphene citrate + hMG. ET: day 2. LPS: progesterone 50mg im daily from day 2 until 11 vs progesterone 50mg im daily from day 2 until 11 + hCG 1500 IU alternate days from day 5 to 15 vs no luteal support
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	"Randomly allocated" Method of randomization 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 method section.

Yanushpolsky 2010

Methods	Randomized 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 hrs 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	Author contacted, the article published in Fertility & Sterility 2011 contains a retrospective analysis of women receiving LPS with E2	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Patients were randomized with equal probability to receive either [...]” Computer generated randomization.
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	Number and reasons reported.
Selective reporting (reporting bias)	Low risk	Planned outcomes reported.

Zegers-Hochschild 2000

Methods	Multicentre (3) randomized 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 versus 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
Notes	Laboratorios Silesia S.A. provided the vaginal rings.
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"On day of oocyte retrieval patient were randomly allocated..." Method of randomization 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.

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 prior to embryo transfer to decrease uterine contractions and therefore improve implantation rates
Abu-Musa 2008a	This RCT investigated the role of 17a-hydroxyprogesterone caproate given prior to embryo transfer to decrease uterine contractions and therefore improve implantation rates
Allahbadia 2004	This comparative study investigated pregnancy outcomes of IM progesterone (n=94) versus 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 using progesterone and estrogen (n=15) vs progesterone alone (n=15) for luteal phase support in IVF-ET cycles
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. Authors previously contacted in 2004

(Continued)

Araujo Filho 1996	Study does not report the percentage of ZIFT cycles.
Baber 1988	This study was excluded in the previous version of this review as in this RCT, allocation to hCG or no treatment only included women with a positive pregnancy test, thus the treatment was not truly luteal phase support
Beckers 2006	This RCT investigated high doses of steroids administered after the LH surge in normo-ovulatory volunteers in order to investigate if this gives rise to endocrine changes and a shortening of the luteal phase
Belaisch-Allart 1988	This is an interim analysis of 295 cases out a total of 525 women. Data is about 451 transfers, author contacted in 2004, not able to provide any information
Ben-Nun 1990	This study was excluded in the previous version of this review as it is not a randomized trial - compared i.m. progesterone to historical controls receiving no progesterone. Treatment was given only for 6 days around the time of oocyte retrieval
Berjis 2008	This study only includes rapid-ZIFT procedures.
Blake 2010	This pharmacokinetic study, does not include patients undergoing ART
Buvat 1988	This is a quasi-RCT.
Buvat 1990	This is a quasi-RCT.
Casini 2003	This study was excluded in the previous version of this review because in this RCT some women contributed more than one cycle to the study (n=201 women, 436 cycles). The author was unable to provide first cycle data
Chang 2008	Not a randomized trial - review about intramuscular progesterone for luteal phase support in IVF
Chang 2009	Not a randomized trial - retrospectively analyzed outcomes of IVF cycles with GnRH antagonist administration on ovulation triggering day
Chantilis 1999	This study was excluded in the previous version of this review as it is not a randomized trial - compared vaginal progesterone to historical controls using i.m. progesterone
Check 2010	This RCT investigated the dosage of progesterone supplementation in frozen embryo transfers only (n=408)
Claman 1992	This RCT includes IVF/ETcycles (n=121) rather than women (n=unknown), author contacted in 2004 and was not able to provide first cycle data
Daya 2009	Not a randomized trial - review about progestogens for luteal support
Ding 2005	This RCT in excluded because it contains more cycles (n=114) than women (n=95). No reply from author

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Erman Akar 2005	This RCT is excluded because it contains more cycles (n=115) than women (n=95). No reply from author
Escriba 2006	This RCT investigated the initiation of progesterone supplementation in donated oocyte transfers only (n=300)
Farhi 2000	This study was excluded in the previous version of this review because in this RCT some women contributed more than one cycle to the study (n=271 women, 285 cycles)
Farrag 2008	This RCT investigated the use of recombinant hCG to induce final oocyte maturation in ICSI cycles
Feliciani 2004	This RCT compared the effect of intravaginal (n=14) and i.m. progesterone (n=14) in frozen/thawed embryo transfers only
Garcia-Velasco 2009	This RCT investigated the effect of letrozole administered during the luteal phase after oocyte retrieval in oocyte donors only
Ghanem 2009	This study is quasi-randomised as randomisation was performed using a sequential allocation method
Gibbons 1998	This study was excluded in 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 randomized trial - review.
Herman 1990	This is a quasi-RCT.
Herman 1996	This is a quasi-RCT.
Ho 2008	Not a randomized trial - retrospective case control study.
Humaidan 2010	This RCT is excluded as it investigates only one dose of hCG as a trigger, not a luteal phase support study
Hutchinson-Williams 1990	This study was excluded in the previous version of this review as it is not a randomized trial - the treatment group was "randomly" selected, but the control group was retrospectively selected and age-matched to the treatment group
Jee 2010	Not a randomized trial - meta-analysis.
Johnson 1999	This study was excluded in the previous version of this review as this RCT compared hCG with no treatment, with primary objective of measuring relaxin levels during the luteal phase. Complete pregnancy outcomes by groups were not reported
Kahraman 2010	This is a quasi-RCT.
Koper 2008	This randomized trial investigated the dose-response relationship of corifollitropin alfa to initiate multifollicular development for the first 7 days of controlled ovarian stimulation

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Krause 2006	This RCT investigated the efficiency and safety of different luteal support regimes in non-IVF cycles (n=36)
Krischker 1998	This study was excluded in the previous version of this review as this RCT compared progesterone i.m., 2 types of oral progesterone, and hCG, using long GnRH α (n=30) or ultrashort GnRH α (n=273). Pregnancy rates by group were provided, but the numbers of transfers in each group were not. Attempts to contact authors were unsuccessful
Lam 2003	This study was excluded in the previous version of this review as this RCT compared hCG plus vaginal progesterone administered only between oocyte retrieval and embryo transfer with hCG alone (n=102). This was the only study found making this comparison
Lan 2007	This RCT compared the efficacy and tolerability of two formulations of vaginal progesterone, Crinone 8% (n=100) and Utrogestan (n=100) in frozen embryo transfers only
Leeton 1985	This is a quasi-RCT.
Lightman 1999	This is a quasi-RCT.
Lukaszuk 2005	This RCT is excluded because it contains more cycles (n=231) than women (n=166). No reply from author
Mahadevan 1985	This is a quasi-RCT.
Marianowski 2000	This study was excluded in the previous version of this review as it is not a randomized trial - compared IM and vaginal progesterone with allocation by the woman's preference (n=79)
Martins 2010	Not a randomized trial - review about luteal phase support.
McBain 1987	This is a quasi-RCT.
Mochtar 1996	This study was excluded in the previous version of this review because in this RCT some women contributed more than one cycle to the study (n=98 women, 176 cycles). An attempt was made to contact the authors, but no reply received
Moraloglu 2008	This study compared the effect of GnRH agonist (n=48) and GnRH antagonist (n=45) use in two matched groups of women undergoing IVF/ICSI
Nader 1988	This study was excluded in the previous version of this review as this RCT compared progesterone to hCG, but was excluded because some women contributed more than one cycle to the study (n=17 women, 20 cycles). The author was unable to provide first cycle data
Nikkanen 1992	This is a quasi-RCT.
Ozcimen 2004	This cross-over study investigated the effect of luteal phase support in non-IVF gonadotropin induction of ovulation

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Papanikolaou 2010	This RCT compares recombinant hCG (n=59) versus urinary hCG (n=60) as a final oocyte maturation trigger
Pirard 2005	This randomized trial includes IUI only.
Polson 1992	This is a quasi-RCT.
Schwarzler 2003	This study was excluded in the previous version of this review because in this RCT some women contributed more than one cycle to the study (n=603 women, 945 cycles)
Simunic 2007	Not a randomized trial - cohort study investigating the efficacy and tolerability of Crinone 8% gel vs Utrogestan capsules
Singh 2010	This randomized trial investigated the supplementation of GnRH agonists during the luteal phase in IUI only
Smith 1989	This is a quasi-RCT.
Smitz 1988	Study does not report the percentage of GIFT cycles.
Smitz 1992	Study includes >20% GIFT/ZIFT cycles.
Smitz 1993	This is a quasi-RCT.
Sordal 1993	This study was excluded in the previous version of this review as this RCT compared progesterone i. m., 2 doses of vaginal progesterone and no treatments (n=40), but pregnancy rates by group were not provided. Attempts to contact the author were unsuccessful
Stadtmauer 2009	This randomized trial compared the effect of progesterone in a vaginal ring (n=10) vs progesterone vaginal gel (n=10) in donor oocytes
Tay 2003	This study divided their population in 2 groups; group A underwent GnRH-a/r-FSH ovarian stimulation followed by IVE, group B underwent CC/r-FSH ovarian stimulation and IUI. After ET or insemination patients were randomized in 2 different luteal phase support protocols. No reply from author in 2004
Trounson 1986	This study was excluded in the previous version of this review as this RCT assessed luteal support with progesterone i.m. or hCG given only around the time of oocyte retrieval (n=42)
Unfer 2004	This RCT is excluded because it contains more cycles (n=284) than women (n=213). No reply from author
Unfer 2004a	This RCT is excluded because it contains more cycles (n=734) than women (n=320). No reply from author
Valentino 2004	This study was excluded in the previous version of this review as this RCT compared vaginal and i.m. progesterone (n=40), but pregnancy rates were not provided (the main outcome measures were side effects and convenience). Attempts to contact the author were unsuccessful

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van Steirteghem 1988	Study does not report the percentage of GIFT procedures.
Var 2011	This is a quasi-RCT, allocation based on application number.
Wang 2009	Not a randomized trial - a cohort study comparing crinone 8% gel vs utrogestan capsules
Wilcox 2001	This study was excluded in the previous version of this review as this RCT compared luteal support with progesterone vaginal gel alone or in combination with IM progesterone in frozen embryo transfer cycles (n=97)
Ye 2009	This RCT investigated luteal estradiol pre-treatment before the GnRH antagonist protocol and the GnRH agonist protocol
Yigit 2002	This study was excluded in the previous version of this review as it is not a randomized trial - according to information from the author, this was a retrospective study comparing vaginal gel and i.m. progesterone
Yovich 1984	This is a quasi-RCT, allocation based on study number. Author contacted in 2004
Yovich 1985	This is a quasi-RCT.
Yovich 1991	This RCT included ZIFT cycles only.

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

Esra 2010

Methods	Randomized controlled trial.
Participants	Women undergoing ICSI, age under 40 (n=288).
Interventions	PD/COH: GnRH analogue. LPS: vaginal progesterone gel + 2 mg oral estradiol vs vaginal progesterone gel + 4 mg oral estradiol vs vaginal progesterone gel + 6 mg oral estradiol. Estradiol from day after ET, progesterone from day of OPU
Outcomes	Clinical pregnancy (not defined).
Notes	Only study with this comparison.

Gallardo 2004

Methods	
Participants	
Interventions	

Gallardo 2004 (Continued)

Outcomes	
Notes	Translation needs to be obtained to assess eligibility.

Humaidan 2006

Methods	Randomized controlled trial.
Participants	Women undergoing IVF/ICSI-ET with a 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 25-40 (n=45)
Interventions	PD/COH: GnRH antagonist 0.25 mg sc + r-FSH 150-200 IU sc. ET: day 2 or 3, 2 embryos transferred. LPS: micronized vaginal progesterone gel 90 mg daily + single bolus hCG 1500 IU im 12 hrs after trigger vs micronized vaginal progesterone gel 90 mg daily + single bolus hCG 1500 IU im 35 hrs 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	Only study with this comparison.

Jung 2010

Methods	Prospective study.
Participants	Women undergoing IVF/ICSI, mean age 33 (n=124).
Interventions	PD/COH: GnRH agonist. ET: mean 2.9 embryos transferred. LPS: progesterone 50 mg IM daily from oocyte retrieval vs progesterone 50 mg IM daily from oocyte retrieval + hCG 2000 IU sc on day 0, 2, 4 from oocyte retrieval vs progesterone 50 mg IM daily from oocyte retrieval + hCG 2000 IU sc on day 0, 2, 4 from oocyte retrieval + estradiol valerate 6 mg oral daily
Outcomes	Clinical pregnancy, OHSS, miscarriage.
Notes	Only abstract available. Author contacted, awaiting reply about randomization

Mochtar 2006

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

Mochtar 2006 (Continued)

	vs micronized 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 fetal heartbeat by transvaginal ultrasound 10 weeks after oocyte retrieval)
Notes	Only study with this comparison.

Paredes 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	Translation needs to be obtained to assess eligibility.

Shamma 1992

Methods	Randomized controlled trial.
Participants	Women undergoing IVF-ET (n=80).
Interventions	PD/COH: GnRH agonist. LPS: Vaginal progesterone 25 mg 3 times daily + 5000 IU hCG im on day 5 and 10 versus vaginal progesterone 25 mg 3 times daily + 0.1 mg transdermal estrogen daily every 3 days from day 5
Outcomes	Clinical pregnancy (not defined), miscarriage.
Notes	Only study with this comparison.

Silverberg 2010

Methods	Prospective trial.
Participants	Women undergoing IVF.
Interventions	PD/COH: FSH. ET: day 3 or 5. LPS: vaginal gel 90 mg daily vs progesterone IM.
Outcomes	Pregnancy (not defined), delivery.

Silverberg 2010 (Continued)

Notes	Authors contacted to obtain information about use of randomization. Awaiting reply
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DATA AND ANALYSES

Comparison 1. Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live Birth Rate	1	38	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.25 [0.37, 13.80]
2 Clinical Pregnancy Rate	5	746	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.90, 1.88]
3 Ongoing Pregnancy Rate	3	527	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [1.09, 2.81]
4 Miscarriage Rate	2	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.32, 6.85]
5 OHSS	1	387	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [1.85, 7.06]
7 Subgroup analysis 1 (Clinical Pregnancy Rate)	5	746	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.90, 1.88]
7.1 clomiphene citrate alone without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 human gonadotropins with clomiphene citrate without GnRH agonists	1	131	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.54, 2.85]
7.3 human gonadotropins with or without GnRH agonists	3	513	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.94, 2.39]
7.4 human gonadotropins with or without GnRH antagonists	1	102	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.34, 1.98]

Comparison 2. Progesterone versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live Birth Rate	1	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.95 [1.02, 8.56]
2 Clinical Pregnancy Rate	7	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.83 [1.29, 2.61]
3 Ongoing Pregnancy Rate	5	642	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [1.19, 2.94]
4 Miscarriage Rate	3	425	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.47, 2.99]
6 Multiple pregnancy	1	34	Peto Odds Ratio (Peto, Fixed, 95% CI)	17.00 [0.28, 1027.28]
7 Subgroup analysis 1 (Clinical Pregnancy Rate)	7	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.83 [1.29, 2.61]
7.1 clomiphene citrate alone without GnRH agonists	1	56	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.73 [0.69, 20.06]
7.2 human gonadotropins with clomiphene citrate without GnRH agonists	2	306	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.86, 2.86]
7.3 human gonadotropins with or without GnRH agonists	4	479	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [1.21, 2.99]

7.4 human gonadotropins with or without GnRH antagonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Subgroup analysis 3 (Clinical Pregnancy Rate)	7	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.83 [1.29, 2.61]
9.1 Stop at pregnancy test	3	257	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.40 [0.74, 2.64]
9.2 Up to 12 weeks	4	584	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.07 [1.35, 3.17]

Comparison 3. Progesterone versus hCG regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live Birth Rate	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 versus hCG	2	203	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.14, 1.18]
1.2 versus progesterone + hCG	1	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.12, 2.16]
2 Clinical Pregnancy Rate	15		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 versus hCG	10	1448	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.90, 1.45]
2.2 versus progesterone + hCG	7	1080	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.74, 1.25]
3 Ongoing Pregnancy Rate	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 versus hCG	3	413	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.66, 1.80]
3.2 versus progesterone + hCG	2	434	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.65, 1.68]
4 Miscarriage Rate	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 versus hCG	5	770	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.69, 2.60]
4.2 versus progesterone + hCG	1	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.21, 3.66]
5 OHSS	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 versus hCG	4	706	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.38, 1.03]
5.2 versus progesterone + hCG	3	713	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.26, 0.79]
6 Multiple pregnancy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 versus hCG	1	147	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.05, 2.88]
6.2 versus progesterone + hCG	1	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.32 [0.04, 2.30]
8 Subgroup analysis 1: Progesterone vs progesterone + hCG (Clinical Pregnancy Rate)	4	722	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.65, 1.29]
8.1 clomiphene citrate alone without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 human gonadotropins with clomiphene citrate without GnRH agonists	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.23, 11.94]
8.3 human gonadotropins with or without GnRH agonists	3	702	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.63, 1.27]

8.4 human gonadotropins with or without GnRH antagonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Subgroup analysis 3: Progesterone vs hCG (Clinical Pregnancy Rate)	6	839	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.81, 1.51]
11.1 Stop at pregnancy test	5	750	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.78, 1.54]
11.2 Up to 12 weeks when pregnant	1	89	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.47, 2.82]

Comparison 4. Progesterone versus progesterone + estrogen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live Birth Rate	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.43, 2.94]
2 Clinical Pregnancy Rate	7	1345	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.63, 1.01]
2.1 Oral	3	642	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.38]
2.2 Transdermal	2	325	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.31, 0.82]
2.3 Vaginal	2	301	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.67, 1.71]
2.4 Oral and transdermal	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.12, 0.94]
3 Ongoing Pregnancy Rate	5	993	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.76, 1.31]
3.1 Oral	2	608	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.62, 1.29]
3.2 Transdermal	2	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.57, 1.66]
3.3 Vaginal	1	166	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.40 [0.76, 2.57]
4 Miscarriage Rate	6	1281	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.70, 1.45]
4.1 Oral	3	743	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.75, 1.93]
4.2 Transdermal	1	160	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.25, 2.87]
4.3 Vaginal	2	301	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.44, 1.90]
4.4 Oral and transdermal	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.05, 1.29]
5 OHSS	1	59	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.21]
5.1 Transdermal	1	59	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.21]
7 Subgroup analysis 1 (Clinical Pregnancy Rate)	6	989	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.76, 1.31]
7.1 clomiphene citrate alone without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 human gonadotropins with clomiphene citrate without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 human gonadotropins with or without GnRH agonists	5	886	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.73, 1.32]
7.4 human gonadotropins with or without GnRH antagonists	2	103	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.52, 2.42]
9 Subgroup analysis 3 (Clinical Pregnancy Rate)	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9.1 Stop at pregnancytest	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

9.2 Up to 12 weeks when pregnant	5	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
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Comparison 5. Progesterone versus progesterone + GnRH agonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live Birth Rate	3	455	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.26, 0.61]
1.1 Single dose	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.17, 0.77]
1.2 Multiple dose	2	301	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.25, 0.70]
2 Clinical Pregnancy Rate	6	1646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.60, 0.90]
2.1 Single dose	3	1324	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.60, 0.93]
2.2 Multiple dose	3	322	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.42, 1.07]
3 Ongoing Pregnancy Rate	2	1170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.60, 0.97]
3.1 Single dose	2	1170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.60, 0.97]
3.2 Multiple dose	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Miscarriage Rate	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.70 [0.41, 7.10]
4.1 Single dose	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Multiple dose	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.70 [0.41, 7.10]
6 Multiple pregnancy	2	724	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.55, 1.26]
6.1 Single dose	2	724	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.55, 1.26]
6.2 Multiple dose	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Subgroup analysis 1 (Clinical Pregnancy Rate)	6	1646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.60, 0.90]
7.1 clomiphene citrate alone without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 human gonadotropins with clomiphene citrate without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 human gonadotropins with or without GnRH agonists	4	1171	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.64, 1.02]
7.4 human gonadotropins with or without GnRH antagonists	3	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.39, 0.83]
9 Subgroup analysis 3 (Clinical Pregnancy Rate)	5	1526	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.63, 0.96]
9.1 Stop at pregnancytest	3	935	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.52, 0.88]
9.2 Up to 12 weeks when pregnant	2	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.70, 1.36]

Comparison 6. Progesterone regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live Birth Rate	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 IM versus Oral	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.14, 3.57]
1.2 IM versus Vaginal/rectal	4	1222	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.91, 1.51]
1.3 Vaginal/rectal versus Oral	2	713	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.66, 1.48]
1.4 Low dose vaginal versus high dose vaginal	2	1485	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.79, 1.24]
1.5 Short protocol versus long protocol	1	97	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.40, 1.95]
1.6 Micronized versus synthetic	2	470	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.52, 1.56]
2 Clinical Pregnancy Rate	31		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 IM versus Oral	3	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [0.89, 4.14]
2.2 IM versus Vaginal/rectal	13	2932	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.97, 1.33]
2.3 Vaginal/rectal versus Oral	6	2735	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.73, 1.04]
2.4 Low dose vaginal versus high dose vaginal	12	4973	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.92, 1.17]
2.5 Short protocol versus long protocol	1	97	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.43, 2.24]
2.6 Micronized versus synthetic	4	2388	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.65, 0.96]
3 Ongoing Pregnancy Rate	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 IM versus Oral	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 IM versus Vaginal/rectal	4	1223	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [1.05, 1.71]
3.3 Vaginal/rectal versus Oral	2	347	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.89, 2.34]
3.4 Low dose vaginal versus high dose vaginal	5	3034	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.85, 1.15]
3.5 Short protocol versus long protocol	1	97	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.33, 1.63]
3.6 Micronized versus synthetic	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Miscarriage Rate	17		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 IM versus Oral	3	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.28, 9.79]
4.2 IM versus Vaginal/rectal	5	1324	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.58, 1.25]
4.3 Vaginal/rectal versus Oral	4	2140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.76, 1.85]
4.4 Low dose vaginal versus high dose vaginal	8	2350	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.53, 1.17]
4.5 Short protocol versus long protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Micronized versus synthetic	2	1793	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.70, 1.91]
5 OHSS	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 IM versus Oral	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.58]
5.2 IM versus Vaginal/rectal	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Vaginal/rectal versus Oral	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Low dose vaginal versus high dose vaginal	1	1211	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.57, 1.46]

5.5 Short protocol versus long protocol	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 Micronized versus synthetic	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.58]
6 Multiple pregnancy	10		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 IM versus Oral	2	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.39 [1.28, 15.01]
6.2 IM versus Vaginal/rectal	1	505	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.60, 1.59]
6.3 Vaginal/rectal versus Oral	1	283	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.50, 2.58]
6.4 Low dose vaginal versus high dose vaginal	4	905	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.63, 1.76]
6.5 Short protocol versus long protocol	2	317	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.75, 3.50]
6.6 Micronized versus synthetic	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Subgroup analysis 1: IM versus Vaginal/rectal (Clinical Pregnancy Rate)	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7.1 clomiphene citrate alone without GnRH agonists	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 human gonadotropins with clomiphene citrate without GnRH agonists	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 human gonadotropins with or without GnRH agonists	10		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 human gonadotropins with or without GnRH antagonists	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Subgroup analysis 1: Low dose vaginal versus high dose vaginal (Clinical Pregnancy Rate)	9	3512	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.91, 1.22]
8.1 clomiphene citrate alone without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 human gonadotropins with clomiphene citrate without GnRH agonists	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 human gonadotropins with or without GnRH agonists	8	3388	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.91, 1.22]
8.4 human gonadotropins with or without GnRH antagonists	1	124	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.49, 2.21]
10 Subgroup analysis 3: IM versus Vaginal/rectal (Clinical Pregnancy Rate)	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
10.1 Stop at pregnancy test	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Up to 12 weeks when pregnant	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Subgroup analysis 3: Vaginal/rectal versus Oral (Clinical Pregnancy Rate)	5	2695	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.71, 1.02]

11.1 Stop at pregnancy test	2	619	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.50, 0.98]
11.2 Up to 12 weeks when pregnant	3	2076	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.75, 1.15]
12 Subgroup analysis 3: Low dose vaginal versus high dose vaginal (Clinical Pregnancy Rate)	10	4811	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.92, 1.17]
12.1 Stop at pregnancy test	3	318	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.67, 1.82]
12.2 Up to 12 weeks when pregnant	7	4493	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.91, 1.17]

Analysis 1.1. Comparison 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome: 1 Live Birth Rate

(1) IM hCG 1500 IU 4 times

Analysis 1.2. Comparison 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome: 2 Clinical Pregnancy Rate

(1) hCG 2000 IU every 3 days

(2) IM hCG 1500 IU 4 times

(3) sc hCG 1500 IU two times

(4) IM hCG 2500 IU 3 times

(5) hCG 1500 IU every other day

Analysis 1.3. Comparison 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment, Outcome 3 Ongoing Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome: 3 Ongoing Pregnancy Rate

(1) IM hCG 1500 IU 4 times

(2) sc hCG 1500 IU two times

(3) IM hCG 2500 IU 3 times

Analysis 1.4. Comparison 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment, Outcome 4 Miscarriage Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome: 4 Miscarriage Rate

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

Review: Luteal phase support for assisted reproduction cycles

Comparison: 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome: 5 OHSS

(1) sc hCG 1500 IU two times

Analysis 1.7. Comparison 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment, Outcome 7 Subgroup analysis 1 (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 1 Human chorionic gonatotropin (hCG) versus placebo or no treatment

Outcome: 7 Subgroup analysis 1 (Clinical Pregnancy Rate)

- (1) CC + hMG
- (2) GnRH agonist + FSH
- (3) GnRH agonist + hMG
- (4) GnRH agonist + hMG
- (5) hMG

Analysis 2.1. Comparison 2 Progesterone versus placebo or no treatment, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 1 Live Birth Rate

(1) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily

Analysis 2.2. Comparison 2 Progesterone versus placebo or no treatment, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 2 Clinical Pregnancy Rate

(1) IM 17-OHPc 341 mg every 3 days

(2) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily

(3) IM progesterone 50 mg daily or vaginal progesterone cream 100 mg daily

(4) Oral dydrogesterone 10 mg 3 times daily

(5) Vaginal progesterone suppositories 100 mg twice daily + oral E2 2 mg 3 times daily

(6) Oral dydrogesterone 10 mg 3 times daily

(7) IM progesterone 50 mg daily

Analysis 2.3. Comparison 2 Progesterone versus placebo or no treatment, Outcome 3 Ongoing Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 3 Ongoing Pregnancy Rate

(1) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily

(2) Oral dydrogesterone 10 mg 3 times daily

(3) Oral progesterone 200 mg 4 times daily

(4) Vaginal progesterone suppositories 100 mg twice daily + oral E2 2 mg 3 times daily

(5) Oral dydrogesterone 10 mg 3 times daily

Analysis 2.4. Comparison 2 Progesterone versus placebo or no treatment, Outcome 4 Miscarriage Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 4 Miscarriage Rate

(1) Oral dydrogesterone 10 mg 3 times daily

(2) Oral progesterone 200 mg 4 times daily

(3) Oral dydrogesterone 10 mg 3 times daily

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

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 6 Multiple pregnancy

(1) Oral progesterone 200 mg 4 times daily

Analysis 2.7. Comparison 2 Progesterone versus placebo or no treatment, Outcome 7 Subgroup analysis I (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 7 Subgroup analysis I (Clinical Pregnancy Rate)

- (1) CC
- (2) Mostly CC+hMG, sometimes FSH, hMG or FSH+hMG
- (3) CC + hMG
- (4) FSH + GnRH agonist
- (5) FSH + GnRH agonist
- (6) FSH + GnRH agonist
- (7) hMG

Analysis 2.9. Comparison 2 Progesterone versus placebo or no treatment, Outcome 9 Subgroup analysis 3 (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 2 Progesterone versus placebo or no treatment

Outcome: 9 Subgroup analysis 3 (Clinical Pregnancy Rate)

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Analysis 3.1. Comparison 3 Progesterone versus hCG regimens, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 1 Live Birth Rate

(1) IM progesterone 100 mg daily vs IM hCG 1000 IU or 2500 IU 4 times

(2) Vaginal progesterone 200 mg 3 times daily vs hCG 5000 IU twice and 2500 IU twice

(3) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + single dose hCG 5000 IU

Analysis 3.2. Comparison 3 Progesterone versus hCG regimens, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 2 Clinical Pregnancy Rate

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Study or subgroup	Progesterone n/N	hCG n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Macrolin 1993 (15)	45/152	43/150		28.1 %	1.05 [0.64, 1.72]
Ugur 2001 (16)	40/137	40/142		25.7 %	1.05 [0.63, 1.77]
Wong 1990 (17)	3/10	2/10		1.8 %	1.66 [0.23, 11.94]
Subtotal (95% CI)	540	540		100.0 %	0.96 [0.74, 1.25]
Total events: 169 (Progesterone), 173 (hCG)					
Heterogeneity: Chi ² = 5.81, df = 6 (P = 0.45); I ² = 0.0%					
Test for overall effect: Z = 0.31 (P = 0.75)					
Test for subgroup differences: Chi ² = 0.93, df = 1 (P = 0.34), I ² = 0.0%					

0.05 0.2 1 5 20
Favours hCG regimen Favours Progesterone

- (1) IM progesterone 50 mg once, then 12.5 mg daily vs hCG 1500 IU 4 times
- (2) IM progesterone 50 mg daily or vaginal progesterone cream 100 mg daily vs hCG 2000 IU every 3 days
- (3) IM progesterone 100 mg daily vs IM hCG 1000 IU or 2500 IU 4 times
- (4) Oral dydrogesterone 10 mg 3 times daily vs IM hCG 2500 IU 3 times
- (5) Vaginal progesterone 200 mg 3 times daily for 9 days + IM hCG 2000 IU 4 times vs IM hCG 2000 IU 4 times
- (6) Information not available
- (7) Vaginal progesterone 200 mg 3 times daily vs hCG 5000 IU twice and 2500 IU twice
- (8) Vaginal progesterone 100 mg 3 times daily vs IM 2500 IU hCG 3 times
- (9) Vaginal progesterone 400 mg daily vs hCG 1500 IU every 3 days
- (10) Vaginal progesterone capsules 200 3 times daily vs IM hCG 1500 IU 3 times
- (11) Vaginal progesterone 400 mg daily vs vaginal progesterone 400 mg daily + sc hCG 1000 IU 3 times
- (12) IM progesterone 25 mg daily vs IM progesterone 25 mg daily + IM hCG 3000 IU 3 times
- (13) Vaginal progesterone daily vs vaginal progesterone + rLH 4 times
- (14) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + single dose hCG 5000 IU
- (15) Vaginal progesterone 400 mg daily vs vaginal progesterone 400 mg daily + hCG 1500 IU every other day 3 times
- (16) Vaginal progesterone 400 mg daily vs vaginal progesterone 400 mg daily + single dose hCG 3000 IU
- (17) IM progesterone 50 mg daily vs IM progesterone 50 mg daily + hCG 1500 IU 6 times

Analysis 3.3. Comparison 3 Progesterone versus hCG regimens, Outcome 3 Ongoing Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 3 Ongoing Pregnancy Rate

(1) Oral dydrogesterone 10 mg 3 times daily vs IM hCG 2500 IU 3 times

(2) Vaginal progesterone 200 mg 3 times daily vs hCG 5000 IU twice and 2500 IU twice

(3) Vaginal progesterone gel 90 mg daily or rectal progesterone 200 mg twice daily or vaginal progesterone 200 mg, 400 mg or 600 mg vs sc hCG 1500 IU twice

(4) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + single dose hCG 5000 IU

(5) Vaginal progesterone 400 mg daily vs vaginal progesterone 400 mg daily + hCG 1500 IU every other day 3 times

Analysis 3.4. Comparison 3 Progesterone versus hCG regimens, Outcome 4 Miscarriage Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 4 Miscarriage Rate

(1) IM progesterone 100 mg daily vs IM hCG 1000 IU or 2500 IU 4 times

(2) Oral dydrogesterone 10 mg 3 times daily vs IM hCG 2500 IU 3 times

(3) Vaginal progesterone 200 mg 3 times daily for 9 days + IM hCG 2000 IU 4 times vs IM hCG 2000 IU 4 times

(4) Vaginal progesterone 200 mg 3 times daily vs hCG 5000 IU twice and 2500 IU twice

(5) Vaginal progesterone 100 mg 3 times daily vs IM 2500 IU hCG 3 times

(6) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + single dose hCG 5000 IU

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

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 5 OHSS

(1) IM progesterone 50 mg once, then 12,5 mg daily vs hCG 1500 IU 4 times

(2) Vaginal progesterone 200 mg 3 times daily vs hCG 5000 IU twice and 2500 IU twice

(3) Vaginal progesterone 100 mg 3 times daily vs IM 2500 IU hCG 3 times

(4) Vaginal progesterone 400 mg daily vs hCG 1500 IU every 3 days

(5) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + single dose hCG 5000 IU

(6) Vaginal progesterone 400 mg daily vs vaginal progesterone 400 mg daily + single dose hCG 3000 IU

Analysis 3.6. Comparison 3 Progesterone versus hCG regimens, Outcome 6 Multiple pregnancy.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 6 Multiple pregnancy

(1) Vaginal progesterone 200 mg 3 times daily vs hCG 5000 IU twice and 2500 IU twice

(2) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + single dose hCG 5000 IU

Analysis 3.8. Comparison 3 Progesterone versus hCG regimens, Outcome 8 Subgroup analysis 1: Progesterone vs progesterone + hCG (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 8 Subgroup analysis 1: Progesterone vs progesterone + hCG (Clinical Pregnancy Rate)

- (1) CC + hMG
- (2) GnRHa + hMG
- (3) GnRH agonist + r-FSH or hMG
- (4) GnRHa + hMG

Analysis 3.11. Comparison 3 Progesterone versus hCG regimens, Outcome 11 Subgroup analysis 3: Progesterone vs hCG (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 3 Progesterone versus hCG regimens

Outcome: 11 Subgroup analysis 3: Progesterone vs hCG (Clinical Pregnancy Rate)

Analysis 4.1. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 1 Live Birth Rate

(1) IM progesterone 50 mg daily vs IM progesterone 50 mg daily E2 2 mg oral daily

Analysis 4.2. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 2 Clinical Pregnancy Rate

- (1) IM progesterone 100 mg daily vs IM progesterone 100 mg daily + E2 valerate 2 mg 3 times daily
- (2) IM progesterone 50 mg daily vs IM progesterone 50 mg daily + E2 2 mg daily
- (3) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily vs IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily + E2 3 mg twice daily
- (4) Vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + transdermal E2 2 mg twice weekly
- (5) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + estradiol 100 µg daily
- (6) IM progesterone 100 mg daily vs IM progesterone 100 mg daily + vaginal E2 valerate 2 mg 3 times daily
- (7) IM progesterone 50 mg daily vs IM progesterone 50 mg daily + vaginal E2 2 mg twice daily
- (8) Oral progesterone 100 mg 3 times daily + vaginal progesterone 200 mg 3 times daily vs oral progesterone 100 mg 3 times daily + vaginal progesterone 200 mg 3 times daily + oral estradiol

Analysis 4.3. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 3 Ongoing Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 3 Ongoing Pregnancy Rate

- (1) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + E2 valerate 2 mg twice daily
- (2) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily vs IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily + E2 3 mg twice daily
- (3) Vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + 2 g twice weekly
- (4) Vaginal progesterone 200 mg twice daily vs vaginal progesterone 200 mg twice daily + E2 10 g daily
- (5) IM progesterone 50 mg daily vs IM progesterone 50 mg daily + vaginal E2 2 mg twice daily

Analysis 4.4. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 4 Miscarriage Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 4 Miscarriage Rate

- (1) IM progesterone 100 mg daily vs IM progesterone 100 mg daily + E2 valerate 2 mg 3 times daily
- (2) Vaginal progesterone 200 mg 3 times daily vs vaginal progesterone 200 mg 3 times daily + E2 valerate 2 mg twice daily
- (3) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily vs IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily + E2 3 mg twice daily
- (4) Vaginal progesterone 200 mg twice daily vs vaginal progesterone 200 mg twice daily + E2 10 g daily
- (5) IM progesterone 100 mg daily vs IM progesterone 100 mg daily + vaginal E2 valerate 2 mg 3 times daily
- (6) IM progesterone 50 mg daily vs IM progesterone 50 mg daily + vaginal E2 2 mg twice daily
- (7) Oral progesterone 100 g 3 times daily + vaginal progesterone 200 g 3 times daily vs oral progesterone 100 g 3 times daily + vaginal progesterone 200 g 3 times daily +oral estradiol

Analysis 4.5. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 5 OHSS.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 5 OHSS

- (1) Vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + transdermal E2 2 g twice weekly

Analysis 4.7. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 7 Subgroup analysis I (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 7 Subgroup analysis I (Clinical Pregnancy Rate)

- (1) GnRH agonist + rFSH
- (2) GnRH agonist + rFSH + hMG
- (3) GnRH agonist + rFSH or rFSH + hMG
- (4) GnRHa + hMG
- (5) GnRH agonist
- (6) GnRH antagonist + rFSH
- (7) GnRH antagonist + rFSH or rFSH + hMG

Analysis 4.9. Comparison 4 Progesterone versus progesterone + estrogen, Outcome 9 Subgroup analysis 3 (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 4 Progesterone versus progesterone + estrogen

Outcome: 9 Subgroup analysis 3 (Clinical Pregnancy Rate)

Analysis 5.1. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 1 Live Birth Rate

(1) Vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU vs vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU + sc leuprolide acetate 0.5 mg on day 6 after

(2) Progesterone 50 mg im daily vs progesterone 50 mg im daily + GnRH agonist 0.25 mg sc daily for 12 days

(3) Cyclogest (not defined) + placebo vs Cyclogest (not defined) + sc triptorelin 0.1 mg 3 times

Analysis 5.2. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 2 Clinical Pregnancy Rate

(1) Vaginal progesterone gel 90 mg daily + placebo vs vaginal progesterone gel 90 mg daily + sc triptorelin 0.1 mg on day 6 after ET

(2) Vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU vs vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU + sc leuprolide acetate 0.5 mg on day 6 after

(3) Vaginal progesterone 400 mg daily + single dose hCG 250 g + E2 valerate injection 4 mg daily vs vaginal progesterone 400 mg daily + single dose hCG 250 g + E2 valerate injection

(4) Progesterone 50 mg im daily vs progesterone 50 mg im daily + GnRH agonist 0.25 mg sc daily for 12 days

(5) vaginal micronized progesterone 200 mg 3x daily vs 200 g GnRH agonist (buserelin) intranasal (IN) followed by 100 g IN every 2 days, daily, 2 or 3 times daily

(6) Cyclogest (not defined) + placebo vs Cyclogest (not defined) + sc triptorelin 0.1 mg 3 times

Analysis 5.3. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 3 Ongoing Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 3 Ongoing Pregnancy Rate

(1) Vaginal progesterone gel 90 mg daily + placebo vs vaginal progesterone gel 90 mg daily + sc triptorelin 0.1 mg on day 6 after ET

(2) Vaginal progesterone 400 mg daily + single dose hCG 250 g + E2 valerate injection 4 mg daily vs vaginal progesterone 400 mg daily + single dose hCG 250 g + E2 valerate injection

Analysis 5.4. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 4 Miscarriage Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 4 Miscarriage Rate

(1) Cyclogest (not defined) + placebo vs Cyclogest (not defined) + sc triptorelin 0.1 mg 3 times

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

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 6 Multiple pregnancy

(1) Vaginal progesterone gel 90 mg daily + placebo vs vaginal progesterone gel 90 mg daily + sc triptorelin 0.1 mg on day 6 after ET

(2) Vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU vs vaginal progesterone 200 mg 3 times daily + single dose hCG 1500 IU + sc leuprolide acetate 0.5 mg on day 6 after

Analysis 5.7. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 7 Subgroup analysis I (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 7 Subgroup analysis I (Clinical Pregnancy Rate)

- (1) GnRH agonist + rFSH
- (2) GnRH agonist + FSH
- (3) GnRH agonist + hMG
- (4) GnRH agonist + rFSH + hMG
- (5) GnRH antagonist + FSH
- (6) hMG/FSH
- (7) GnRH antagonist + rFSH + hMG

Analysis 5.9. Comparison 5 Progesterone versus progesterone + GnRH agonist, Outcome 9 Subgroup analysis 3 (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 5 Progesterone versus progesterone + GnRH agonist

Outcome: 9 Subgroup analysis 3 (Clinical Pregnancy Rate)

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Study or subgroup	Progesterone n/N	Progesterone + GnRH agonist n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 294 (Progesterone), 340 (Progesterone + GnRH agonist)					
Heterogeneity: $\chi^2 = 7.52$, $df = 4$ ($P = 0.11$); $I^2 = 47\%$					
Test for overall effect: $Z = 2.39$ ($P = 0.017$)					
Test for subgroup differences: $\chi^2 = 3.04$, $df = 1$ ($P = 0.08$), $I^2 = 67\%$					
<div>0.01 0.1 1 10 100</div> <div>Favours Progesterone + GnRH agonist Favours Progesterone</div>					

Analysis 6.1. Comparison 6 Progesterone regimens, Outcome 1 Live Birth Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 1 Live Birth Rate

Study or subgroup	Treatment A n/N	Treatment B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 IM versus Oral					
Iwase 2008 (1)	3/20	4/20		100.0 %	0.71 [0.14, 3.57]
Subtotal (95% CI)	20	20		100.0 %	0.71 [0.14, 3.57]
Total events: 3 (Treatment A), 4 (Treatment B)					
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.41$ ($P = 0.68$)					
2 IM versus Vaginal/rectal					
Abate 1999a (2)	11/52	4/52		5.5 %	2.95 [0.99, 8.75]
Dal Prato 2008 (3)	36/138	73/274		30.2 %	0.97 [0.61, 1.54]
Propst 2001 (4)	39/99	25/102		18.5 %	1.98 [1.09, 3.58]
Zegers-Hochschild 2000 (5)	81/262	77/243		45.8 %	0.96 [0.66, 1.41]
Subtotal (95% CI)	551	671		100.0 %	1.17 [0.91, 1.51]
Total events: 167 (Treatment A), 179 (Treatment B)					
Heterogeneity: $\chi^2 = 7.41$, $df = 3$ ($P = 0.06$); $I^2 = 60\%$					
Test for overall effect: $Z = 1.23$ ($P = 0.22$)					
<div>0.01 0.1 1 10 100</div> <div>Favours treatment B Favours treatment A</div>					

(Continued ...)

(... Continued)

- (1) chlormadione acetate 6 mg oral 2x daily vs progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14
- (2) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (3) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily or vaginal progesterone gel 90 mg twice daily
- (4) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (5) IM progesterone 50 mg daily vs vaginal progesterone ring 1 mg
- (6) Vaginal progesterone 200 mg 3 times daily vs oral dydrogesterone 10 mg twice daily
- (7) Vaginal progesterone gel 90 mg daily vs oral progesterone 300 mg daily
- (8) Crinone 8% vs Crinone 8% twice daily
- (9) Crinone 8% vs vaginal progesterone 100 mg twice daily or vaginal progesterone 100 mg 3 times daily
- (10) progesterone 50 mg IM for 11 days vs progesterone 50 mg IM for 6 weeks
- (11) Vaginal progesterone 200 mg 3 times daily vs oral dydrogesterone 10 mg twice daily
- (12) Progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14 vs chlormadione acetate 6 mg oral 2x daily

Analysis 6.2. Comparison 6 Progesterone regimens, Outcome 2 Clinical Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 2 Clinical Pregnancy Rate

(Continued ...)

(... Continued)

- (1) chlormadione acetate 6 mg oral 2x daily vs progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14
- (2) IM progesterone 50 mg daily vs oral progesterone 200 mg 3 times daily
- (3) IM progesterone 50 mg daily vs oral progesterone 400 mg daily
- (4) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (5) IM progesterone 50 mg daily vs vaginal progesterone cream 100 mg daily
- (6) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily or vaginal progesterone gel 90 mg twice daily
- (7) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (8) IM progesterone 50 mg daily vs vaginal Endometrin (not defined)
- (9) IM progesterone 50 mg daily vs vaginal progesterone 200 mg daily
- (10) IM progesterone 50 mg daily vs vaginal progesterone 200 mg daily
- (11) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (12) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (13) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (14) IM progesterone 50 mg daily vs vaginal progesterone 600 mg daily
- (15) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (16) 50 mg progesterone IM vs progesterone vaginal ring 1 mg
- (17) Vaginal progesterone 200 mg 3 times daily vs oral dydrogesterone 10 mg twice daily
- (18) Vaginal progesterone 100 mg twice daily vs oral progesterone 200 mg 4 times daily
- (19) Vaginal progesterone 200 mg 3 times daily or vaginal progesterone gel 90 mg daily vs oral dydrogesterone 10 mg daily
- (20) Vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + oral dydrogesterone 20 mg daily
- (21) Vaginal progesterone gel 90 mg daily vs oral progesterone 300 mg daily
- (22) Vaginal progesterone gel 90 mg daily vs oral progesterone 400 mg daily
- (23) Crinone 8% vs Crinone 8% twice daily
- (24) Crinone 8% vs vaginal progesterone 100 mg twice daily
- (25) Crinone 8% vs vaginal progesterone pessaries 400 mg twice daily
- (26) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (27) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (28) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (29) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (30) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (31) Progesterone capsules 100 mg 2 times daily vs Progesterone pessaries 400 mg 2 times daily
- (32) Crinone 8% vs vaginal progesterone capsule 200 mg twice daily or vaginal progesterone suppositories 200 mg daily
- (33) Vaginal gel vs vaginal ring
- (34) Crinone 8% vs Utrogestan (not defined)
- (35) progesterone 50 mg IM for 11 days vs progesterone 50 mg IM for 6 weeks

Luteal phase support for assisted reproduction cycles (Review)

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- (36) Vaginal progesterone 200 mg 3 times daily vs oral dydrogesterone 10 mg twice daily
- (37) Vaginal progesterone 200 mg 3 times daily or vaginal progesterone gel 90 mg daily vs oral dydrogesterone 10 mg twice daily
- (38) Progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14 vs chlormadione acetate 6 mg oral 2x daily
- (39) Vaginal progesterone 600 mg daily vs vaginal progesterone 600 mg daily + oral dydrogesterone 20 mg daily

Analysis 6.3. Comparison 6 Progesterone regimens, Outcome 3 Ongoing Pregnancy Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 3 Ongoing Pregnancy Rate

(Continued ...)

(... Continued)

- (1) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (2) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily or vaginal progesterone gel 90 mg twice daily
- (3) IM progesterone 50 mg daily vs vaginal progesterone 200 mg daily
- (4) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (5) Vaginal progesterone 100 mg twice daily vs oral progesterone 200 mg 4 times daily
- (6) Vaginal progesterone gel 90 mg daily vs oral progesterone 300 mg daily
- (7) Crinone 8% vs Crinone 8% twice daily
- (8) Crinone 8% vs vaginal progesterone 100 mg twice daily or vaginal progesterone 100 mg 3 times daily
- (9) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (10) Vaginal gel vs vaginal ring
- (11) Crinone 8% vs rectal progesterone 200 mg twice daily or vaginal progesterone 200 mg, 400 mg or 600 mg daily
- (12) progesterone 50 mg IM for 11 days vs progesterone 50 mg IM for 6 weeks

Analysis 6.4. Comparison 6 Progesterone regimens, Outcome 4 Miscarriage Rate.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 4 Miscarriage Rate

(Continued ...)

(... Continued)

- (1) chlormadione acetate 6 mg oral 2x daily vs progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14
- (2) IM progesterone 50 mg daily vs oral progesterone 200 mg 3 times daily
- (3) IM progesterone 50 mg daily vs oral progesterone 400 mg daily
- (4) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily or vaginal progesterone gel 90 mg twice daily
- (5) IM progesterone 50 mg daily vs vaginal Endometrin (not defined)
- (6) IM progesterone 50 mg daily vs vaginal progesterone 200 mg daily
- (7) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (8) IM progesterone 50 mg daily vs vaginal progesterone gel 90 mg daily
- (9) Vaginal progesterone 200 mg 3 times daily vs oral dydrogesterone 10 mg twice daily
- (10) Vaginal progesterone 100 mg twice daily vs oral progesterone 200 mg 4 times daily
- (11) Vaginal progesterone 200 mg 3 times daily or vaginal progesterone gel 90 mg daily vs oral dydrogesterone 10 mg daily
- (12) Vaginal progesterone gel 90 mg daily vs oral progesterone 300 mg daily
- (13) Crinone 8% vs Crinone 8% twice daily
- (14) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (15) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (16) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (17) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (18) Progesterone capsules 100 mg 2 times daily vs Progesterone pessaries 400 mg 2 times daily
- (19) Crinone 8% vs vaginal progesterone suppositories 200 mg daily or vaginal progesterone capsule 200 mg twice daily
- (20) Crinone 8% vs Utrogestan (not defined)
- (21) Vaginal progesterone 200 mg 3 times daily vs oral dydrogesterone 10 mg twice daily
- (22) Vaginal progesterone 200 mg 3 times daily or vaginal progesterone gel 90 mg daily vs oral dydrogesterone 10 mg daily

Analysis 6.5. Comparison 6 Progesterone regimens, Outcome 5 OHSS.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 5 OHSS

(1) Progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14 vs chlormadione acetate 6 mg oral 2x daily

(2) Crinone 8% vs vaginal progesterone 100 mg twice daily or vaginal progesterone 100 mg 3 times daily

(3) Progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14 vs chlormadione acetate 6 mg oral 2x daily

Analysis 6.6. Comparison 6 Progesterone regimens, Outcome 6 Multiple pregnancy.

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 6 Multiple pregnancy

(Continued ...)

(... Continued)

Study or subgroup	Treatment A n/N	Treatment B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
5 Short protocol versus long protocol					
Goudge 2010 (9)	12/51	4/46		52.3 %	2.90 [1.00, 8.45]
Kohls 2010 (10)	6/110	7/110		47.7 %	0.85 [0.28, 2.60]
Subtotal (95% CI)	161	156		100.0 %	1.62 [0.75, 3.50]
Total events: 18 (Treatment A), 11 (Treatment B)					
Heterogeneity: Chi ² = 2.42, df = 1 (P = 0.12); I ² = 59%					
Test for overall effect: Z = 1.22 (P = 0.22)					
6 Micronized versus synthetic					
Subtotal (95% CI)	0	0		0.0 %	0.0 [0.0, 0.0]
Total events: 0 (Treatment A), 0 (Treatment B)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi ² = 5.80, df = 4 (P = 0.21), I ² = 31%					

0.01 0.1 1 10 100
Favours treatment A Favours treatment B

- (1) chlormadione acetate 6 mg oral 2x daily vs progesterone im 25 mg daily from day 2 to 6, 50 mg daily from day 7 to 14
- (2) IM progesterone 50 mg daily vs oral progesterone 200 mg 3 times daily
- (3) 50 mg progesterone IM vs progesterone vaginal ring 1 mg
- (4) Vaginal progesterone gel 90 mg daily vs oral progesterone 300 mg daily
- (5) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (6) Crinone 8% vs vaginal progesterone capsule 200 mg 3 times daily
- (7) Progesterone capsules 100 mg 2 times daily vs Progesterone pessaries 400 mg 2 times daily
- (8) Crinone 8% vs Utrogestan (not defined)
- (9) progesterone 50 mg IM for 11 days vs progesterone 50 mg IM for 6 weeks
- (10) Progesterone vaginal 200 mg twice daily until US vs progesterone vaginal 200 mg twice daily until 8 weeks pregnant

Analysis 6.7. Comparison 6 Progesterone regimens, Outcome 7 Subgroup analysis 1: IM versus Vaginal/rectal (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 7 Subgroup analysis 1: IM versus Vaginal/rectal (Clinical Pregnancy Rate)

(1) GnRH agonist + FSH

(2) GnRH agonist + FSH + hMG

(3) GnRH agonist + FSH

(4) GnRH agonist + rFSH

(5) GnRH agonist + FSH

(6) GnRH agonist

(7) GnRH agonist + rFSH

(8) GnRH agonist + FSH

(9) GnRH agonist

(10) GnRH antagonist + Menopur or r-FSH

Analysis 6.8. Comparison 6 Progesterone regimens, Outcome 8 Subgroup analysis I: Low dose vaginal versus high dose vaginal (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 8 Subgroup analysis I: Low dose vaginal versus high dose vaginal (Clinical Pregnancy Rate)

(Continued ...)

(... Continued)

Study or subgroup	Low dose n/N	High dose n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: $\chi^2 = 10.58$, $df = 8$ ($P = 0.23$); $I^2 = 24\%$ Test for overall effect: $Z = 0.67$ ($P = 0.50$) Test for subgroup differences: $\chi^2 = 0.00$, $df = 1$ ($P = 0.98$), $I^2 = 0.0\%$					
			0.01 0.1 1 10 100		
			Favours high dose Favours low dose		
(1) GnRH agonist + FSH					
(2) GnRH agonist + hMG (Menopur) + FSH (Bravelle)					
(3) GnRH agonists + FSH					
(4) GnRH agonist + FSH					
(5) GnRH agonist + hMG or FSH					
(6) GnRH agonist					
(7) GnRH agonist + hMG					
(8) GnRH agonist + hMG					
(9) GnRH antagonist + rFSH + LH + hCG					

Analysis 6.10. Comparison 6 Progesterone regimens, Outcome 10 Subgroup analysis 3: IM versus Vaginal/rectal (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 10 Subgroup analysis 3: IM versus Vaginal/rectal (Clinical Pregnancy Rate)

Analysis 6.11. Comparison 6 Progesterone regimens, Outcome 11 Subgroup analysis 3: Vaginal/rectal versus Oral (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 11 Subgroup analysis 3: Vaginal/rectal versus Oral (Clinical Pregnancy Rate)

Analysis 6.12. Comparison 6 Progesterone regimens, Outcome 12 Subgroup analysis 3: Low dose vaginal versus high dose vaginal (Clinical Pregnancy Rate).

Review: Luteal phase support for assisted reproduction cycles

Comparison: 6 Progesterone regimens

Outcome: 12 Subgroup analysis 3: Low dose vaginal versus high dose vaginal (Clinical Pregnancy Rate)

ADDITIONAL TABLES

Table 1. Sensitivity analysis for studies with outlying results in comparison 3.2.1

	Peto OR	95% CI
Before SA	1.14	[0.90, 1.45]
After SA	1.19	[0.94, 1.52]

Without [Golan 1993](#)

Table 2. Sensitivity analysis for studies with outlying results in comparison 3.5.2

	Peto OR	95% CI
Before SA	0.45	0.45 [0.26, 0.79]
Without Ludwig 2001	0.26	0.26 [0.13, 0.51]
Without Ugur 2001	0.89	0.89 [0.37, 2.16]

Table 3. Sensitivity analysis for studies with outlying results in comparison 4.2

	Peto OR	95% CI
Before SA	0.80	0.80 [0.63, 1.01]
After SA	1.06	[0.38, 2.94]

Without [Gorkemli 2004](#)

Table 4. Sensitivity analysis for studies with high risk of bias in comparison 4.3

	Peto OR	95% CI
Before SA	1.00	[0.76, 1.31]
After SA	0.94	[0.72, 1.22]

Without [Faremi 2006](#)

Table 5. Sensitivity analysis for studies with high risk of bias in comparison 4.4

	Peto OR	95% CI
Before SA	1.01	[0.70, 1.45]
After SA	1.03	[0.69, 1.53]

Without [Fatemi 2006](#)

Table 6. Sensitivity analysis for studies with outlying results in comparison 5.2

	Peto OR	95% CI
Before SA	0.74	[0.60, 0.90]
After SA	0.73	[0.60, 0.89]

Without [Pirard 2006](#)

Table 7. Sensitivity analysis for studies with high risk of bias in comparison 6.1.1

	Peto OR	95% CI
Before SA	1.40	[0.28, 7.02]
After SA		

Without [Iwase 2008](#): not possible, as this is the only included study in this comparison

Table 8. Sensitivity analysis for studies with high risk of bias in comparison 6.1.6

	Peto OR	95% CI
Before SA	0.90	[0.52, 1.56]
After SA	0.93	[0.52, 1.66]

Without [Iwase 2008](#)

Table 9. Sensitivity analysis for studies with high risk of bias in comparison 6.2.1

	Peto OR	95% CI
Before SA	1.92	[0.89, 4.14]
After SA	2.21	[0.90, 5.44]

Without [Iwase 2008](#)

Table 10. Sensitivity analysis for studies with outlying results in comparison 6.2.2

	Peto OR	95% CI
Before SA	1.14	[0.97, 1.33]
After SA	1.05	[0.89, 1.24]

Without [Perino 1997](#)

Table 11. Sensitivity analysis for studies with high risk of bias in comparison 6.2.4

	Peto OR	95% CI
Before SA	1.04	[0.92, 1.17]
After SA	1.02	[0.91, 1.16]

Without [Ludwig 2002](#)

Table 12. Sensitivity analysis for studies with high risk of bias in comparison 6.2.6

	Peto OR	95% CI
Before SA	0.79	[0.65, 0.96]
After SA	0.79	[0.65, 0.96]

Without [Iwase 2008](#)

Table 13. Sensitivity analysis for studies with outlying results in comparison 6.3.2

	Peto OR	95% CI
Before SA	1.34	[1.05, 1.71]
After SA	1.04	[0.79, 1.39]

Without [Perino 1997](#)

Table 14. Sensitivity analysis for studies with high risk of bias in comparison 6.3.4

	Peto OR	95% CI
Before SA	0.99	[0.85, 1.15]
After SA	0.98	[0.84, 1.14]

Without [Ludwig 2002](#)

Table 15. Sensitivity analysis for studies with high risk of bias in comparison 6.4.1

	Peto OR	95% CI
Before SA	1.66	[0.28, 9.79]
After SA	0.59	[0.06, 5.85]

Without [Iwase 2008](#)

Table 16. Sensitivity analysis for studies with outlying results in comparison 6.4.1

	Peto OR	95% CI
Before SA	1.66	[0.28, 9.79]
After SA	7.65	[0.78, 75.00]

Without [Licciardi 1999](#)

Table 17. Sensitivity analysis for studies with outlying results in comparison 6.4.2

	Peto OR	95% CI
Before SA	0.85	[0.58, 1.25]
After SA	0.83	[0.57, 1.22]

Without [Saucedo 2000](#)

Table 18. Sensitivity analysis for studies with outlying results in comparison 6.4.3

	Peto OR	95% CI
Before SA	1.18	[0.76, 1.85]
After SA	1.27	[0.80, 2.01]

Without [Friedler 1999](#)

Table 19. Sensitivity analysis for studies with high risk of bias in comparison 6.4.4

	Peto OR	95% CI
Before SA	0.79	[0.53, 1.17]
After SA	0.76	[0.50, 1.13]

Without [Ludwig 2002](#)

Table 20. Sensitivity analysis for studies with high risk of bias in comparison 6.5.1

	Peto OR	95% CI
Before SA	1.00	[0.06, 16.58]
After SA		

Without [Iwase 2008](#): not possible, as this is the only included study in this comparison

Table 21. Sensitivity analysis for studies with high risk of bias in comparison 6.5.6

	Peto OR	95% CI
Before SA	1.00	[0.06, 16.58]
After SA		

Without [Iwase 2008](#): not possible, as this is the only included study in this comparison

Table 22. Sensitivity analysis for studies with high risk of bias in comparison 6.6.1

	Peto OR	95% CI
Before SA	4.14	[1.13, 15.13]
After SA	4.39	[1.28, 15.01]

Without [Iwase 2008](#)

APPENDICES

Appendix I. CENTRAL search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2011>

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (1475)

2 embryo transfer\$.tw. (830)

3 in vitro fertili?ation.tw. (1251)

4 ivf-et.tw. (241)

5 (ivf or et).tw. (5634)

6 icsi.tw. (604)

7 intracytoplasmic sperm injection\$.tw. (370)

8 (blastocyst adj2 transfer\$).tw. (59)

9 exp Insemination, Artificial/ (254)

10 Insemination\$.tw. (574)

11 iui.tw. (257)

12 or/1-11 (7219)

13 exp Luteal Phase/ (402)

14 (luteal adj5 support\$).tw. (191)

15 (luteal adj5 phase).tw. (821)

16 (ischemic adj5 phase).tw. (104)

17 post ovulat\$.tw. (11)

18 (post adj5 transfer\$).tw. (41)

19 (after adj5 transfer\$).tw. (5503)

20 (post adj5 trigger\$).tw. (9)

21 (after adj5 trigger\$).tw. (1908)
 22 or/13-21 (8262)
 23 12 and 22 (1414)
 24 exp Progesterone/ (2063)
 25 Progesterone\$.tw. (2091)
 26 dydrogesterone.tw. (142)
 27 utrogest.tw. (7)
 28 17 alpha-hydroxyprogesterone.tw. (66)
 29 Prontogest.tw. (5)
 30 exp chorionic gonadotropin/ or exp chorionic gonadotropin, beta subunit, human/ (569)
 31 HCG.tw. (934)
 32 crinone.tw. (33)
 33 chorionic gonadotropin\$.tw. (375)
 34 chorionic gonadotrophin\$.tw. (231)
 35 or/24-34 (4352)
 36 23 and 35 (517)
 37 limit 36 to yr="2004 -Current" (176)

Appendix 2. MEDLINE search strategy

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

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (27911)
 2 embryo transfer\$.tw. (6799)
 3 in vitro fertilization.tw. (14234)
 4 ivf-et.tw. (1585)
 5 (ivf or et).tw. (143650)
 6 icsi.tw. (4216)
 7 intracytoplasmic sperm injection\$.tw. (3918)
 8 (blastocyst adj2 transfer\$).tw. (383)
 9 exp Insemination, Artificial/ (9085)
 10 Insemination\$.tw. (10982)
 11 iui.tw. (955)
 12 or/1-11 (176082)
 13 exp Luteal Phase/ (4163)
 14 (luteal adj5 support\$).tw. (451)
 15 (luteal adj5 phase).tw. (7790)
 16 (ischemic adj5 phase).tw. (735)
 17 post ovulat\$.tw. (584)
 18 (post adj5 transfer\$).tw. (811)
 19 (after adj5 transfer\$).tw. (14407)
 20 (post adj5 trigger\$).tw. (259)
 21 (after adj5 trigger\$).tw. (1864)
 22 or/13-21 (27661)
 23 12 and 22 (3711)
 24 exp Progesterone/ (59378)
 25 Progesterone\$.tw. (59979)
 26 dydrogesterone.tw. (323)
 27 utrogest.tw. (4)
 28 17 alpha-hydroxyprogesterone.tw. (1141)
 29 Prontogest.tw. (5)
 30 exp chorionic gonadotropin/ or exp chorionic gonadotropin, beta subunit, human/ (27265)
 31 HCG.tw. (19044)

32 crinone.tw. (43)
 33 chorionic gonadotropin\$.tw. (12102)
 34 chorionic gonadotropin\$.tw. (3926)
 35 or/24-34 (115420)
 36 23 and 35 (1351)
 37 randomized controlled trial.pt. (299607)
 38 controlled clinical trial.pt. (81716)
 39 randomized.ab. (215850)
 40 placebo.tw. (129148)
 41 clinical trials as topic.sh. (152093)
 42 randomly.ab. (159397)
 43 trial.ti. (92430)
 44 (crossover or cross-over or cross over).tw. (49454)
 45 or/37-44 (732909)
 46 exp animals/ not humans.sh. (3532377)
 47 45 not 46 (677343)
 48 36 and 47 (273)
 49 (2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$).ed. (5591829)
 50 48 and 49 (113)

Appendix 3. EMBASE search strategy

EMBASE <1980 to 2011 Week 06>

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (40509)
 2 embryo\$ transfer\$.tw. (8875)
 3 in vitro fertili?ation.tw. (16194)
 4 ivf-et.tw. (1916)
 5 icsi.tw. (6134)
 6 intracytoplasmic sperm injection\$.tw. (4671)
 7 (blastocyst adj2 transfer\$).tw. (542)
 8 (ivf or et).tw. (267654)
 9 exp artificial insemination/ (10631)
 10 Insemination\$.tw. (11124)
 11 iui.tw. (1292)
 12 or/1-11 (306873)
 13 exp luteal phase/ (5832)
 14 (luteal adj5 support\$).tw. (583)
 15 (luteal adj5 phase).tw. (7986)
 16 (ischemic adj5 phase).tw. (880)
 17 post ovulat\$.tw. (521)
 18 (post adj5 transfer\$).tw. (941)
 19 (after adj5 transfer\$).tw. (15304)
 20 (post adj5 trigger\$).tw. (316)
 21 (after adj5 trigger\$).tw. (2141)
 22 or/13-21 (29757)
 23 12 and 22 (4718)
 24 exp PROGESTERONE/ (61175)
 25 Progesterone\$.tw. (60300)
 26 dydrogesterone.tw. (391)
 27 utrogest.tw. (31)
 28 17 alpha-hydroxyprogesterone.tw. (452)
 29 Prontogest.tw. (59)
 30 exp chorionic gonadotropin/ (32624)

31 HCG.tw. (20115)
 32 crinone.tw. (234)
 33 chorionic gonadotropin\$.tw. (11827)
 34 chorionic gonadotropin\$.tw. (3894)
 35 or/24-34 (120217)
 36 23 and 35 (2001)
 37 Clinical Trial/ (826633)
 38 Randomized Controlled Trial/ (289177)
 39 exp randomization/ (53408)
 40 Single Blind Procedure/ (13857)
 41 Double Blind Procedure/ (101415)
 42 Crossover Procedure/ (30112)
 43 Placebo/ (174852)
 44 Randomized controlled trial\$.tw. (59579)
 45 Rct.tw. (6444)
 46 random allocation.tw. (1018)
 47 randomly allocated.tw. (15167)
 48 allocated randomly.tw. (1692)
 49 (allocated adj2 random).tw. (683)
 50 Single blind\$.tw. (10736)
 51 Double blind\$.tw. (116027)
 52 ((treble or triple) adj blind\$.tw. (232)
 53 placebo\$.tw. (155118)
 54 prospective study/ (163294)
 55 or/37-54 (1118108)
 56 case study/ (11164)
 57 case report.tw. (196960)
 58 abstract report/ or letter/ (769582)
 59 or/56-58 (973999)
 60 55 not 59 (1085709)
 61 36 and 60 (513)
 62 (2010\$ or 2011\$).em. (1278972)
 63 61 and 62 (93)

Appendix 4. PsycINFO search strategy

PsycINFO <1806 to February Week 2 2011>

1 exp Reproductive Technology/ (1044)
 2 embryo transfer\$.tw. (74)
 3 in vitro fertilization.tw. (409)
 4 ivf-et.tw. (14)
 5 (ivf or et).tw. (74694)
 6 icsi.tw. (35)
 7 intracytoplasmic sperm injection\$.tw. (26)
 8 (blastocyst adj2 transfer\$).tw. (2)
 9 Insemination\$.tw. (526)
 10 iui.tw. (15)
 11 or/1-10 (75914)
 12 (luteal adj5 support\$).tw. (1)
 13 (luteal adj5 phase).tw. (703)
 14 (ischemic adj5 phase).tw. (24)
 15 post ovulat\$.tw. (10)

16 (post adj5 transfer\$.tw. (104)
 17 (after adj5 transfer\$.tw. (856)
 18 (post adj5 trigger\$.tw. (22)
 19 (after adj5 trigger\$.tw. (136)
 20 or/12-19 (1846)
 21 11 and 20 (62)
 22 exp Progesterone/ (1589)
 23 Progesterone\$.tw. (2864)
 24 dydrogesterone.tw. (8)
 25 utrogest.tw. (0)
 26 17 alpha-hydroxyprogesterone.tw. (4)
 27 Prontogest.tw. (0)
 28 exp Gonadotropic Hormones/ (3296)
 29 HCG.tw. (57)
 30 crinone.tw. (0)
 31 chorionic gonadotropin\$.tw. (65)
 32 chorionic gonadotrophin\$.tw. (8)
 33 or/22-32 (6137)
 34 21 and 33 (2)

Appendix 5. MDSG search strategy

MV263 MDSG Search string

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 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"

Searched on 17 February 2011, 85 Results.

Appendix 6. CINAHL search strategy

From 1982 to Present

#	Query
S12	S10 and S11
S11	S1 or S2
S10	S3 or S4 or S5 or S6 or S7 or S8 or S9
S9	“vaginal micronised progesterone”
S8	(MH “Gonadotropins, Chorionic”) OR “hCG”
S7	“dydrogestrone”
S6	(MH “Gonadotropins, Chorionic”) OR “human chorionic gonadotrophin”
S5	“progesterone micronized”
S4	“progesterone gel”
S3	(MH “Progesterone”) OR “progesterone”
S2	“luteal support”
S1	(MM “Luteal Phase”) OR “luteal phase”

Appendix 7. The Cochrane Library - DARE search strategy

ID	Search
#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

(Continued)

#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. Web of Knowledge search strategy

Set	Results	
#9	97	#7 <i>Databases=SCI-EXPANDED, CPCI-S Timespan=2004-2011</i>
#8	233	#7 <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#7	233	#5 AND #6 <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>
#6	28,648	TS=(embryo transfer) OR TS=(ivf) OR TS=(in vitro fertilisation) OR TS=(in vitro infertilization) OR TS=(iui) OR TS=(icsi) <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>
#5	631	#1 AND #4 <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>
#4	3,540	#3 AND #2 <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>
#3	24,758	TS=(hcg) OR TS=(chorionic gonadotropin) OR TS=(chorionic gonadotrophin) OR TS=(human chorionic gonadotropin) OR TS=(human chorionic gonadotrophin) <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>
#2	64,007	TS=(progesterone) OR TS=(progesteron) OR TS=(dydrogesterone) OR TS=(utrogest) OR TS=(prontogest) OR TS=(17 alpha-hydroxyprogesterone) <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>
#1	7,275	TS=(Luteal phase) OR TS=(luteal support) OR TS=(Luteal phase support) <i>Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years</i>

Appendix 9. 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?				
	When used: GIFT or ZIFT < 20%?				
Interventions	No frozen ET?				
	No other substances than progesterone / hCG / estrogen?				
	No ET from donated oocytes?				
	No ET from frozen oocytes/frozen ovarian tissue?				
	No in vivo maturation (IVM)?				

(Continued)

	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 10. Data extraction form

General information

Study ID	
ID Review author	
Date form completed	
Complete reference	
Published?	☐ Yes ☐ No
Publication type	Journal / Abstract / other (specify)

(Continued)

Report author contact details	
-------------------------------	--

Notes:

Study eligibility

Confirm eligibility	☐ Included
	☐ Excluded <i>Reason for exclusion:</i>
	☐ Unclear <i>Reason:</i> <i>Action undertaken:</i>

Study details

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

Methods

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

Participants

Participants	Description	Reference
Total # randomised		
Total # analysed		
Reason why not analysed		
#Cycles per woman		

(Continued)

# allocated to each intervention group		
# and reasons for exclusions for each intervention groups		
Age (median, mean, range if available)		
# IVF		
# ICSI		
# previous cycles		
# transferred embryo's		

Intervention group

Group name:		
Intervention	Description	Reference
Type		
Dosage		
# doses		
Route		
Duration		
Duration of follow-up		
Protocol for ovulation induction		
Scheme for trigger		
GnRH	<ul style="list-style-type: none"> o Agonist o Antagonist 	
GnRH scheme	<ul style="list-style-type: none"> o Duration o Dose o Route of administration 	

Comparison group

Group name:		
Comparison	Description	Reference
Type		
Dosage		
# doses		
Route		
Duration		
Duration of follow-up		
Protocol for ovulation induction		
Scheme for trigger		
GnRH	<ul style="list-style-type: none"> o Agonist o Antagonist 	
GnRH scheme	<ul style="list-style-type: none"> o Duration o Dose o Route of administration 	

Outcome

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

Results

Copy table for each comparison.

Comparison				
ITT?				
Results	Intervention:		Comparison:	
	Events	# participants	Events	# participants
ET				
CPR				
OPR				
LBR				
OHSS				
MR				
MultiP				
# 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		

(Continued)

Correspondence required (specify)	<ul style="list-style-type: none"> o No o Yes o E-mail sent on o Letter sent on o Fax sent on <p>Reaction received: Yes / No</p> <p>USE NEW FORM WITH COMPLETE INFO</p>	
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Appendix 11. Risk of Bias

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

WHAT'S NEW

Last assessed as up-to-date: 25 May 2011.

Date	Event	Description
2 April 2014	Amended	Correction to analyses: all now set to record "event" rather than "non-event". No change to conclusions

HISTORY

Protocol first published: Issue 6, 2011

Review first published: Issue 10, 2011

Date	Event	Description
4 June 2012	Amended	Correction to Summary of main results: Progesterone and estrogen 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. There is a new authoring team

CONTRIBUTIONS OF AUTHORS

MvdL, MM and KB extracted data. MvdL entered data and wrote the review. CF acted as a third reviewer in case of disagreements, helped drafting the review, acted as a clinical expert and commented on the review. JK acted as a clinical expert and commented on the review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- MDSG, Not specified.

External sources

- Stichting Nijmeegs Universiteitsfonds, Netherlands.

Scholarship to support students from the Radboud University Nijmegen to study, do an internship or 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

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 in subfertile women undergoing assisted reproductive technology”. We made this change because we not only investigated the use of luteal phase support but also the different ways of luteal phase support.

In the protocol we stated 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 are able to include new agents.

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 estrogen;
5. progesterone versus progesterone and GnRH agonist;
6. comparison of the different methods of administration of progesterone: IM versus vaginal versus rectal versus oral;
7. micronized versus synthetic progesterone;
8. hCG versus placebo or no treatment;
9. urinary versus recombinant hCG;
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
 - i) progesterone versus hCG,
 - ii) progesterone versus progesterone and hCG;

4. progesterone versus progesterone and estrogen;
5. progesterone versus progesterone and GnRH agonist;
6. progesterone regimens
 - i) IM progesterone versus oral progesterone,
 - ii) IM progesterone versus vaginal or rectal progesterone,
 - iii) vaginal or rectal progesterone versus oral progesterone,
 - iv) low dose vaginal progesterone (≤ 100 mg) versus high dose vaginal progesterone (> 100 mg),
 - v) micronized progesterone versus synthetic progesterone.

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 which researched different types and dosages of vaginal progesterone administration. Therefore we added comparison nine: low dose vaginal progesterone versus high dose vaginal progesterone. We also found some studies comparing different durations of progesterone administration, which we included in comparison 10: short protocol progesterone versus long protocol progesterone.

We did not find any studies comparing urinary hCG and recombinant hCG or studies comparing only single-dose GnRH agonist versus placebo, but we did come across some studies using 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 the comparisons for urinary hCG versus recombinant hCG and GnRH agonist versus placebo will be made in the future, as hCG is an older method for luteal phase support and is known for its high risk of OHSS; we do not expect new trials will be conducted 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 investigating the effect of GnRH agonists for luteal phase support versus a placebo. For these reasons we chose to remove these comparisons.

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Reproductive Techniques, Assisted; Chorionic Gonadotropin [*therapeutic use]; Estrogens [*therapeutic use]; Gonadotropin-Releasing Hormone [*agonists]; Live Birth [epidemiology]; Luteal Phase [*drug effects; physiology]; Progesterone [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy