Vaginal progesterone gel for luteal phase support in IVF/ICSI cycles: a meta-analysis

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CRD summary
This review concluded that no significant difference existed, in clinical pregnancy rate, between vaginal gel and all other vaginal progesterone forms, for luteal-phase support, in women undergoing in-vitro fertilisation or intracytoplasmic sperm injection. These conclusions reflect the evidence presented, and are likely to be reliable.

Authors' objectives
To investigate whether vaginal progesterone gel has similar or higher pregnancy rates, compared with all other vaginal progesterone forms, when used for luteal-phase support.

Searching
MEDLINE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without language restrictions, to August 2009; search terms were reported. The reference lists of eligible studies were searched to identify further studies.

Study selection
Eligible studies were randomised controlled trials comparing vaginal progesterone gel, with vaginal progesterone in any other form, for luteal-phase support, in women undergoing in-vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). Trials of frozen then thawed embryos were excluded. The primary outcome was the clinical pregnancy rate.

Most included trials compared the gel once or twice daily, with daily capsules (Utrogestan or Utrogest); inserts (Endometrin) and pessaries (Cyclogest) were also studied. Most trials used a gonadotropin-releasing hormone agonist, with human menopausal gonadotropin or recombinant follicle stimulating hormone protocols. In most trials the day of initiation of luteal-phase support was the day of embryo transfer, or one day after oocyte retrieval. The median patient age ranged from 30.1 to 34.8 years. The number of embryos transferred ranged from two to four (where reported). The recruitment periods ranged from 1999 to 2000, to 2005 to 2006.

Two reviewers independently selected trials for inclusion, with disagreements resolved by a third reviewer.

Assessment of study quality
It seems that two reviewers independently assessed the methods of randomisation, allocation concealment and blinding, with disagreements resolved by a third reviewer.

Data extraction
Data on clinical pregnancy were extracted to calculate odds ratios, with 95% confidence intervals. In trials with more than one comparator, these outcome data were pooled.

Two reviewers independently extracted the data, with disagreements resolved by a third reviewer.

Methods of synthesis
Meta-analyses were performed to calculate pooled odds ratios, with 95% confidence intervals. A random-effects model was used where heterogeneity was present, otherwise a fixed-effect model was used. Heterogeneity was assessed using I² and X². Sensitivity analyses examined the impact of removing specific individual trials.

Results of the review
Seven randomised controlled trials (2,447 patients) were included. Samples ranged from 60 to 1,211 patients. Four trials had adequate methods of allocation concealment, three had adequate methods of randomisation, and one blinded the outcome assessors to allocation.

There was no significant difference between administration modes for clinical pregnancy (OR 1.05, 95% CI 0.88 to
1.25; seven trials; $\theta^2=0$). The results were similar for the four trials of gel (once or twice daily), compared with standard treatment (three 200mg capsules), and for the six trials using only gonadotropin-releasing hormone agonists (and not antagonist IVF protocols).

The sensitivity analyses yielded similar results to the main analyses. Three trials reported adverse events, and found no significant differences.

**Authors' conclusions**
No significant difference existed, in clinical pregnancy rate, between vaginal gel and all other vaginal progesterone forms, for luteal-phase support.

**CRD commentary**
The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts were made to identify relevant trials, in any language, by searching electronic databases and checking references. It was unclear whether unpublished trials were specifically sought. Suitable methods (independent duplicate processes) were used to reduce the risk of reviewer error and bias throughout the review.

Trial quality was assessed, but the results were not used in interpreting the findings of the review. The basic quality assessment results were presented, and it seems that most of the trials were unlikely to have been biased; drop-out rates were not reported. Appropriate methods were used to pool the data, and to assess and investigate variation.

The authors' conclusions reflect the evidence presented, and are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that women undergoing IVF or ICSI cycles could use vaginal progesterone gel, for luteal-phase support, and anticipate the same success rate as with conventional treatment, with the potential of an easier and more convenient treatment mode.

**Research:** The authors did not state any implications for research.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
20171629

**DOI**
10.1016/j.fertnstert.2009.12.058

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Administration, Intravaginal; Adult; Algorithms; Female; Fertilization in Vitro /methods; Humans; Luteal Phase /drug effects /physiology; Pregnancy; Pregnancy Rate; Progesterone /administration & dosage; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic /methods; Vaginal Creams, Foams, and Jellies

**AccessionNumber**
12010007702

**Date bibliographic record published**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.