
Luteal phase support in infertility treatment: a meta-analysis of the randomized trials

Pritts E A, Atwood A K

Authors' objectives

To determine whether luteal phase support increases reproductive success in modern in vitro fertilisation (IVF) cycles.

Searching

MEDLINE and the Cochrane Library were searched and the bibliographies of identified studies were cross-referenced. The proceedings for the American Society of Reproductive Medicine, European Society of Human Reproduction and Embryology, Society for Gynecologic Investigation and Pacific Coast Reproductive Society were handsearched from 1995 to 2001. Publications in any language were considered.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion in the review. Only studies that clearly stratified patient data according to the length of GnRH agonist treatment were included. However, it was only possible to confirm that 8 of the included studies were randomised; the other included studies were either semi-random or the method of treatment allocation was unknown. In several studies, randomisation was done at the start of the treatment and many patients were subsequently excluded post-randomisation on account of hyperstimulation, poor ovarian response or lack of embryos.

Specific interventions included in the review

Comparisons of luteal phase hormonal support with either placebo or no treatment were eligible if progesterone or human chorionic gonadotrophin (hCG) luteal supplementation was begun within 2 days of embryo transfer. Only studies that used gonadotrophin-releasing hormone (GnRH) agonists in the stimulation were eligible. Most of the included studies used the long protocol of GnRH agonist treatment, but a few also used the short or flare protocol. The included studies compared the following drugs, either with each other or with a placebo or no treatment control: 7-alpha hydroxyprogesterone caproate, progesterone (intramuscular, oral and vaginal), progesterone/estradiol (intramuscular and oral), micronised progesterone, hCG and crinone. The duration of treatment varied up to 12 weeks.

Participants included in the review

Studies of women undergoing IVF were eligible. Studies of IVF-embryo transfer cycles, zygote intra-fallopian transfer, gamete intra-fallopian transfer and intra-cytoplasmic sperm injection were included if the proportions of each assisted reproduction type were similar in each group.

Outcomes assessed in the review

The outcomes assessed in the review were:

the clinical pregnancy rate (PR), where a clinical pregnancy was accepted as foetal heart activity documented by ultrasound;

the ongoing PR, where ongoing pregnancies were defined as those achieving 24 or more weeks of gestation;

the delivery rate (DR), where deliveries were accepted as single events regardless of the number of children delivered; and

the miscarriage rate (SAB), where miscarriages were defined as those pregnancies that spontaneously failed in the first trimester.

The weeks of gestation were reported as menstrual weeks of gestation.

How were decisions on the relevance of primary studies made?

Both authors selected the studies for inclusion and any disagreements were resolved through discussion and consensus.

Assessment of study quality

Validity was assessed using the method of randomisation. Both authors assessed validity and any disagreements were resolved through discussion and consensus.

Data extraction

Both authors extracted the data and any disagreements were resolved through discussion and consensus. Data were extracted on the interventions compared, the outcome measures and the number of patients. Participants included in multiple publications were counted only once in the analysis.

Methods of synthesis

How were the studies combined?

The studies were combined in a meta-analysis using the Mantel-Haenszel method. Studies that used the short protocol for GnRH agonist treatment were excluded from the meta-analysis. The relative risk (RR) and 95% confidence intervals (CIs) were calculated. The statistics for clinical PR, ongoing PR and DR were formatted to show the benefits associated with these outcomes; the statistics for SAB were formatted to show the reduction in these events.

How were differences between studies investigated?

Statistical heterogeneity was tested using the chi-squared test.

Results of the review

Thirty RCTs were included. There were 3,978 women in 27 RCTs, plus an unknown number of women undergoing 466 cycles in 3 RCTs.

Most of the studies evaluated only one treatment cycle per patient.

On the basis of 4 studies, the clinical PR was significantly better with intramuscular (i.m.) HCG compared with no treatment (RR 2.72, 95% CI: 1.56, 4.90). There was no significant difference in the ongoing PR or SAB.

On the basis of 2 studies, i.m. progesterone showed a significantly better clinical PR (RR 2.38, 95% CI: 1.36, 4.27) and ongoing PR (RR 3.8, 95% CI: 1.42, 11.38) than no treatment or placebo. One study showed a significant improvement in DR compared with no treatment (RR 5.50, 95% CI: 1.25, 35.53).

There was no difference in clinical PR between i.m. progesterone and i.m. hCG (5 studies). The DR, ongoing PR and SAB also showed no difference, but each was reported in only one study. Four studies showed no difference between i.m. progesterone and vaginal progesterone.

Progesterone i.m. significantly improved the clinical PR and DR compared with vaginal preparations (5 studies).

There was no difference in the clinical PR, DR or SAB when oral oestrogen was added to progesterone (1 study).

Meta-analysis graphs were not shown, and the results of tests for heterogeneity were not reported.

Authors' conclusions

The evidence suggests that luteal supplementation is beneficial. Intramuscular progesterone is no more effective than hCG, but is more effective than vaginal progesterone. There is also some evidence that the addition of oestrogen to progesterone may increase implantation rates, hence clinicians should consider adding oestrogen for luteal supplementation.

CRD commentary

The aims of the review were stated and the inclusion criteria were defined in terms of the study design, participants and interventions. Several relevant sources were searched, no language restrictions were applied, and the methods used to select the studies were described. Only RCTs were eligible, but other inadequately randomised studies and studies of unknown design were also included. Hence, the quality of the evidence was unclear. The study selection, quality assessment and data extraction processes were conducted in duplicate, which should minimise bias and errors. Some aspects of validity were discussed in the text, but validity was not taken into account in the conclusions. Many outcome comparisons were reported in the review; this increased the probability of finding statistically-significant differences by chance alone. The results for most comparisons were based on only a few studies. Only some outcomes found any significant difference between the treatments, and it was unclear which of the many outcomes reported were the most important clinically. In view of the above, the authors' conclusions should be interpreted with caution, as they are stronger than the evidence presented.

Implications of the review for practice and research

Practice: The authors state that there is a need for luteal supplementation and that both hCG and i.m. progesterone improve fertility outcomes in women undergoing modern IVF cycles. Also, given the increased risk of ovarian hyperstimulation syndrome associated with hCG use, i.m. progesterone is favoured for luteal phase supplementation with the addition of oestrogen.

Research: The authors state that further trials are required to determine the optimal length of treatment.

Bibliographic details

Pritts E A, Atwood A K. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. *Human Reproduction* 2002; 17(9): 2287-2299

PubMedID

12202415

Original Paper URL

<http://humrep.oxfordjournals.org/cgi/reprint/17/9/2287>

Indexing Status

Subject indexing assigned by NLM

MeSH

Administration, Intravaginal; Chorionic Gonadotropin /administration & dosage /therapeutic use; Dose-Response Relationship, Drug; Drug Therapy, Combination; Female; Fertilization in Vitro; Hormones /administration & dosage /therapeutic use; Humans; Infertility /therapy; Injections, Intramuscular; Luteal Phase; Progesterone /administration & dosage /therapeutic use; Randomized Controlled Trials as Topic

AccessionNumber

12002002085

Date bibliographic record published

30/06/2003

Date abstract record published

30/06/2003

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.

