Estrogen addition to progesterone for luteal phase support in cycles stimulated with GnRH analogues and gonadotrophins for IVF: a systematic review and meta-analysis

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CRD summary
This review investigated whether the probability of pregnancy was increased by adding oestrogen to progesterone for luteal phase support in patients treated by in vitro fertilisation (IVF). The authors concluded that adding oestrogen to progesterone did not increase pregnancy in IVF. This review appeared to be generally well-conducted, however, the paucity of data made the reliability of the conclusions unclear.

Authors' objectives
To investigate whether the probability of pregnancy is increased by adding oestrogen to progesterone for luteal phase support in patients treated by in vitro fertilisation (IVF).

Searching
Searches were performed in MEDLINE and EMBASE (to July 2007), Cochrane Central register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3, 2007) and the Cochrane Menstrual Disorders and Subfertility Group trial registry (25th June 2007). Search terms were reported. References of all relevant publications and review articles and meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were searched. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) of women who underwent IVF after ovarian stimulation with gonadotrophins and gonadotrophin releasing hormone (GnRH) analogues, that had a pregnancy outcome were eligible for inclusion. Included studies had to compare patients who received progesterone only with those who received progesterone plus oestrogen (for luteal support). Studies that used pseudo-randomisation methods (including studies in which patients had contributed more than one cycle) were excluded.

Included studies were published between 2006 and 2007. Patient ages ranged from less than 39 to 44 years old where reported. Recombinant gonadotrophins were used in all studies. Urinary human chorionic gonadotrophin (hCG) was used to trigger final oocyte maturation in most of the included studies. Type, dose and route of administration, timing of initiation and duration of luteal support with oestrogen and progesterone varied. Fertilisation methods included were intra-cytoplasmicsperm injection (ICSI) with or without IVF. Primary outcomes were achievement of pregnancy expressed as positive hCG, clinical pregnancy and live birth rate. Secondary outcomes included biochemical miscarriage per patient with positive hCG, clinical miscarriage per patient with a clinical pregnancy and total miscarriage per patient with positive hCG.

Two reviewers independently selected studies. Disagreements were resolved by discussion.

Assessment of study quality
Methodological quality was assessed in terms of timing and method of randomisation, number of centres and allocation concealment. It appeared that two reviewers performed validity assessment.

Data extraction
Data for the outcomes positive hCG rate, clinical pregnancy rate, live birth rate and biochemical, clinical and total miscarriage rates were extracted. Authors were contacted for missing information if necessary. Dichotomous outcomes were expressed as relative risk (RR) and corresponding 95% confidence intervals (CIs). Rate differences were calculated for continuous outcomes.

Data were extracted independently by two reviewers and disagreements were resolved by discussion.
Methods of synthesis
Relative risk and 95% CIs were pooled using either a fixed-effects Mantel-Haenszel model or random-effects DerSimonian and Laird model. Rate differences were pooled using the inverse variance method and DerSimonian and Laird model to produce weighted mean differences (WMDs) and corresponding 95% CIs. A fixed-effects model was used if there was no statistically significant heterogeneity and a random-effects model was used in the presence of significant heterogeneity (assessed with the I^2 test). Publication bias was assessed by Egger's test. A priori sensitivity analyses were conducted to assess the effects of pseudo-randomisation or unclear methods of randomisation. Additional subgroup analyses were planned for: GnRH analogue used for LH surge inhibition; type and dose of oestrogen; timing of initiation of oestrogen administration; type of patients; and type and dose of the signal used to trigger final oocyte maturation, but there were insufficient data to conduct meaningful subgroup analysis.

Results of the review
Four RCTs were included (n = 587). Study size ranged from 60 to 201 patients. Two of the studies reported allocation concealment.

There were no statistically significant differences between patients who received oestrogen in addition to progesterone for the outcomes positive hCG, clinical pregnancy, live birth, biochemical miscarriage, clinical miscarriage and total miscarriage. Results were similar for studies that were excluded due to pseudo or unknown methods of randomisation. No statistically significant heterogeneity or publication bias was detected.

Authors' conclusions
The addition of oestrogen to progesterone for luteal phase support did not increase the probability of pregnancy in IVF.

CRD commentary
The research question was defined in terms of participants, intervention, outcomes and study design. The search included all languages and unpublished sources, which reduced the possibility of publication and language biases. Two reviewers were involved in study selection, validity assessment and data extraction, which reduced the risk of reviewer error and bias. Validity was assessed and taken into consideration in the analysis. Statistical heterogeneity was assessed, but it was unclear whether clinical differences between studies should have precluded data pooling. The use of meta-analysis appeared appropriate, although the use of a heterogeneity assessment to determine the employment of a fixed-effect or random-effects model may not have been advisable. The authors reported that the sample size was less than that required to detect clinically important difference between treatment groups. This review appeared to be generally well-conducted, however, the paucity of data made the reliability of the authors' conclusions unclear.

Implications of the review for practice and research
Practice: The authors stated that based on the best available evidence, routine use of oestrogen addition during progesterone supported luteal phase in IVF cycles stimulated with GnRH analogues and gonadotrophins was not justified.

Research: The authors stated that further RCTs were required to examine the effect of oestrogen added to progesterone for luteal support on the probability of pregnancy.

Funding
Not stated.

Bibliographic details

PubMedID
18408017
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.