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## The use of estradiol for luteal phase support in in vitro fertilization/intracytoplasmic sperm injection cycles: a systematic review and meta-analysis

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### CRD summary

This review concluded, from limited evidence, that the addition of oestradiol to progesterone for luteal phase support in women undergoing in vitro fertilisation or intracytoplasmic sperm injection cycles had no beneficial effect on the rate of pregnancy or implantation. Overall, despite concerns about the data and review methods, the authors' cautious conclusions reflect the evidence presented.

### Authors' objectives

To assess the effect of luteal phase oestradiol supplementation for luteal phase support on the pregnancy rate of in vitro fertilisation/intracytoplasmic sperm injection cycles.

### Searching

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and the UK National Research Register were searched without language restrictions up to March 2007. Search terms were reported. Reference lists of retrieved articles and reviews were checked for further studies. Searches using the names of lead authors from included studies were made on MEDLINE in order to identify further studies. Several leading journals in the field were handsearched over a period of several years (details not reported). Meeting abstracts were included if they reported sufficient relevant outcome data.

### Study selection

Randomised controlled trials (RCTs) comparing the pregnancy rates and implantation rates of luteal phase hormonal supplementation with progesterone alone versus progesterone plus oestradiol, in women undergoing in vitro fertilisation or intracytoplasmic sperm injection, were eligible for inclusion in the review. Women undergoing stimulated intrauterine insemination or induction of ovulation with clomiphene citrate or gonadotropins were excluded. Trials of other support regimens including human chorionic gonadotropin alone, or human chorionic gonadotropin plus progesterone were also excluded. Where trials included three study arms, at least two had to be of relevant comparators; any non-relevant comparators were excluded.

The included trials assessed total daily progesterone dosages ranging from 50 mg to 600 mg, and daily oestradiol dosages mostly ranging from 2 mg to 6 mg. The majority of trials administered progesterone vaginally and oestradiol orally. Most included women were undergoing in vitro fertilisation either alone or in combination with intracytoplasmic sperm injection or embryo transfer. Where stated, women's ages ranged from less than 40 years to less than 44 years. In addition to the main outcomes, reported outcomes included clinical pregnancy rate, ongoing pregnancy rate, and the number of cancelled cycles, miscarriages, ectopic pregnancies, early pregnancy losses and multiple pregnancies.

Two reviewers selected studies for inclusion in the review. Discrepancies were resolved through consensus with a third reviewer.

### Assessment of study quality

Two reviewers assessed study validity according to the following criteria: randomisation method, concealment of allocation, blinding, co-intervention, sample size calculation, study withdrawals, and differentiation between participants and treatment cycles. Trials that showed gross 'deficiencies in design' were excluded from the review.

### Data extraction

Two reviewers extracted the study data. For each trial the number of pregnancies and the number of implantations were extracted and used to calculate relative risks with 95% confidence intervals.

### Methods of synthesis

Trials were combined by outcome and pooled relative risks with 95% confidence intervals calculated using a random-effects analysis. Statistical homogeneity was assessed using the Cochrane's Q-test;  $\chi^2$  and  $I^2$  statistics were reported. Further analyses were carried out grouping trials according to the use of only gonadotrophin releasing hormone analogue and different doses of oestradiol.

### Results of the review

Ten RCTs, including a total of 2,280 embryo transfer cycles (range 63 to 666 cycles), were included in the review.

There were no statistically significant differences between progesterone alone and oestradiol plus progesterone for pregnancy rate (eight RCTs), clinical pregnancy rate (five RCTs), and ongoing pregnancy rate (three RCTs) and implantation rate (four RCTs) per embryo transfer. All analyses showed significant levels of statistical heterogeneity, with  $I^2$  values ranging from 54.9% to 81%.

Subgroup analyses, according to the use of gonadotrophin releasing hormone analogue and different doses of oestradiol (2mg, 4mg and 6mg per day), showed improved pregnancy rates, clinical pregnancy rates, and/or implantation rates per embryo transfer, in favour of the use of combined progesterone and oestradiol in comparison with progesterone alone (further details reported in the review). However, most analyses were not statistically significant and a number showed significant statistical heterogeneity.

### Authors' conclusions

The limited evidence included in this review suggested that the addition of oestradiol to progesterone for luteal phase support in women undergoing in vitro fertilisation or intracytoplasmic sperm injection cycles had no beneficial effect on the rate of pregnancy or implantation.

### CRD commentary

This review assessed a clear review question supported by inclusion criteria for study design, population, intervention and outcomes. Searches were made for both published and unpublished data, but no unpublished studies were identified. No language limitations were used, so the risk of language bias was low. Attempts were made to reduce the risk of reviewer error and bias when selecting trials for inclusion, assessing trial quality and extracting the trial data. Trial validity was assessed, but its findings were not reported. This made it difficult to assess the reliability of the findings. The trials varied considerably in terms of interventions, populations and outcomes, with pooled effects sizes also showing evidence of significant statistical heterogeneity. The reliability of the meta-analyses is therefore questionable, although some attempts were made to investigate possible sources of heterogeneity. The authors acknowledged these limitations and suggested a cautious interpretation of their findings. Overall, despite concerns about the data and review methods, the authors' cautious conclusions reflect the evidence presented.

### Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that in order to clarify the role of luteal oestradiol supplementation for in vitro fertilisation/intracytoplasmic sperm injection, there is a need for a large, well-designed, multicentre randomised controlled trial to investigate the optimal dose and route of administration.

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