Recombinant LH supplementation to recombinant FSH during induced ovarian stimulation in the GnRH-antagonist protocol: a meta-analysis


CRD summary
This review found no statistically significant differences in implantation and pregnancy rates when supplementing recombinant follicle stimulating hormone with recombinant luteinising hormone for women undergoing ovarian stimulation for in vitro fertilisation. Overall, the potential for publication bias, the paucity of data, and the limited reporting of study methods suggest the conclusions should be interpreted with caution.

Authors' objectives
To compare the efficacy of supplementing recombinant follicle stimulating hormone (r-FSH) with recombinant luteinising hormone (r-LH) during ovarian stimulation in the gonadotrophin-releasing hormone antagonist protocol for in vitro fertilisation (IVF)/intracytoplasmic sperm injection cycles.

Searching
MEDLINE, EMBASE, Science Citation Index, the Cochrane Controlled Trials Register and Ovid were searched from 1990 to 2006 using the reported search terms. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing r-FSH ovarian stimulation with or without r-LH supplementation for IVF were eligible for inclusion. The included studies used low-dose (0.25 mg cetrorelix) or fixed-dose (3 mg cetrorelix) regimens. The majority of included studies administered a dose of 225 IU r-FSH (Gonal F) for at least 5 days; some studies varied this dose (75 to 450 IU) dependent on patient characteristics. The dose of r-LH (Luveris) was predominantly 75 IU; one study used a dose of 150 IU. Details of the individual intervention protocols were provided.

Participants included in the review
Studies of normogonadotrophic or ‘good prognosis’ women requiring assisted reproduction were eligible for inclusion. Individual inclusion criteria varied between the studies and were reported in detail, but most of the included women were aged between 18 and 39 years. Some studies only included women within a certain range of body mass index, usually with a maximum body mass index of between 30 and 35.

Outcomes assessed in the review
The primary outcomes were: the number of days of stimulation; the total amount of r-FSH administered; serum oestradiol concentrations on the day of human chorionic gonadotrophin administration; and the number of retrieved and mature (MII) oocytes. The secondary outcome measures included clinical pregnancy rate per oocyte retrieval, implantation rate and miscarriage rate.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the methodological rigour of each study and the potential for bias. The authors did not state the specific criteria used, but reported how studies were randomised, if allocation was concealed, whether studies were blinded, and other details of the study methods.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Study authors were contacted for missing data. Odds ratios with 95% confidence intervals (CIs) were reported for dichotomous outcomes and means with standard deviations for continuous outcomes.

**Methods of synthesis**

How were the studies combined?
The studies were combined and pooled odds ratios or weighted mean differences (WMDs) calculated, along with 95% CIs, using a fixed-effect model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using Cochran’s Q and the Breslow-Day test. Some clinical differences between the studies were also described narratively.

**Results of the review**

Five RCTs (n=432), of which one appeared to be a quasi-RCT, were included in the review.

Three studies used a computer-generated randomisation procedure, one used sealed envelopes, and a third appeared to use quasi-random methods (birth year) in at least one of its three study centres. Three of the studies reported that they were open or unblinded studies.

Five RCTs showed that significantly higher serum oestradiol concentrations (WMD 514, 95% CI: 368, 660) and a greater number of retrievable mature oocytes (WMD 0.88, 95% CI: 0.21, 1.54) were present in women using r-LH compared with those not using it. No statistically significant differences between r-LH and r-FSH protocols were found for number of days of stimulation (5 RCTs), total r-FSH administered (4 RCTs), number of oocytes retrieved (4 RCTs), clinical pregnancy rate per oocyte retrieved (4 studies), implantation rate (3 RCTs) and miscarriage rate (2 RCTs). No evidence of significant statistical heterogeneity was detected in any of the groups of pooled studies.

**Authors’ conclusions**
The evidence failed to show any statistically significant differences in implantation and pregnancy rates between r-LH supplementation in IVF and r-FSH for ovarian stimulation.

**CRD commentary**
This review answered a clear research question, but may be at risk from publication bias as it did not appear to make any specific attempts to identify unpublished material. It is also difficult to assess the risk of reviewer error and bias since the review methods were poorly described. Two reviewers independently assessed study methodology and the risk of bias, but the authors did not state what criteria were used, nor did they discuss their review findings with respect to the quality of the studies. Statistical heterogeneity was considered although, as the authors acknowledged, the power of these tests is low given the small number of studies included in the review. Some clinical differences were evident from the review text, but a summary table of study characteristics would have been helpful to the reader. Overall, given the potential for publication bias, the paucity of data and the limited reporting of the study methods, it is difficult to assess the reliability of the authors’ conclusions and a cautious interpretation is advised. The authors’ statement about the probable lack of harmful effects also does not seem appropriate given the scope of the analysis presented.

**Implications of the review for practice and research**
Practice: The authors stated ‘there is probably no reason to be concerned that the use of r-LH supplementation imposes a harmful effect’.

Research: The authors stated that further well-planned RCTs controls to test the effects of r-LH supplementation are required.

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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.