Highly purified hMG achieves better pregnancy rates in IVF cycles but not ICSI cycles compared with recombinant FSH: a meta-analysis

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CRD summary
This review compared highly purified human menopausal gonadotrophin (HP-hMG) with recombinant follicle stimulatcing hormone (rFSH) for pregnancy in assisted fertilisation. The authors concluded that HP-hMG was superior to rFSH for women using in vitro fertilisation. There were several weaknesses in the review methods and the authors’ conclusions appear to be optimistic; caution is needed when interpreting them.

Authors’ objectives
To determine if highly purified human menopausal gonadotrophin (HP-hMG) was superior to recombinant follicle stimulating hormone (rFSH) in achieving pregnancy with assisted fertilisation.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL, 2007, Issue 2), NRR, and Current Controlled Trials were searched for articles included to September 2007 in any language. Search terms were reported, reference lists of relevant articles were searched, and manufacturers and experts in the field were contacted for ongoing and unpublished studies.

Study selection
Randomised controlled trials (RCTs) comparing HP-hMG with rFSH in women undergoing assisted fertilisation, with either in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) were eligible for inclusion. RCTs were excluded if they combined rFSH with HP-hMG, or if the human menopausal gonadotrophin was not highly purified. The RCTs had to provide sufficient data on clinical pregnancy rate and ongoing pregnancy or live birth rate as well as miscarriage rate and ovarian hyperstimulation syndrome.

The included RCTs all compared HP-hMG (mainly Menopur, either long protocol or fixed-antagonist protocol) with rFSH (mainly Gonal-F, given at doses of 150 to 300 international units) in women undergoing assisted fertilisation. The method of fertilisation included IVF alone, ICSI alone, or a case-by-case approach using either IVF or ICSI as appropriate. The reported mean age of participants was 26 to 31 years, and all trials excluded women with polycystic ovary syndrome.

The authors did not state how many of them performed the selection process.

Assessment of study quality
The included RCTs were assessed on: method of randomisation; blinding to treatment; allocation concealment; number of patients randomised; intention to treat; and duration, timing and location of trial.

The authors did not state how many of them performed the validity assessment.

Data extraction
Data were extracted on the key outcomes, such as the clinical pregnancy rate and ongoing pregnancy or live birth rate, and used to calculate odds ratios and 95% confidence intervals.

The authors did not state how many of them performed the data extraction.

Methods of synthesis
The pooled odds ratios and 95% confidence intervals were calculated using a fixed-effect meta-analysis. Heterogeneity
was assessed using the $I^2$ and $\chi^2$ statistics. Publication bias was assessed in a funnel plot analysis.

**Results of the review**

Six RCTs (n=2,371 patients) were included in the review. Three of them were multi-centre and three were single-centre trials. Publication bias was not apparent from the funnel plot inspection. Heterogeneity was not present in any of the analyses ($I^2$ 0).

HP-hMG bordered on being statistically better at improving the pregnancy rate than rFSH (OR 1.21, 95% CI 1.00 to 1.45; six RCTs). It was statistically better at improving the ongoing pregnancy or live birth rate in IVF patients only (OR 1.31, 95% CI 1.02 to 1.68; four RCTs). There was no statistical difference between HP-hMG and rFSH for ongoing pregnancy or live birth rate for all patients (six RCTs) and for ICSI patients only (three RCTs). There was also no statistical difference between HP-hMG and rFSH in miscarriage rate and ovarian hyperstimulation syndrome.

**Authors' conclusions**

HP-HMG was preferred over rFSH in women undergoing assisted reproduction, especially if IVF was the method of fertilisation.

**CRD commentary**

The inclusion criteria were clearly defined and several relevant sources were searched. There was some attempt to locate unpublished studies and publication bias was assessed and was not found. It was unclear how many reviewers selected trials and extracted the data, which may have introduced error and bias into the review. Some form of validity assessment was undertaken, but the results were not reported, which may mean that poor-quality trials were included. The RCTs were combined using meta-analysis and heterogeneity was appropriately explored. The results of the review marginally favoured HP-HMG, but this was not enough to warrant the authors' conclusion that HP-HMG should be used over rFSH.

There were several weaknesses in the review methods and the authors’ conclusions appear to be optimistic, which means that caution is warranted when interpreting them.

**Implications of the review for practice and research**

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

**Research:** The authors stated that future trials should determine whether there was a difference between fresh and cryopreserved embryos. Investigators should also consider whether delaying denudation for four hours after ovum pick-up might allow for better interaction between cumulus oocytes, with ICSI fertilisation.

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