Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction

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Authors' objectives
To assess the effect of recombinant versus urinary follicle stimulating hormone for ovarian stimulation on pregnancy rates in assisted reproduction.

Searching
The authors searched the electronic database MEDLINE (1990 to 1999) using the search terms: 'pregnancy', 'gonadotrophin', and 'fertilization in vitro', and publication type 'randomized controlled trial'. The authors also searched EMBASE (1985 to October 1998) using the keywords: 'recombinant FSH', 'IVF', and 'randomized' via the Excerpta Medica fertility database CD, which may contain additional publications on human reproduction. The authors searched the bibliographies of relevant publications and review articles, abstracts of major scientific meetings from 1992 to 1999, and The Cochrane Menstrual Disorders and Subfertility Specialized Register. When needed, authors of relevant abstracts were contacted for detailed data on their studies and peer consultation was sought for additional relevant studies. The pharmaceutical companies that manufactured the gonadotropin preparations were consulted for additional information.

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

Specific interventions included in the review
Recombinant follicle stimulating hormone (rFSH) (either follitrophin alpha or follitrophin beta) versus urinary follicle stimulating hormone (uFSH) (either urofollitrophin or urofollitrophin HP). Trials were included whether or not the stimulation protocol included pituitary down-regulation with gonadotropin releasing hormone agonists (GnRHa).

Participants included in the review
Infertile women undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). Women were aged 18 to 39 years for inclusion in the studies.

Outcomes assessed in the review
Clinical pregnancy rates per started cycle, defined as a gestational sac seen by ultrasonography.

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

Assessment of study quality
Each trial was assessed using an 8-criteria predetermined scoring system covering the criteria of randomisation, concealment, blinding, co-intervention, completeness of follow-up, sample size calculation, cross-over design, and patient and cycles differentiated. The maximum possible score was 21 and the lowest possible score was 3. Two authors independently assessed each trial for methodological validity. Any disagreement between the two reviewers was resolved by consensus whenever possible. In the event of persistent disagreement, a third reviewer was consulted.

Data extraction
The process of data extraction is not clearly reported but the authors do report that data were extracted and checked for
accuracy by a second reviewer.

Data were extracted for the categories of: study identification, setting, number of cycles, drugs compared, type of randomisation, inclusion criteria, exclusion criteria, use of GnRHa, FSH, HCG criteria, embryo transfer, luteal phase support, main outcome, definition of pregnancy, and ongoing pregnancy.

Odds ratios (ORs) and risk differences (RD) were calculated for each included individual trial.

**Methods of synthesis**

How were the studies combined?

Pooled Peto odds ratios (ORs) and risk differences (RD) with 95% confidence intervals (CIs) were calculated for the studies using the Mantel-Haenszel fixed-effect model.

A funnel plot was used to detect publication bias.

How were differences between studies investigated?

The Breslow-Day test for homogeneity was performed across all trials. Where there was no heterogeneity, a fixed-effect model was used, otherwise a random-effects model was used.

Subgroup analyses were performed to identify whether the two types of follitrophin (i.e. alpha or beta) and the two types of fertilisation procedure (i.e. ICSI or IVF) had any effect on the overall combined result. The data were recorded according to these variables and subjected to logistic regression analysis to identify the model that best predicted pregnancy per started cycle.

**Results of the review**

Twelve trials were included in the review with 2,875 participants (1,556 allocated to rFSH and 1,319 allocated to uFSH). In four trials, both IVF and ICSI were performed, in seven trials only IVF was performed, and in one trial only ICSI was performed.

The pooled OR was 1.20 (95% CI: 1.02, 1.42; P = 0.03) in favour of rFSH which was statistically significant. The risk difference represented a 3.7% (95% CI: 0.5, 6.9%) increase in clinical pregnancy rate per cycle started with rFSH, compared with uFSH. There was no significant heterogeneity of treatment effect across all trials (Breslow-Day statistic = 7.5, P = 0.94).

In the subgroup analysis of follitrophin alpha with uFSH (9 trials, 1,639 cycles, 13 comparative assessments), the OR was 1.21 (95% CI: 0.97, 1.51; P = 0.09) in favour of rFSH which was not statistically significant. The risk difference was 3.7% (95% CI: -0.5, 7.9%). There was no significant heterogeneity of treatment effect across all trials (Breslow-Day statistic = 7.3, P = 0.84).

In the subgroup analysis of follitrophin beta with uFSH (3 trials, 1,236 cycles), the OR was 1.19 (95% CI: 0.93, 1.53; P = 0.16) in favour of rFSH which was not statistically significant. The risk difference was 3.7% (95% CI: -1.5, 8.8%). There was no significant heterogeneity of treatment effect across all trials (Breslow-Day statistic = 0.20, P = 0.91).

In the analysis of the trials of IVF data, (11 trials, 2,308 cycles), the OR was 1.26 (95% CI: 1.05, 1.52; P = 0.02) in favour of rFSH which was statistically significant. The risk difference was 4.4% (95% CI: 0.9, 8.0%). There was no significant heterogeneity of treatment effect across all trials (Breslow-Day statistic = 5.0, P = 0.89).

In the analysis of the trials of ICSI data, (5 trials, 567 cycles), the OR was 1.02 (95% CI: 0.72, 1.45; P = 0.92) in favour of rFSH which was not statistically significant. The risk difference was 0.3% (95% CI: -7.4, 7.9%). There was no significant heterogeneity of treatment effect across all trials (Breslow-Day statistic = 1.4, P = 0.84).

In the logistic regression analysis, the clinical pregnancy rate was significantly higher when ICSI was performed, compared with IVF (OR 1.3, 95% CI: 1.1, 1.6). Similarly, rFSH was associated with a significantly higher clinical pregnancy rate, compared with uFSH (OR 1.2, 95% CI: 1.1, 1.5).
The pregnancy rate with the alpha preparation of rFSH was statistically significantly higher than with uFSH in IVF cycles.

The funnel plot analysis showed a symmetrical distribution of data indicating that publication bias was unlikely. No trial was designed with adequate power to test the null hypothesis of no difference in pregnancy rates between the two gonadotropin preparations.

Cost information
None, however the authors do state that a cost-effectiveness analysis is currently being undertaken to determine if there are additional advantages, in terms of cost savings, of using one preparation versus the other.

Authors' conclusions
The authors state that until more comparative data become available to supplement the data in this meta-analysis, these results indicate that there is a statistically significant difference in clinical pregnancy rates when rFSH is compared with uFSH. This finding, and the knowledge that the recombinant preparations have batch-to-batch consistency, are free from urinary protein contaminants and have the potential of being produced in limitless quantities, indicate that rFSH is more appealing for clinical use than uFSH.

CRD commentary
The authors have clearly stated the research question and some inclusion and exclusion criteria. The literature search appears to be thorough. It is not clear whether there were any language restrictions on the search but it is unlikely that additional relevant studies were missed. The quality of the included studies was formally assessed with a wide-ranging scoring system and the authors have reported who performed the data extraction.

The data extraction is reported in tables. Statistical pooling was performed where there were sufficient data and there were tests for heterogeneity.

The authors' conclusions appear to follow from the results, however, because of some methodological limitations in the process of the review, the authors' conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

Research: The authors state that further research is needed and should be designed as a four-arm randomised trial with sufficient power and with several biological end points, including cycle performance characteristics, oocyte and embryo quality, and incidence of ovarian hyperstimulation syndrome, spontaneous abortion, clinical pregnancy and live birth.

Bibliographic details

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Other publications of related interest
1. Girard M. Meta-analysis on recombinant versus urinary follicle stimulating hormone. Hum Reprod 2000;15:1650-1651. This additional published commentary may also be of interest. Koninckx PR. Meta-analysis of
recombinant and urinary FSH. Hum Reprod 2001;16:196-197.

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