A Markov model of the cost-effectiveness of human-derived follicle-stimulating hormone (FSH) versus recombinant FSH using comparative clinical trial data


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of recombinant versus human follicle-stimulating hormone (rFSH versus hFSH) for in vitro fertilisation (IVF) and intra-uterine insemination (IUI). Both one cycle and three cycles were examined.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of infertile women undergoing IVF.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published in 2003. Some cost and resource use data came from two studies published in 2002 and 2003. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A Markov model was constructed to examine the costs and effectiveness of one cycle, as well as three cycles, of rFSH versus hFSH in a hypothetical cohort of women undergoing IVF. Details on the cycle length and time horizon of the model were not reported. However, an outline of the model was provided. The health states considered were start of cycle, oocyte retrieval, embryo success or failure, chemical pregnancy, clinical pregnancy and ovarian hyperstimulation syndrome (OHSS).

Outcomes assessed in the review
The outcomes estimated from the literature were:

cancelled ovum pick-up.
the number of oocytes recovered,
the number of fertilisations,
the number of embryo transfers,
the number of chemical pregnancies,
the number of clinical pregnancies,
the number of continuing pregnancies,
the number of live births,
the number of multiple births,
the number of premature births, and
cases of OHSS.

Study designs and other criteria for inclusion in the review
The primary studies appear to have been identified selectively and a systematic review of the literature was not undertaken. The two studies were both prospective, randomised, multi-centre, comparative clinical trials. Details of the study samples and patients’ characteristics were reported.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The validity of the primary studies was ensured by selecting only randomised clinical trials.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Two studies provided evidence.

Methods of combining primary studies
The primary estimates were pooled. Further details were not provided.

Investigation of differences between primary studies
The authors stated that the two studies were identically designed.

Results of the review
All of the outcomes were reported as the number of patients in the hFSH or rFSH arm and the number of patients remaining in the pool. There were 120 patients in the hFSH arm and 118 patients in the rFSH arm.

The numbers of patients in the hFSH arm and remaining in the pool were, respectively:
7 and 113 for cancelled ovum pick-up,
0 and 113 for oocytes recovered,
2 and 111 for fertilisations,
0 and 111 for embryo transfers,
53 and 58 for chemical pregnancies,
7 and 51 for clinical pregnancies,
3 and 48 for continuing pregnancies,
6 and 42 for live births, 28 and 14 for multiple births,
34 and 8 for premature births, and
114 and 6 for cases of OHSS.

The numbers of patients in the rFSH arm and remaining in the pool were, respectively:
3 and 115 for cancelled ovum pick-up,
0 and 115 for oocytes recovered,
2 and 113 for fertilisations,
0 and 113 for embryo transfers,
63 and 50 for chemical pregnancies,
5 and 45 for clinical pregnancies,
1 and 44 for continuing pregnancies,
6 and 38 for live births,
23 and 15 for multiple births,
29 and 9 for premature births, and
115 and 3 for cases of OHSS.

Measure of benefits used in the economic analysis
The summary benefit measure was the rate of continuing pregnancy. Other model outputs were the rates of successful fertilisations, chemical pregnancy and clinical pregnancy.

Direct costs
Discounting was not relevant since the costs were incurred during a short timeframe. The unit costs were not presented separately from the quantities of resources used, and only the total costs associated with each health states were reported. The economic evaluation included the costs of the agents, ovarian stimulation, oocyte retrieval, embryo success or failure, chemical pregnancy, clinical pregnancy and treatment of OHSS. The cost/resource boundary of the analysis was unclear. The drug dosages came from the trials that provided clinical evidence. The costs were estimated from wholesale prices and a published study. All the costs were inflated to 2003 values using the medical service
component of the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case. However, a probabilistic sensitivity analysis provided standard deviations for the total costs in each arm.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
A one-way sensitivity analysis was carried out to approximate the estimated costs and benefits of using either agent in a more nationally representative IVF patient population. Thus, alternative estimates for transition probabilities were used. A probabilistic sensitivity analysis (Monte Carlo simulation) was also carried out.

**Estimated benefits used in the economic analysis**
The rate of continuing pregnancy with one cycle (three cycles) was 0.40 +/- 0.05 (0.78 +/- 0.05) with hFSH and 0.37 +/- 0.05 (0.75 +/- 0.05) with rFSH.

The rate of successful fertilisation with one cycle (three cycles) was 0.92 +/- 0.03 (1.81 +/- 0.10) with hFSH and 0.96 +/- 0.02 (1.93 +/- 0.10) with rFSH.

The rate of chemical pregnancy with one cycle (three cycles) was 0.48 +/- 0.05 (0.94 +/- 0.06) with hFSH and 0.42 +/- 0.05 (0.85 +/- 0.06) with rFSH.

The rate of clinical pregnancy with one cycle (three cycles) was 0.42 +/- 0.05 (0.83 +/- 0.05) with hFSH and 0.38 +/- 0.05 (0.77 +/- 0.05) with rFSH.

**Cost results**
The estimated costs with one cycle (three cycles) were $11,584.19 +/- 211.15 ($22,712.05 +/- 1,106.68) with hFSH and $12,761.79 +/- 170.41 ($24,934.79 +/- 1,205.29) with rFSH.

**Synthesis of costs and benefits**
The costs and benefits were not combined since hFSH was more effective and less costly than rFSH. The probabilistic sensitivity analysis showed that hFSH was less costly in 100% of simulations and was more effective in 65% of simulations. Further, the selection of hFSH could result in lower costs and better outcomes 65% of the time, and lower costs 100% of the time.

**Authors' conclusions**
Compared with recombinant follicle-stimulating hormone (rFSH), human follicle-stimulating hormone (FSH) was a cost-effective agent for ovarian stimulation in in vitro fertilisation (IVF).

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which represented two available agents for ovarian stimulation in
the USA. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of two published clinical trials, which had been selectively identified. The validity of the sources was ensured by the robust design and the comparable characteristics of the studies. The two studies were pooled in order to obtain single clinical estimates. Some characteristics of the patient groups were reported. Uncertainty around the estimates was addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study and is not comparable with the benefits of other health care interventions. However, pregnancy rate represents a commonly used measure for ovarian stimulation agents.

Validity of estimate of costs
The perspective adopted in the study was not explicitly stated and a detailed breakdown of the cost items was not provided. In fact, the costs were presented as macro-categories, which limits the possibility of replicating the analysis in other settings. The costs were mainly derived from a published study and no information on the cost estimates was provided. The price year was reported, which aids reflation exercises. The costs were treated stochastically in the probabilistic sensitivity analysis.

Other issues
The authors did not compare their findings with those from other studies. They addressed the issue of the generalisability of their results to other settings by reporting the average costs of IVF treatments in other countries. In particular, the authors stated that costs for IVF cycles in the USA were higher than those estimated for other countries. However, few sensitivity analyses were carried out. The study referred to women undergoing ovarian stimulation and this was reflected in the authors' conclusions.

Implications of the study
The study results supported the use of hFSH as a stimulating agent in IVF.

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Other publications of related interest
Dickey RP, Nicholls JE, Steinkampf MP, et al. Highly purified human-derived follicle stimulating hormone (Bravelle) has equivalent efficacy to rFSH (Follistim) in infertile women undergoing in vitro fertilization. Reproductive Biology and Endocrinology 2003;1:63.


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