The cost-effectiveness of IVF in the UK: a comparison of three gonadotrophin treatments

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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
Three gonadotrophin treatments for infertile women undergoing in vitro fertilisation (IVF) procedures were examined. The treatments were recombinant follicle stimulating hormone (rFSH, Puregon), highly purified urinary FSH (uFSH, Metrodin-HP) and human menopausal gonadotrophin (HMG, Menogon).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women aged 18 to 39 years with:

- a cause of infertility potentially solvable by IVF;
- a maximum of three prior IVF or other assisted reproduction attempts in which oocytes were collected at least once;
- normal ovulatory cycles;
- good physical and mental health; and
- a body weight of 80 to 130% of the ideal body weight.

The exclusion criteria were:

- infertility caused by endocrine abnormalities such as hyperprolactinaemia, polycistic ovary syndrome, and absence of ovarian function;
- male infertility;
- any ovarian and/or abdominal abnormality that would interfere with adequate ultrasound investigation;
- hypertension;
- chronic cardiovascular, hepatic, renal, or pulmonary disease;
- a history of (within 12 months) or current abuse of alcohol or drugs;
- administration of non-registered investigational drugs within 3 months prior to screening.

Setting
The setting was IVF provider clinics throughout Europe. The economic study was conducted in the UK.

**Dates to which data relate**
The study patients were recruited between March 1992 and August 1993. However, the exact dates during which the effectiveness and resource use data were collected were not stated. The price year was 1999.

**Source of effectiveness data**
The effectiveness evidence was derived from a published study (see Other Publications of Related Interest) and assumptions made by an expert panel.

**Link between effectiveness and cost data**
The costing was, in part, conducted prospectively on the same sample of patients as that used in the effectiveness study.

**Study sample**
Power calculations were based on an earlier study. They suggested that a sample of 1,000 patients was required, assuming that at least 850 women had an oocyte retrieval and embryo transfer. Such a sample size ensured that very small differences between the two groups, in terms of the pregnancy rate and number of oocytes, were detected with a high probability. With a significance of 5%, 1,000 women provided 80% power to detect statistically significant differences in the outcome. An initial sample of 1,027 women was recruited from several centres. Of these, 981 began FSH treatment. There were 585 patients in the rFSH group and 396 in the uFSH group. The mean age in the rFSH group was 32.2 years and the mean duration of infertility was 6.3 years. The mean age in the uFSH group was 32.3 years and the mean duration of infertility was 6.1 years.

**Study design**
This was an assessor-blind, randomised clinical trial, which was conducted in 18 different IVF centres in Europe. Randomisation was conducted using a list that corresponded to patient boxes in which the medication was kept. The ratio of patients between rFSH and uFSH was 3:2. Double-blinding was not feasible for technical reasons. The patients were followed until the third cycle of IVF was conducted. However, the actual length of and loss to follow-up were not reported.

**Analysis of effectiveness**
The basis for the analysis of the clinical study was intention to treat. The health outcomes used in the effectiveness study were several measures, which were converted into probability values:

- hospitalisation due to ovarian hyperstimulation syndrome (OHSS),
- pregnant-fresh after embryo transfer,
- pregnant-frozen after thawed transfer,
- thawed transfer after no pregnancy,
- embryo transfer after stimulation, and
- stimulated after no embryo transfer.

The pregnancy rate was the main outcome measure. The study groups were shown to have been comparable at baseline in terms of the demographic and infertility characteristics.
Effectiveness results
The probability values for all cycles were as follows.

The probability of hospitalisation due to OHSS was 0.019 with uFSH, and 0.032 (first and second cycles) and 0.03 (third cycle) with rFSH.

The probability of being pregnant-fresh after embryo transfer was 0.2202 with uFSH and 0.2597 with rFSH.

The probability of being pregnant-frozen after thawed transfer was 0.076 with uFSH and 0.164 with rFSH.

The probability of thawed transfer after no pregnancy was 0.409 with uFSH and 0.527 with rFSH.

The probability of embryo transfer after stimulation 0.831 with uFSH and 0.855 with rFSH.

The probability of stimulation after no embryo transfer was 1 with both uFSH and rFSH.

Clinical conclusions
The effectiveness evidence showed that rFSH was statistically more effective than uFSH in terms of pregnancy rates, but the probability of OHSS was slightly higher with rFSH. The remaining probability values were used as model inputs.

Modelling
A decision tree model was constructed to evaluate the cost-effectiveness of the three alternative treatments for infertile women. The model joined the medical cost and associated outcome per woman undergoing IVF. Following the structure of the tree, women who became pregnant after the first cycle of treatment were considered as a success. Those who did not become pregnant either received a further cycle of IVF treatment or dropped out for non-medical reasons. The process was exhausted when all women had received a maximum of three cycles of treatment. The model was constructed in DATA (version 3.5, TreeAge Software).

Methods used to derive estimates of effectiveness
An expert panel was contacted for data reflecting treatment patterns in the UK and to estimate probability values that were unavailable in the literature. Each member of the panel was sent a questionnaire and their responses were then fed back to the entire group. Any differences in the responses were discussed until a group agreement was obtained.

Estimates of effectiveness and key assumptions
The values of HMG were not estimated directly but were assumed to be similar to those observed with uFSH. The drop-out rate for non-medical reasons was assumed to be 0.2 in the first cycle and 0.4 in the second cycle, regardless of the treatment chosen. The probability of becoming pregnant over the first three cycles of IVF treatments was assumed to be constant.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the cumulative ongoing pregnancy rate after three cycles, which was estimated through the decision model.

Direct costs
Discounting was not relevant because the costs were considered over the first 12 weeks of pregnancy only. The unit costs were analysed separately from the quantities of resources used. The health services included in the economic analysis were IVF procedure, with or without embryo transfer, and drugs (uFSH, HMG, rFSH, nafarelin, progesterone, and human chorionic gonadotrophin). The cost/resource boundary of the study was that of the IVF provider clinic.
Resource use was estimated using actual data that were gathered alongside the clinical trial, supported with information provided by the expert panel. The unit costs were derived using the average costs taken from a sample of price lists from 20 IVF provider clinics in the UK. The drug costs came from UK list prices. The total costs associated with each treatment were obtained through the decision model. The time during which the resource use data were collected was not reported. The price year was 1999.

**Statistical analysis of costs**
No statistical tests were conducted on the costs or resources used.

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

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
One-way sensitivity analyses were conducted on most model inputs to estimate the robustness of the cost-effectiveness ratios. The three main variations investigated were the price of an IVF procedure (range: 750 - 2,500 with embryo transfer; 400 - 1,500 without embryo transfer), the effect of a lower chance of pregnancy (7% for cycle 2 and 12% for cycle 3), and the dose of gonadotrophins (+/- 30%).

**Estimated benefits used in the economic analysis**
The cumulative ongoing pregnancy rate after three cycles was 57.1% for rFSH and 44.4% for both uFSH and HMG.

**Cost results**
The estimated cost per IVF treatment was 5,135 with rFSH, 4,806 with uFSH, and 4,202 with HMG.

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the three treatments.

The average cost per ongoing pregnancy was 8,992 with rFSH, 10,834 with uFSH, and 9,472 with HMG.

The incremental cost per ongoing pregnancy with rFSH was 2,583 in comparison with uFSH, and 7,321 in comparison with HMG.

When only one cycle of treatment was considered, the cost per ongoing pregnancy was 8,992 with rFSH, 10,743 with uFSH, and 9,831 with HMG.

The sensitivity analysis showed that the incremental cost per pregnancy with rFSH, with embryo transfer, ranged between 2,188 and 2,879 relative to uFSH and between 6,926 and 7,617 relative to HMG. Without embryo transfer, the corresponding ranges were 2,274 to 2,876 (relative to uFSH) and 7,012 to 7,614 (relative to HMG).

The estimated cost per pregnancy was quite insensitive to variations in the pregnancy rate. However, the change in dose had the strongest impact on the study results. The incremental cost per pregnancy of rFSH ranged from 1,439 to 3,723 relative to uFSH, and from 4,757 to 9,883 relative to HMG.
Authors' conclusions
Although initially more expensive due to its high acquisition cost, treatment with recombinant follicle stimulating hormone (rFSH) during in vitro fertilisation (IVF) procedures was cost-effective in the UK, compared with urinary FSH (uFSH) and human menopausal gonadotrophins (HMG). This conclusion was fairly robust to variations carried out in the sensitivity analysis.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. HMG was selected because it represented the standard approach for the stimulating fertility of women during IVF procedures. The use of uFSH was justified since it represented a widely use alternative treatment. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised trial, which was appropriate for the study question. The methods of sample selection and randomisation were described and the study was conducted in several centres across Europe. Power calculations were conducted in the preliminary phase of the study and the analysis of the clinical study was conducted on an intention to treat basis. The study groups were shown to have been comparable at baseline and the patients' characteristics were reported. All these issues tend to enhance the internal validity of the analysis. Some of the effectiveness evidence came from the opinions of experts who were selected to represent the different geographical contexts and the public/private mix within UK. A process similar to a Delphi panel was used. The assumptions made were investigated in the sensitivity analysis. The authors stressed that the assumptions made in the decision model were conservative and did not favour the rFSH arm of the tree.

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was disease-specific. This limited the scope for comparing the benefits of the present study with those of other interventions. The measure was obtained through a decision model, which was depicted and described appropriately.

Validity of estimate of costs
The perspective adopted in the study was explicitly stated. It appears that all the relevant categories of costs have been included in the economic evaluation. The authors stated that the indirect and non-medical costs were not considered, but the impact of their exclusion on the estimated costs of the interventions was unclear. Many details on the cost analysis were reported, such as the unit costs, resource use and the price year. This facilitates the replication of the study in other settings. The costs were treated deterministically in the base-case, but the impact of changes in the main cost driver (IVF procedure) was investigated. Changes in doses were also considered.

Other issues
The authors did not address the issue of the generalisability of the study results to other settings and their analysis was focused on the UK context. However, several comparisons with other studies were made. These highlighted the problems associated in comparison to alternative fertility treatments, such as surgery or other procedures for male infertility. The study referred to women with fertility problems solvable by IVF and this was reflected in the conclusions of the study.

Implications of the study
The study results suggested that, despite its initial high acquisition cost, IVF based on rFSH represented a cost-effective alternative treatment to uFSH and HMG.

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