Pharmaco-economic aspects of in-vitro fertilization in Italy

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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
Follitropin-beta, a recombinant follicle stimulating hormone (r-FSH), was compared with urinary follitropin (u-FSH) in women requiring in-vitro fertilisation (IVF).

Type of intervention
Treatment

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women undergoing IVF. The model used a hypothetical cohort of 10,000 patients undergoing IVF in Italy.

Setting
The setting was secondary care. The economic study was carried out in Italy.

Dates to which data relate
The efficacy data related to studies published between 1995 and 1997. The cost data related to studies published between 1994 and 1997. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a synthesis of completed studies, and from the opinions of experts.

Modelling
A Markov chain model was used to estimate the clinical and economic outcomes of the r-FSH and u-FSH over three cycles.

Outcomes assessed in the review
The model used the probabilities of the following outcomes:

- an embryo transfer;

- undergoing a frozen procedure;

- a thawed embryo transfer;
ovarian hyperstimulation syndrome (OHSS),
a direct pregnancy;
a frozen pregnancy;
total pregnancy; and
the pregnancy rate.

**Study designs and other criteria for inclusion in the review**
The review included the results from a meta-analysis of 3 prospective multi-centre, randomised and comparative trials, and those from a clinical trial. No inclusion criteria were reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
One primary study and a meta-analysis of 3 primary studies were included in the review.

**Methods of combining primary studies**
The study used the results of a meta-analysis, but did not report the methods that were used to combine the primary studies.

**Investigation of differences between primary studies**
The authors did not investigate the differences between the primary studies.

**Results of the review**
The probabilities reported for r-FSH were:

85.5% for an embryo transfer;
63.2% for undergoing a frozen procedure;
33.3% for a thawed embryo transfer;
3.2% for OHSS;
22.2% for a direct pregnancy;
5.4% for a frozen pregnancy;
27.7% for total pregnancy; and
22.9% for the pregnancy rate.

The probabilities for u-FSH were:
83.1% for an embryo transfer;
64.7% for undergoing a frozen procedure;
26.5% for a thawed embryo transfer;
2.0% for OHSS;
18.2% for a direct pregnancy;
2.0% for a frozen pregnancy;
20.4% for total pregnancy; and
17.9% for the pregnancy rate.

Methods used to derive estimates of effectiveness
The estimates of effectiveness were derived from the opinions of experts. Seven Italian IVF specialists were identified and interviewed for the details of local treatment and management pathways, to which the results of published clinical trials were applied.

Estimates of effectiveness and key assumptions
The estimates of effectiveness were used to augment the data obtained from published studies. However, the values used for the input parameters of the model were not reported clearly.

Measure of benefits used in the economic analysis
The measure of benefit used in the economic analysis was the number of pregnancies.

Direct costs
The costs and quantities were not reported separately. The following direct costs were included in the model:

hospitalisation, 2,388,000 L (for only 1% of the cases);
transvaginal echocardiogram, 18,000 L;
laboratory tests, 250,000 L;
thawed embryo transfer, 510,000 L;
embryo thawing, 150,000 L;
anaesthesia, 250,000 L;
pick-up, 900,000 L;
embryo transfer, 180,000 L; and
The average weighted private cost was also estimated. This was approximately 5.85 L per patient.

The total drug costs were 1,504,140 L for u-FSH, 3,206,250 L for r-FSH, 353,500 L for gonadotrophin-releasing hormone (GnRH), and 10,700 L for human chorionic gonadotrophin (HCG).

The unit costs for the drugs were 631 L for u-FSH, 1,500 L for r-FSH, 94,267 L for GnRH, and 2.14 L for HCG.

The authors reported that private tariffs were used as a proxy for the costing of IVF treatment, because 70 to 90% of the IVF cycles were performed in the private setting. The drug costs, however, were estimated using an NHS perspective since the NHS reimburses these costs. The study assumed that r-FSH was reimbursed at the same level as u-FSH.

The price year was not explicitly reported. Discounting was irrelevant due to the short timeframe of the model (1 year).

**Statistical analysis of costs**
No statistical analysis was reported.

**Indirect Costs**
The indirect costs of the interventions were not reported.

**Currency**
Italian lira (L). The conversion rate was US$1 = 1,690 L.

**Sensitivity analysis**
One-way sensitivity analyses were conducted in which r-FSH efficacy, the cost of the procedure, and the cost of r-FSH were varied by plus or minus 20%. The study also reported a two-way sensitivity analysis on the effectiveness and cost of r-FSH.

**Estimated benefits used in the economic analysis**
In a cohort of 10,000 women, there were 4,966 pregnancies in women treated with u-FSH and 6,221 in those treated with r-FSH.

**Cost results**
The total costs for the public sector were 106,950 L for u-FSH and 139,590 L for r-FSH.

The total costs for the private sector were 187,592 L for u-FSH and 211,713 L for r-FSH.

The total costs for the current Italian situation of 80% private and 20% public sector were 171,603 L for u-FSH and 197,113 L for r-FSH.

The estimated total cost of IVF treatment therefore varied between 106.9 and 211.7 billion L (US$63.2 to 125.2 million), depending on the setting and type of treatment.

**Synthesis of costs and benefits**
The authors calculated the average and incremental cost-effectiveness ratios for the private sector, the public sector and the current situation in Italy. These were expressed in terms of millions L per ongoing live pregnancy. The average
cost-effectiveness ratios were:

for the public sector, 21.54 for r-FSH and 22.44 for u-FSH;

for the private sector, 37.78 for r-FSH and 34.03 for u-FSH; and

for the current situation, 34.56 for r-FSH and 31.69 for u-FSH.

The incremental cost-effectiveness ratio for r-FSH, compared with u-FSH, was 26.01 for the public sector, 19.22 for the private sector, and 20.33 for the current situation.

The incremental cost-effectiveness ratio therefore varied between 19.2 and 26 million L (US$11,300 to 15,400), depending on the setting and type of treatment.

The authors reported that the incremental cost-effectiveness ratios were highly sensitive to changes in the efficacy or effectiveness of r-FSH, although the actual values for the sensitivity analyses were not reported.

Authors’ conclusions
Follitropin-beta, a recombinant follicle stimulating hormone (r-FSH) had a favourable and reasonable cost-effectiveness profile when compared with urinary follitropin (u-FSH). Although the acquisition cost of r-FSH was at least double the cost of u-FSH, the total cost of treating IVF patients with r-FSH was estimated to be approximately 13 to 31% higher, depending on the treatment setting. In terms of the average cost-effectiveness ratios, r-FSH performed better than u-FSH.

CRD COMMENTARY - Selection of comparators
The comparator was justified on the grounds that u-FSH products were used widely for the treatment of fertility in Italy. You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. No information was provided on how the studies were identified, or the criteria on which they were selected and assessed. It was unclear if the authors used data from the available studies selectively, or if they considered the impact of differences between the studies used in the review. The authors did not report the methods used to derive the estimates of effectiveness. In addition, they did not adopt a weighting scheme to reflect differences in the sample sizes.

A panel of seven IVF specialists were interviewed in order to determine national treatment and management pathways for IVF. The physicians were selected to represent seven different Italian regions: Lombardia, Toscana, Emilia-Romagna, Lazio, Puglia, Campania and Sicilia. These corresponded to the areas where 63% of the total Italian population reside, and where IVF treatment is most widely performed. The authors did not report the process by which the physicians were selected. It was unclear if the views of the selected physicians were representative of the views of the wider population of Italian physicians. The authors caution that this may limit the generalisability of these results to other settings.

The estimates of effectiveness were investigated in the sensitivity analysis. The ranges used in the sensitivity analysis seem to have been appropriate.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov chain model used to derive the measure of health benefit was appropriate.

Validity of estimate of costs
The costs and quantities were not reported separately. The resource use was estimated from an expert panel rather than from published data. The authors did not acknowledge the uncertain reliability of their conclusions in the light of using data from an expert panel. The study chose to report a range of perspectives and the associated costs. The relevant direct costs appear to have been included in the analysis. The analysis did not include indirect costs. The cost of absence from work and the patients' travel expenses would have to be included in order to estimate the cost to society. These costs were omitted, which means that the cost-effectiveness of the intervention may have been overestimated.

A sensitivity analysis was conducted, but was presented graphically instead of reporting the actual values. This made the interpretation of the sensitivity analysis difficult. Appropriate currency conversions were performed. The price year was not reported. Discounting was irrelevant since the costs were incurred over a one-year period.

Charges were used to proxy prices. The authors justified their decision to estimate costs in this manner by the fact that 70 to 90% of IVF cycles were performed in the private setting in Italy. The use of charges, rather than unit prices, limited the generalisability of the study's findings.

**Other issues**
The issue of generalisability to other settings was not addressed explicitly, due in part, to the use of charges rather than unit prices. The authors reported difficulties in comparing their findings with those from other studies. However, they also reported that their findings appeared to be in line with the most recent analyses of the costs and effects of IVF treatments. The authors pointed out that most analyses have been conducted in different countries, with different health care systems, and have not addressed the economic benefits of the interventions.

The authors reported further limitations to their study. For example, the analysis used published data that had been adapted to the Italian patterns of care. The quality of this adaptation relied on how well the data obtained from the panel of experts reflected the views of the wider population of Italian physicians.

**Implications of the study**
The authors suggested that, when the incremental cost-effectiveness was considered, r-FSH showed a reasonable ratio, between 19.2 and 26 million L per ongoing pregnancy. The authors considered this ratio represented a reasonable amount to pay, considering that approximately 98% of these pregnancies will culminate in a new-born baby. The authors cautioned that this was the first study to investigate IVF in Italy, and ideally, further research should be performed using prospective economic evaluations.

**Source of funding**
Supported by a financial contribution from Organon Italia SpA.

**Bibliographic details**

**PubMedID**
10221226

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Cost-Benefit Analysis; Female; Fertilization in Vitro /economics; Follicle Stimulating Hormone /economics /therapeutic use; Humans; Male; Ovulation Induction /economics; Pregnancy; Recombinant Proteins /economics /therapeutic use
AccessionNumber
21999000787

Date bibliographic record published
30/06/2002

Date abstract record published
30/06/2002