Recombinant versus urinary follicle-stimulating hormone in intrauterine insemination cycles: a prospective, randomized analysis of cost effectiveness

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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
The use of recombinant versus urinary follicle-stimulating hormone (FSH) in intrauterine insemination (IUI) cycles. The recombinant preparation was injected subcutaneously, starting on day 2 of the cycle, at a dose of 50 IU/day. The urinary product was administered subcutaneously, starting on day 2 of the cycle, at a dose of 75 IU/day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women with a history of infertility. The inclusion criteria were ovulatory factor (polycystic ovary syndrome, clomiphene resistant, normogonadotropic anovulation), endometriosis (Stage I or II), mild male factor infertility, and unexplained infertility. The exclusion criteria were tubal factor, male factor infertility not suitable for IUI (<10 million motile sperm in the ejaculate), and hypergonadotropism.

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

Dates to which data relate
The effectiveness and resource use data were gathered between March 2000 and December 2002. The price year was not explicitly stated, but it appears to have been 2001.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of women as that included in the effectiveness study.

Study sample
Power calculations were not reported. A total of 140 cycles in a sample of 67 women was included. There were 32 women in the urinary FSH group and 35 women in the recombinant FSH group. However, a patient in each group asked to be withdrawn from one of the cycles for personal reasons, and these two cycles were not considered. The mean age was 31.7 (±/− 3.4) years in the urinary FSH group and 31.2 (±/− 3.2) years in the recombinant FSH group. The average
duration of infertility was 2.8 (+/- 1.3) years in the urinary group and 2.9 (+/- 1.5) years in the recombinant group.

**Study design**

This was a prospective, randomised clinical trial that was presumably carried out at two institutions, the University Hospital in Perugia, and A.G.UN.CO. Obstetrics and Gynaecology Centre in Rome. The patients were allocated to the study groups on the basis of a randomisation table. The length of follow-up was not reported. No patient was lost to the follow-up assessment. No blinding was performed.

**Analysis of effectiveness**

All of the patients included in the initial study sample were taken into consideration in the analysis of effectiveness. The outcome measures used were:

- the number of follicles larger than 17 mm,
- days of stimulation,
- the number of ampoules per cycle,
- the rate of biochemical pregnancy,
- the rate of clinical pregnancy,
- the rate of spontaneous abortion, and
- the rate of cancelled cycles.

The cases of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies were also reported. A biochemical pregnancy was defined as a small and transitory increase in beta-human chorionic gonadotropin levels. A clinical pregnancy was determined by the visualisation of an embryo with cardiac activity at 6 to 7 weeks of pregnancy. Spontaneous abortion was classified as the loss of the pregnancy between the fifth and 12th week of gestation. The study groups were comparable at baseline in terms of the demographic and clinical factors.

**Effectiveness results**

The number of follicles larger than 17 mm was 2.6 (+/- 1.7) in the urinary group and 2.9 (+/- 1.4) in the FSH group.

There were 9.2 (+/- 2.1) days of stimulation in the urinary group and 10.0 (+/- 1.9) in the FSH group.

There were 10.9 (+/- 3.6) ampoules per cycle in the urinary group and 11.9 (+/- 4.1) in the FSH group.

The rate of biochemical pregnancy was 1.5% in the urinary group and 1.4% in the FSH group.

The rate of clinical pregnancy was 11.9% in the urinary group and 12.7% in the FSH group.

The rate of spontaneous abortion was 12.5% in the urinary group and 11.1% in the FSH group.

The rate of cancelled cycles was 6.0% in the urinary group and 7.0% in the FSH group.

No OHSS cases or multiple pregnancies were observed.

None of the differences in clinical outcomes reached statistical significance.

**Clinical conclusions**

The effectiveness analysis showed that the two study groups were equally effective.
Measure of benefits used in the economic analysis
The summary benefit measure used was the rate of clinical pregnancy. This was derived directly from the effectiveness study.

Direct costs
The perspective adopted in the study was not stated. However, only the cost of the ampoules of FSH was considered. The unit cost of the ampoule was presented separately from the quantities of ampoules used. The resource use data were derived from the sample of women included in the clinical trial. The costs of FSH came from the Italian Formulary in 2001, which might have been the price year. Discounting was not relevant as the costs were incurred during a short timeframe.

Statistical analysis of costs
Statistical analyses were carried out to test the statistical significance of differences in the total costs.

Indirect Costs
The indirect costs were not considered.

Currency
Euros (Euro).

Sensitivity analysis
Sensitivity analyses were not carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The number of IU per cycle was 815.5 (+/- 284.9) (95% confidence interval, CI: 711.3 - 924.8) in the urinary FSH group and 596.0 (+/- 253.8) (95% CI: 565.7 - 680.8) in the recombinant group. The difference of 219.5 cycles was statistically significant, (p<0.0001).

The cost per cycle was Euro 220.73 (+/- 94.72) (95% CI: 165.7 - 278.4) in the urinary FSH group and Euro 318.50 (+/- 125.21) (95% CI: 225.6 - 369.1) in the recombinant FSH group. The difference was Euro 97.77, (p<0.0001).

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

The average cost per clinical pregnancy obtained was Euro 1,848.61 in the urinary FSH group and Euro 2,512.61 in the recombinant FSH group.

Authors’ conclusions
Both FSH preparations were effective in achieving pregnancy rates in infertile women. The urinary preparation was the most cost-effective because of its lower acquisition cost.
CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as the two FSH preparations were widely used in IUI. 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 clinical trial, which was appropriate for the study question. The method of randomisation was described and should have reduced the impact of selection bias. The approach used to select the sample of participating women was reported, but it was not stated whether any patients refused to participate or were excluded for any reasons from the initial study sample. The study groups were well balanced at baseline with respect to not only their demographics, but also the history of infertility. However, the trial was open-label, thus assessment bias might have affected the results of the study. In addition, the sample size was not justified and this might explain the lack of statistically significant differences between the groups in all outcome measures. These issues might limit the internal validity of the analysis. Different definitions of pregnancy were used, and this represents a strength of the study.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It would not be comparable with the benefits of other health care interventions. However, the pregnancy rate is a typical outcome used in studies assessing the efficacy of assisted reproductive techniques.

Validity of estimate of costs
The analysis of the costs was restricted to the cost of the FSH preparations. Other resources associated with different aspects of treatment were not included. This was justified on the basis of the equal efficacy of the two treatments and on the lack of side effects related to the interventions. The unit cost of the preparations was provided along with its source, which represented a typical source of Italian costs. The quantities of resources used were also provided, which enhance the possibility of replicating the analysis in other settings. The authors carried out some statistical analyses of the costs, but the cost estimates were specific to the study setting. The price year was implicitly stated, which will assist in reflating the results of the study in other time periods.

Other issues
The authors reported the results of other published economic evaluations of recombinant versus urinary FSH preparations, and found contrasting results. The issue of the generalisability of the study results to other settings was not explicitly addressed. In addition, sensitivity analyses were not carried out, which might limit the external validity of the study. The analysis referred to a specific population of infertile women and this was reflected in the authors’ conclusions. The authors noted that different doses of FSH were used (50 IU for recombinant FSH and 75 IU for urinary FSH), although the choice of these was justified on the basis of drug availability in Italy, a supposedly higher efficacy and bioactivity of the product, and the risk of OHSS and multiple pregnancies.

Implications of the study
The study results did not support the use of the most expensive FSH preparation for ovarian stimulation in IUI cycles. The authors recommended that more prospective randomised trials be carried out to confirm the results of the current study in larger samples of patients.

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Other publications of related interest


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