Recombinant versus highly-purified, urinary follicle-stimulating hormone (r-FSH vs. HP-uFSH) in ovulation induction: a prospective, randomized study with cost-minimization analysis


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 study investigated the use of highly purified urinary follicle-stimulating hormone (HP-uFSH; Metrodin HP Serono). This intervention was compared with recombinant follicle-stimulating hormone (r-FSH; Gonal-F Serono).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised the women of couples with a history of infertility of at least one year, and who were undergoing ovulation induction associated with timed intercourse.

Setting
The study setting was outpatient secondary care. The economic study was carried out at the University of Turin, Italy.

Dates to which data relate
The dates from which the effectiveness and resource use data were derived were not reported. The price year was not reported.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample that provided the effectiveness data.

Study sample
The sample size was determined in the planning phase of the study to assure a certain power. Using evidence from another study, the authors found that 130 patients per arm would be needed for a detection power of 95%, at a significance level of 0.05, in order to obtain a 17% reduction in costs in favour of HP-uFSH. A total of 260 women undergoing ovulation induction associated with timed intercourse at the Reproductive Medicine and IVF units were enrolled in the study. No patients were excluded from the initial sample and no patient refused to participate in the study. Of the 260 patients included in the study, 130 were in the HP-uFSH group and 130 in the r-FSH group. The authors also reported that only the first ovulation induction cycle of each patient was considered in the study.

Study design
This was a prospective, randomised study that was undertaken at a single centre. Randomisation was performed using a computer-generated random assignment schedule, which consisted of a blocking method that ensured an equal number of patients in the two treatment groups. The authors did not report if clinicians and/or patients were blinded to the treatment given. The maximum duration of follow-up appears to have been until delivery. There appears to have been no loss to follow-up, although the authors reported that a total of 50 cycles were cancelled (27 in the HP-uFSH group and 23 in the r-FSH group; p>0.05).

Analysis of effectiveness
The analysis appears to have been conducted on an intention to treat basis. The primary health outcomes used were:

the monofollicular response rate,
the length of the follicular phase,
the total FSH dose,
the number of follicles between 12 and 17 mm on the day of human chorionic gonadotropin (hCG) administration,
the diameter of the leading follicle and endometrial thickness on the day of hCG administration,
the twinning rate,
the incidence of ovarian hyperstimulation syndrome, and
the delivery rate.

The patients were comparable in terms of their body mass index, age, duration of infertility, type of infertility and indication to treatment.

Effectiveness results
The delivery rate was 10% (95% confidence interval, CI: 4.5 to 15.2) for the HP-uFSH group compared with 13.1% (95% CI: 7.3 to 18.9) for the r-FSH group. However, this difference did not reach statistical significance.

The total mean FSH dose was 844 IU (standard deviation, SD=305) in the HP-uFSH group compared with 688 (SD=276) in the r-FSH group, (p<0.0003).

Differences in other health outcomes between the two groups were not statistically significant.

Clinical conclusions
r-FSH was associated with an increase in the delivery rate, albeit a non significant increase, in comparison with HP-uFSH.

Measure of benefits used in the economic analysis
Although the authors reported that a cost-minimisation analysis was undertaken, the measure of benefit used in the economic analysis was the number of pregnancies.

Direct costs
The direct costs included in the analysis were those to the Italian Health Service. These only comprised the cost per vial at the time of the clinical trial. The authors reported that the economic impact of other health resources was the same for both study groups and, therefore, was not considered. While the resource use data were derived from the effectiveness study, the source of the unit costs was not reported. Discounting was not relevant, as the costs were
incurred during a short time, and was appropriately not conducted. The price year was not reported. The authors reported the average costs. The unit cost and quantity of each vial used were reported.

**Statistical analysis of costs**
Resource use was reported as means together with their 95% CIs. The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**
No productivity costs were evaluated.

**Currency**
Euros (EUR).

**Sensitivity analysis**
The authors undertook a series of sensitivity analyses by calculating the cost per delivery after having considered the mean number of FSH vials consumed and the delivery rate for a started cycle around the 95% CIs.

**Estimated benefits used in the economic analysis**
The number of pregnancies was 13 (95% CI: 6 to 20) in the HP-uFSH group compared with 17 (95% CI: 9 to 25) in the r-FSH group.

**Cost results**
The average cost per cycle was EUR 175.71 in the HP-uFSH group compared with EUR 208.26 in the r-FSH group.

**Synthesis of costs and benefits**
The costs and benefits were combined using an average cost-effectiveness ratio (i.e. the cost per delivery).

The average cost per delivery was EUR 1,757.15 in the HP-uFSH group compared with EUR 1,591.20 in the r-FSH group.

The results of the sensitivity analysis showed the cost per delivery to be lower with r-FSH after correcting for the CI of delivery rate. The cost-reduction ranged from 2.7 to 21.9% with r-FSH.

**Authors’ conclusions**
When considering the significantly lower number of vials per patient and the slight, non significant, increase in the delivery rate with recombinant follicle-stimulating hormone (r-FSH), the analysis showed a 9.4% reduction in the overall therapy cost per born baby in favour of r-FSH.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using HP-uFSH as the comparator. It represented current practice in the authors’ setting. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a prospective, randomised controlled study. This was appropriate for the study question, as well-conducted randomised controlled trials are considered to be the ‘gold’ standard study design when comparing
health care interventions. The study sample appears to have been representative of the study population, and the patient groups were shown to be comparable in terms of their age, body mass index, and duration and type of infertility. The method of randomisation, study design, sample and analysis were all reported, suggesting that the internal validity of the study is likely to be good. The analysis of effectiveness was also handled credibly, with the authors performing appropriate statistical analyses to investigate if differences between the groups were statistically significant. Although power calculations were undertaken, these were undertaken to detect differences in costs. Consequently, the study might have had insufficient power to detect differences in effectiveness.

Validity of estimate of measure of benefit
The number of pregnancies was used as the summary benefit measure. This was obtained directly from the effectiveness analysis.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of the Italian Health Service paying for the fertility treatment. The cost analysis was very limited, comprising only of the cost of the vials used in each cycle. The authors reported that other health resources (such as ultrasound monitoring) were not included as they were the same for both study groups. However, relevant costs appear to have been omitted from the analysis. For example, although differences in delivery rates were not significant, the costs of pregnancy and delivery should have been included in the analysis as their cumulative impact could have generated considerable cost-differences. Whilst resource use was derived from the effectiveness study, the source of the unit costs was not reported. The costs were appropriately not discounted as they were incurred during less than one year. The authors performed a sensitivity analysis by varying the number of FSH vials and the number of pregnancies. The costs and resource use were reported separately, which will enhance the generalisability of the authors' results to other settings.

Other issues
The authors reported that two other studies calculating the cost-effectiveness of r-FSH and HP-uFSH had concluded that the urinary preparation was more cost-effective. The issue of generalisability to other settings was only partially addressed in the sensitivity analysis. The authors did not present their results selectively, and their conclusions reflected the scope of the analysis. The authors reported no limitations to their study.

Implications of the study
The authors reported that both HP-uFSH and r-FSH could be used safely and effectively for ovulation induction.

Source of funding
None stated.

Bibliographic details

Other publications of related interest
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Clomiphene /therapeutic use; Cost Savings; Drug Resistance; Female; Follicle Stimulating Hormone, Human /therapeutic use; Humans; Infertility, Female /drug therapy /economics; Ovulation Induction /economics /methods; Polycystic Ovary Syndrome /drug therapy; Pregnancy; Pregnancy Rate; Recombinant Proteins /therapeutic use; Urofollitropin /therapeutic use

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