Cost-Effectiveness of Recombinant Versus Urinary Follicle-Stimulating Hormone in Assisted Reproduction Techniques in the Spanish Public Health Care System

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Purpose: To evaluate the relative cost-effectiveness of recombinant and urinary follicle-stimulating hormone (FSH) in assisted reproduction techniques in the Spanish National Health Service.

Methods: Markov modelling was used to compare costs and outcomes of three complete treatment cycles using recombinant or urinary FSH for controlled ovarian stimulation. Cost and effectiveness estimates were obtained from the literature and from Spanish clinicians. A Monte Carlo technique was used to randomise the distribution of outcomes at each stage. The analysis was performed by passing a virtual population of 100,000 patients through the computer simulation in each of 5000 Monte Carlo simulations.

Results: The cost per pregnancy was €12,791 ± 1202 (\$11,346 ± 1066) with recombinant and €13,007 ± 1319 (\$11,537 ± 1170) with urinary FSH ($p < 0.0001$). The mean number of cycles per pregnancy was 4.69 and 5.21, respectively.

Conclusions: Recombinant FSH is more cost-effective than urinary FSH in the Spanish public health care system.

KEY WORDS: Cost-effectiveness; Markov modelling; recombinant human FSH; Spain; urinary FSH.

INTRODUCTION

It is estimated that about 30,000 cycles of assisted reproduction techniques (ART) are performed annu-

ally in Spain. Of these, some 25% take place in public hospitals and clinics, where treatment and medication costs are fully reimbursed through the Spanish National Health Service (NHS). The available resources are not sufficient to meet demand, resulting in long waiting times for treatment (over 2 years in some centres). The Spanish Parliament recently approved a generic mandate for the reimbursement of the costs of a limited number of ART cycles for couples suffering from infertility. Details of the coverage of this mandate (e.g., the number of cycles per couple) will be defined at a central level by the Inter-Territorial Council of the NHS and the mandate will be developed and implemented locally in each of the

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17 autonomous communities that make up the NHS. Against this background, it is important to ensure that the drugs and procedures used in the NHS are the most cost-effective available.

Recombinant human follicle-stimulating hormone (r-hFSH) is widely used for controlled ovarian stimulation (COS) in ART. r-hFSH has many advantages over the older products derived from urine (urinary hFSH; u-hFSH). These include improved purity, higher specific activity, and greater consistency between different batches (1). Meta-analysis indicates that pregnancy rates per started cycle are higher when r-hFSH is used compared with cycles using u-hFSH (2). However, the price of r-hFSH is higher than that of u-hFSH and for this reason u-hFSH is still used in some centres. This raises the question of whether the greater efficacy of r-hFSH might result in cost savings that outweigh its higher acquisition cost. In other words, is r-hFSH more cost-effective than u-hFSH for ART programmes in a situation of heavy pressure on available resources?

Preliminary studies using a Markov modelling (3) approach suggested that r-hFSH might be more cost-effective than u-hFSH in the health care systems of Greece (4) and Italy (5). In Markov modelling, patients are assigned a specific "health state" that reflects their position in the treatment cycle. Health states in an ART programme might include ovarian stimulation, oocyte retrieval, embryo transfer, etc. Patients progress through the model in a series of health states where the probability of progressing from one state to another (e.g., from ovarian stimulation to successful oocyte retrieval) is estimated from clinical data. A more detailed Markov model was subsequently developed and applied to the NHS in the United Kingdom (6) and to the insurance-based system of the USA (7).

In this paper, we report the results of applying the same model to the conditions of the Spanish NHS.

MATERIALS AND METHODS

The Markov model used for this study was developed specifically for the cost-effectiveness analysis of ART programmes. It involves the use of a customised computer simulation that was written after commercially available software packages were found to be inadequate for the level of complexity involved in modelling ART programmes. The development of the model has been described in detail elsewhere (6). Briefly, the model as applied to the

Spanish health care system compares the costs and clinical outcomes of three complete treatment cycles using either r-hFSH (Gonal-F[®], Serono) or urinary FSH (Neo-Fertinorm[®], Serono) for controlled ovarian stimulation. The first cycle involves a fresh embryo transfer, while subsequent cycles (if necessary) can involve either fresh or frozen embryo transfers. A simplified representation of the model is shown in Fig. 1, which illustrates all of the possible combinations of fresh and frozen embryo treatment cycles and their possible outcomes (success or abandoned cycle). Each fresh embryo transfer cycle involves 61 different health states, while a frozen embryo transfer cycle involves 13 health states. A total of 283 different health states are considered across the three complete cycles.

The probability of transition between different health states within a cycle (e.g., from oocyte retrieval to embryo transfer) was estimated using data from randomised clinical trials, data from the Catalan regional IVF registry (8), and expert opinion. Confidence limits for the probability estimates were obtained from a panel of Spanish clinicians with expertise in ART. For each probability value, the panel was asked to estimate the range (R) that would include 95% of patients. For a 95% confidence interval, $R = 2$ (1.96 Standard Deviation). Hence, the standard deviation (SD) was calculated using the formula $SD = R/(2 \times 1.96)$. The estimated transition probabilities and associated SDs are shown in Table I.

A Monte Carlo technique (9) was used to randomise the distribution of outcomes at each stage of the cycle in order to allow determination of SDs for the final outcomes (number of ongoing pregnancies, cost per pregnancy, and number of cycles required to achieve pregnancy). An ongoing pregnancy was defined as a pregnancy at 12 weeks confirmed by ultrasound scanning.

Cost data were derived from a representative sample of ART clinics in the Spanish public health care system. All costs, with the exception of drug costs, were adjusted upwards by 50% in order to take into account structural costs in the public sector, according to a specific cost survey in key Spanish public hospitals. The costs included in the model are shown in Table II. Conversion from euros (€) into US dollars (\$) was done using the exchange rate of €1 = \$0.887.

The cost-effectiveness analysis was performed by passing a virtual population of 100,000 patients (the "Markov cohort") through the computer simulation of the ART programme in each of 5000 Monte Carlo simulations. This number of patients and runs ensures the statistical validity of the computer simulation

Fig. 1. General architecture of the Markov model in ART illustrating the various pathways available to a patient undergoing a single ART treatment cycle (IVF/ICSI) after stimulation treatment option, e.g., r-hFSH or u-hFSH (a) and a single frozen embryo transfer cycle (b).

results and allows confidence limits to be generated for the outcomes.

RESULTS

The total number of ongoing pregnancies ($\pm$ SD) generated by running 5000 Monte Carlo simulations on a Markov cohort of 100,000 patients was $42,811 \pm$

3218 with r-hFSH and $39\,306 \pm 3251$ with u-hFSH ($p < 0.0001$). The cost per pregnancy achieved was $\text{€}12,791 \pm 1202$ ($\text{\$}11,346 \pm 1066$) and $\text{€}13,007 \pm 1,319$ ($\text{\$}11,537 \pm 1,170$), respectively. The difference between treatments was statistically significant in favour of r-hFSH ($p < 0.0001$). Overall treatment cost per pregnancy was reduced by 1.66% by replacing u-FSH with r-hFSH.

Table 1. Estimated Transition Probabilities and Associated Standard Deviations

Description	Probability (mean; SD)
Cancelled ovum pick-up	
r-hFSH	0.044; 0.01276
u-hFSH	0.064; 0.01276
No oocytes recovered	
r-hFSH	0.022; 0.00765
u-hFSH	0.026; 0.00765
IVF/ICSI split	0.550; 0.05102
No fertilization (IVF)	
r-hFSH	0.092; 0.01276
u-hFSH	0.082; 0.01276
No fertilization (ICSI)	
r-hFSH	0.092; 0.00510
u-hFSH	0.082; 0.00510
No embryo transfer (IVF)	0.040; 0.00510
No embryo transfer (ICSI)	0.030; 0.00510
No pregnancy (IVF)	
r-hFSH	0.650; 0.05612
u-hFSH	0.680; 0.05612
No pregnancy (ICSI)	
r-hFSH	0.640; 0.02041
u-hFSH	0.660; 0.02041
No OHSS (IVF)	0.990; 0.00510
No OHSS (ICSI)	0.985; 0.00765
Abnormal pregnancy with OHSS (IVF)	0.200; 0.02551
Abnormal pregnancy without OHSS (ICSI)	0.200; 0.02551
Abnormal pregnancy with OHSS (ICSI)	0.200; 0.02551
No embryos survived for frozen embryo transfer	0.400; 0.05102
No pregnancy after frozen embryo transfer	0.825; 0.06378
Abnormal pregnancy after frozen embryo transfer	0.260; 0.03061

Note. ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome; IVF = in vitro fertilization.

The model allows the number of treatment cycles required to obtain a successful outcome (i.e., ongoing pregnancy) to be calculated. Taking into account cycles cancelled before oocyte retrieval, and considering fresh and frozen embryo cycles together, the mean number of cycles per pregnancy was 4.69 with r-hFSH and 5.21 with u-hFSH.

DISCUSSION

This study shows that the use of r-hFSH rather than u-hFSH for controlled ovarian stimulation in ART is associated with significant cost-effectiveness gains for the Spanish public health care system. The use of r-hFSH results in a higher likelihood of achieving pregnancy in any given treatment cycle and the savings resulting from this intervention outweigh the

higher acquisition costs of r-hFSH compared with u-hFSH. The Markov model used in this study was developed specifically to compare cost-effectiveness of therapeutic regimen used in ART programmes. It uses specially written software and takes into account a large number of possible "health states." This model is thus able to represent the complex range of situations that arise in real ART programmes. The model has previously been applied to the UK National Health Service (6) and to the insurance-based health system of the USA (7) with broadly similar results. In adapting the inputs to the model to the Spanish situation, we have used the best available information, including results from published clinical trials and meta-analyses and the advice of a panel of Spanish clinicians with expertise in ART. The model used an evidence-based approach to discriminate between r-hFSH and u-hFSH (2). Clinical trials have repeatedly shown that the number of mature oocytes available for collection is higher following stimulation with r-hFSH compared with u-hFSH (10–16). Increased oocyte retrieval generates more embryos and hence more opportunities to use frozen embryos in subsequent cycles if necessary. This results in cost savings because frozen embryo cycles are less expensive than cycles using fresh embryos. Total consumption of FSH tends to be lower with r-hFSH than u-hFSH, reflecting a lower daily dose over a shorter treatment period (12,15,17,18). The greater efficiency of using r-hFSH offsets the higher acquisition costs of the drug compared with u-hFSH. Finally the higher efficacy of r-hFSH compared with u-hFSH is confirmed by a meta-analysis (2) showing that across all relevant trials pregnancy rate per started cycle is higher with r-hFSH (Follitropin- α , Gonal-F[®]) than with u-hFSH. The available evidence thus supports the key assumption of the model.

A limitation of the model is that only the direct costs of medication, medical procedures, and laboratory tests are considered. Other costs to the patient and to society such as time off work and travel expenses are not included. The use of r-hFSH would be expected to reduce these costs because its greater efficacy means that on average fewer cycles are required to obtain a pregnancy and hence less travel and time off work is required. However, this conclusion must be regarded as tentative until a study that explicitly includes such costs is carried out.

The results of this study are only valid for r-hFSH and u-hFSH in the context of a complete ART cycle. A reliable estimate of the cost-effectiveness of other drugs would require recalculation of the transition probabilities in the Markov model to take account

Table II. Cost Estimates for ART Procedures Included in the Model

Procedure	Cost (€/\$) ^a
<i>Fresh cycle</i>	
Ovarian stimulation	
r-hFSH (Gonal-F® 75 IU unit cost)	€30.63/\$27.17
u-hFSH (Neo-Fertinorm® /Metrodin® HP 75 IU unit cost)	€18.08/\$16.04
Other hormones (GnRH _a , hCG)	€167.41–282.71/\$148.49–250.76
Ultrasound (3–4)	€91.05–121.40/\$80.76–107.68
Consultations (3–4)	€89.33–111.66/\$79.24–99.04
Oocyte pick-up	
Ultrasound	€60.70/\$53.84
Fees	€535.97/\$475.41
Laboratory	
Fertilization (IVF)	€185.71/\$164.72
Fertilization (ICSI)	€492.23/\$436.61
Embryo transfer (catheter + disposables)	€166.72/\$147.88
OHSS	€1,669.52/\$1,480.86
Pregnancy determination	
HCG	€11.14/\$9.88
Ultrasound	€91.05/\$80.76
<i>Frozen cycle</i>	
Cryopreservation and embryo preparation	€313.67/\$278.23
Frozen embryo transfer	€178.74/\$158.54

^a€1 = \$0.887.

of any known differences in efficacy. The results are also specific to the circumstances of the Spanish public health system. Application of the model to other countries' health systems would require input from clinicians familiar with ART practice in that country, as has been done for the health systems of the UK (6) and the USA (7).

The use of a modelling approach rather than a comparative trial to perform an economic evaluation deserves some discussion. There is no doubt that the ideal situation, requires a randomised clinical trial, with sufficient power, stratification for important covariates, and comprehensiveness to account for all the possible scenarios involved in the multistep, multicycle treatment that is typical of ART, so that both costs and consequences can be ascertained adequately. Unfortunately, such a trial has never been undertaken. Consequently, one has to resort to economic modelling to address the issues regarding cost-effectiveness of interventions in the field of ART. This approach can provide information on the scale of the potential benefit (or harm) relative to cost of the intervention in question because all possible outcome scenarios can be evaluated. Further, the data gathered would help answer the question of whether a comprehensive trial is indicated, and what would be its design and sample size requirement. It would also guide researchers on what data should be collected.

The use of modelling is well established in many nonmedical sectors (e.g., modelling of aeronautical or

spatial trajectories, flood barrier deployment, and so on). It is also used in the medical sector in many areas, including assessment of cardiovascular prognosis and prediction of metabolic complications. However, because assumptions and estimation are critical elements in the use of modelling for economic evaluation, there are some limitations to this approach. First, modelling generally assumes that a relationship exists among the important variables being studied. Second, the estimates used are derived from the best evidence that is available so that bias can be minimized. Unfortunately, in the field of ART, most of the relevant data are obtained from randomised trials that have insufficient power to provide a high level of confidence in the estimates that can be used. Consequently, one has to resort to a synthesis of the available evidence using meta-analysis to obtain more reliable estimates, an approach that is not without controversy. Despite these concerns, modelling has the advantage of formalizing the evaluation process by forcing the investigators to explore all the possible outcomes and interactions among variables so that they can be incorporated in the model. No other techniques (except for a clinical trial that takes all these factors into account) would be powerful enough to account for all the variables that participate in achieving a successful outcome. Thus, modelling is appropriate for use when information from actual patient data is insufficient, incomplete, or not readily available, and it is not possible to await the results from trials

exploring all possible combinations of confounding variables and their influence on the outcomes in question, and reasonable assumptions can be made about the missing information. Furthermore, because clinical trials are expensive, modelling is particularly useful in reducing unnecessary waste of research resources in evaluating techniques and interventions that, even though effective, are unlikely to be cost-effective (19). In fact, economic modelling carried out before a trial is designed and funded will aid investigators in improving the quality and efficiency of the research (19).

There have been few previous studies on the pharmacoeconomics of ART in Spain. Some studies have considered the costs of the programme as a whole (i.e., cost per pregnancy or per live birth) rather than evaluating specific interventions (20,21). The estimates of cost per live birth derived from these studies ranged from €10,295 (\$9132) to €17,858 (\$15,840) and were thus broadly in line with our estimated cost per pregnancy (€12,791 with r-hFSH and €13,007 with u-hFSH; \$11,346 and \$11,537, respectively). Peinado and Peiró (22) evaluated four different regimens for controlled ovarian stimulation and concluded that highly purified u-hFSH was more cost-effective than human menopausal gonadotropin. This study provides evidence that the cheapest drug regimen is not necessarily the most cost-effective.

A direct cost-effectiveness comparison of u-hFSH and r-hFSH was performed by Larizgoitia *et al.* (23). These authors carried out a meta-analysis of published trials comparing u-hFSH and r-hFSH and concluded that the urinary preparation is the more cost-effective. The cost per pregnancy was estimated as €5,048 (\$4476) for r-hFSH and €3606 (\$3199) for u-hFSH. However, this study focused on pharmacological costs only and did not take into account savings in other areas that may result from the higher efficacy of r-hFSH. This omission casts doubt on the conclusions of the study. Balasch and Barri (24) performed a sensitivity analysis taking into account the entire cost of an ART cycle. They concluded that r-hFSH is more cost-effective than u-hFSH when all relevant costs are included and found that the break-even occurred when the cost of an ART cycle was between €600–900 (\$532–798). Our data indicate that the average cost of a cycle in the Spanish National Health System is approximately €1500–2000 (\$1331–1774). In the present study we have developed the work of Balasch and Barri by calculating more detailed cost estimates and by testing the assumptions behind their work using the computer simulation (Markov model).

These refinements provide strong support for the basic conclusions reached by Balasch and Barri.

Our findings have clear implications for clinicians and policymakers. The Markov model indicates that r-hFSH is more cost-effective than u-hFSH, while there is strong evidence from clinical trials that the recombinant product is more clinically effective. Hence, those clinicians who still use u-hFSH in their ART programmes should consider switching to the more effective r-hFSH. On the basis of our results, reimbursement of the cost of r-hFSH through the NHS should be seriously considered in spite of the higher acquisition costs of r-hFSH compared with u-hFSH.

The results presented here refer specifically to the public health sector in Spain. Markov modelling has also been applied using data from the private clinics that carry out the majority of ART cycles in Spain and the results will be reported elsewhere. Further cost-effectiveness studies of r-hFSH versus u-hFSH in different health systems are awaited.

CONCLUSIONS

Computer simulation using a robust Markov modelling procedure indicates that r-hFSH is more cost-effective than u-hFSH for ART in the Spanish National Health Service. This is due to the superior efficacy of r-hFSH, which means that fewer cycles are required on average to achieve pregnancy and overall drug consumption is lower. Clinicians and policymakers should favour the more effective recombinant product in spite of its higher acquisition cost.

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