Articles

Impact of urinary FSH price: a cost-effectiveness analysis of recombinant and urinary FSH in assisted reproduction techniques in the USA

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Abstract

This study compares the cost-effectiveness of recombinant human FSH (r(h)FSH, Gonal-F®) and urinary FSH (uFSH) in assisted reproduction techniques in the USA, using several hypothetical prices for uFSH. A specifically designed Markov model and Monte-Carlo simulation techniques were used to model the possible outcomes during three treatment cycles. Data included in the model were derived from randomized clinical trials and databases. An expert panel determined probability distributions for each decision point throughout each virtual treatment cycle. The assumed unit cost of r(h)FSH was $58.52 (based on the average retail cost) and three unit prices ($49, $45, $40) were used for uFSH. A total of 5000 simulations was performed on a virtual cohort of 100,000 patients. The mean number of assisted reproduction treatment cycles/success (ongoing pregnancy at 12 weeks) was 4.34 with r(h)FSH and 4.75 with uFSH. The total number of pregnancies achieved was 40,665 and 37,890, respectively. The mean cost per successful pregnancy with r(h)FSH was $40 688. For uFSH at unit costs of $40, $45 and $49, the mean costs per successful pregnancy were $43,500, $44,400 and $45,000, respectively (each $P < 0.0001$ versus r(h)FSH). Thus, despite its greater cost per unit dose, r(h)FSH is more cost-effective than uFSH over a wide range of uFSH prices, reflecting the greater clinical efficacy of r(h)FSH.

Keywords: *assisted reproduction techniques, computer modelling, health economics, recombinant FSH, urinary FSH*

Introduction

Infertility is estimated to affect at least 2.1×10^6 couples in the USA (Abma *et al.*, 1997) and is often associated with significant psychological distress and impaired social well-being. Refinements in assisted reproduction techniques such as IVF have enabled many previously infertile couples to conceive a child successfully. However, the costs of such treatment are high and, although 13 states have mandated insurance companies to provide some form of infertility treatment, the financial burden is usually borne by the couple themselves (Van Voorhis *et al.*, 1997). It is therefore important to identify measures that could reduce the overall cost of infertility treatment.

Health care policy makers, regulatory authorities, insurers and medical professionals are increasingly demanding cost-effectiveness analyses of medical interventions. Such analyses, however, are both expensive and technically difficult to perform in complex treatments such as assisted reproduction. Although conventional clinical trials can clearly demonstrate the efficacy of different interventions, they are usually inadequate to evaluate the cost-effectiveness of complex multi-step, multi-cycle assisted reproduction treatment regimens. A trial specifically designed to evaluate the cost-effectiveness of all possible treatment options in a typical assisted reproduction treatment programme would require an extremely large patient population and a long follow-up period, and hence is unlikely to be performed. For this reason,

computer-simulated pharmacoeconomic models have been developed to reproduce the conditions that exist in complex treatments and follow the progress of each patient through the treatment regimen.

In one such approach, Markov modelling (Briggs and Sculpher, 1998), patients are assigned a specific 'health state' that reflects their position in a treatment cycle; for example, in the case of assisted reproduction treatment, health states include ovarian stimulation, oocyte retrieval, fertilization, etc. Patients then progress through the programme in a series of changing health states according to estimated transition probabilities derived from clinical data (e.g. probability of successful or cancelled oocyte retrieval, probability of successful or failed oocyte recovery, probability of successful or unsuccessful fertilization, etc.).

Markov modelling studies in Greece and Italy have suggested that recombinant human FSH (r(h)FSH) is more cost-effective than urinary FSH (uFSH) in women undergoing assisted reproduction treatment (Mantovani *et al.*, 1999; Van Loon *et al.*, 2000). This finding is of particular interest, because uFSH preparations have a lower acquisition cost and remain widely used in assisted reproduction treatment, despite the fact that r(h)FSH has been shown consistently to result in both a greater oocyte yield (Out *et al.*, 1995, 1997; Recombinant Human FSH Study Group, 1995; Fisch *et al.*, 1995; Bergh *et al.*, 1997; Lenton *et al.*, 2000; Frydman *et al.*, 2000; Daya and Gunby, 2001) and a higher clinical pregnancy rate (Daya and Gunby, 1999), compared with uFSH. Although widely accepted, the previous Markov modelling studies used data from a limited number of clinical trials and included a relatively small number of health states. Furthermore, confidence limits for the clinical outcomes were not provided, making it impossible to determine whether the observed differences between treatments were statistically significant.

In view of the high costs associated with assisted reproduction treatment, it is essential to identify potential savings that could result from the use of more effective treatments; importantly, such savings could outweigh increased drug acquisition costs. For this reason, a Markov model was used to compare the cost-effectiveness of r(h)FSH and uFSH in assisted reproduction treatment cycles in the USA (Silverberg *et al.*, 2002). The results from this first study showed that r(h)FSH was more cost-effective than uFSH. Here, the validity of the outcome of the first study was tested using a range of hypothetical, but significantly lower, prices for uFSH. This approach allowed the impact of the price differential between r(h)FSH and uFSH on the relative cost-effectiveness of treatment to be evaluated.

Materials and methods

The Markov model used was developed by means of a customized computer program written in Pascal specifically for this study, because commercial software packages had previously been shown to be inadequate. The model has been described in detail elsewhere (Daya *et al.*, 2001; Silverberg *et al.*, 2002). In brief, the model compared the clinical and economic outcomes of r(h)FSH (Gonal-F®, Serono Inc., Rockland, MA, USA) and u-FSH (Fertinex®, Serono Inc.) during up to three complete treatment cycles. Virtual patients were passed through the model until they achieved either a clinical pregnancy or completed three treatment cycles,

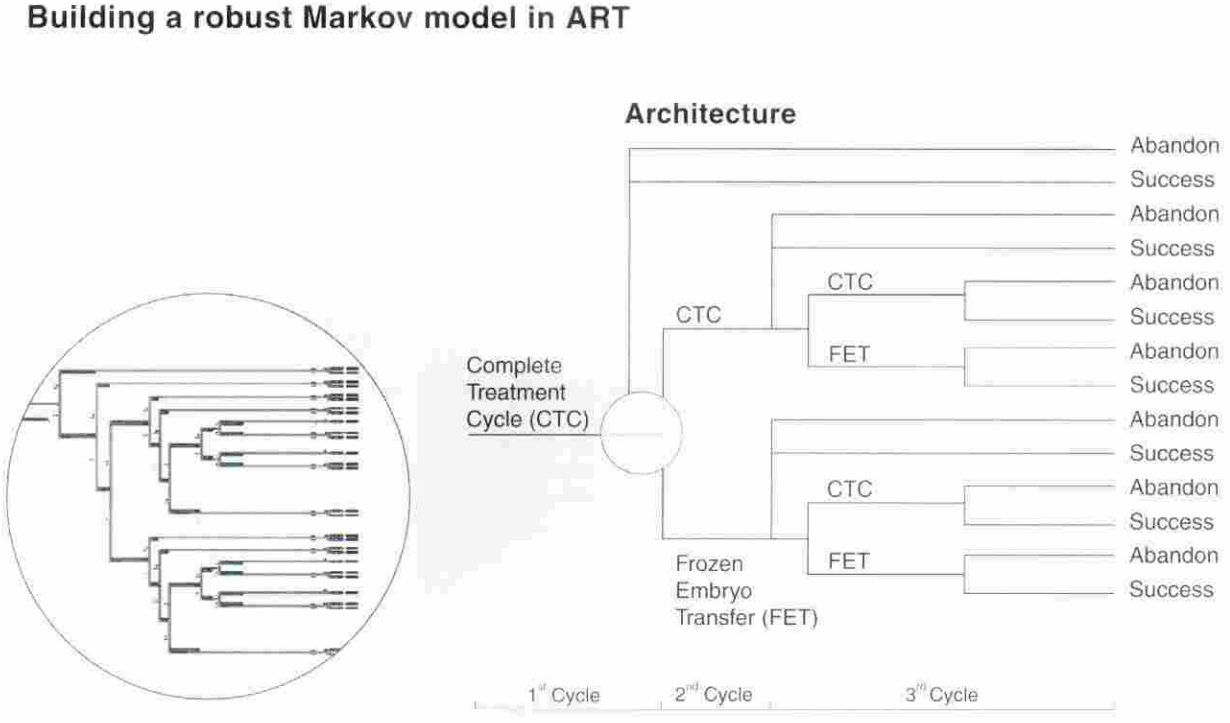

Figure 1. Simplified representation of the Markov model, illustrating all possible complete treatment and frozen embryo transfer cycles that can occur during a three-cycle assisted reproduction treatment programme with recombinant human FSH (r(h)FSH) or urinary FSH (uFSH) (Silverberg *et al.*, 2002). The insert shows the possible options during a single treatment cycle. (Reproduced with permission.)

whichever came first. By definition, the first cycle involved a fresh embryo transfer, while subsequent cycles (if needed) could involve either fresh or frozen embryo transfers. A simplified representation of the model is shown in **Figure 1**, which presents all the possible complete treatment cycle combinations that could occur.

The probabilities of transition between health states (for example, from oocyte retrieval to embryo transfer) were estimated from data from randomized clinical trials and from national IVF databases, such as that of the Society for Assisted Reproduction Technology (CDC). Because confidence limits for these estimates were not available, expert opinions were obtained from an international panel of practising clinicians with experience in clinical trials, epidemiology and statistics. For each probability associated with a health state, the panellists were asked to estimate the range that would include 95% of patients; from these ranges, the standard deviation for each probability was derived using the formula SD = range/(2 × 1.96). The estimated transition probabilities and associated standard deviations are those used in the original study (Silverberg *et al.*, 2002).

A Monte-Carlo technique (Doubilet *et al.*, 1985) was used to randomize the dispersion of outcomes at each stage of the treatment programme, in order to allow determination of standard deviations for the final outcomes (number of ongoing pregnancies, cost per pregnancy, number of cycles required per pregnancy).

A cost analysis for each health state included in the model was performed from a societal perspective (total costs) and from an insurer's perspective; for the latter analysis, it was assumed that managed care providers would reimburse 70% of total costs. Cost data were validated by a geographically representative survey of 100 assisted reproduction treatment clinics. The unit price of r(h)FSH was fixed at $58.52, because this represented the average retail cost obtained from a survey of 60 infertility speciality pharmacies. For uFSH, three hypothetical unit costs were used: $40, $45 and $49. These were chosen arbitrarily to represent significant savings on the cost of r(h)FSH. The additional costs included in the model are shown in **Table 1**.

The cost-effectiveness analysis was performed by passing a virtual population of 100,000 patients (the Markov cohort) through the computer simulation of the assisted reproduction treatment programme in each of 5000 Monte-Carlo simulations. This large number of patients and runs enhances the statistical accuracy of the simulation predictions and allows confidence intervals to be generated for the outcomes. The endpoints of this analysis were defined as ongoing pregnancy (confirmed by ultrasound) at 12 weeks for both fresh and frozen embryo transfers, and the overall cost of pregnancy achieved with either r(h)FSH or uFSH.

Results

After a maximum of three transfers, the total number of ongoing pregnancies was 40,665 ± 747 (SD) with r(h)FSH, compared with 37,890 ± 966 with uFSH ($P < 0.0001$). For the whole population, the mean number of assisted reproduction treatment cycles per success (ongoing pregnancy at 12 weeks) was 4.34 with r(h)FSH, compared with 4.75 with uFSH.

The mean societal cost per successful pregnancy in r(h)FSH cycles was $40,688. For uFSH at unit costs of $40, $45 and

Table 1. Procedures and associated costs included in the Markov model (Silverberg *et al.*, 2002).

Cycle	*Procedure*	*Detail*	*Cost ($)*
Fresh	*Ovarian stimulation*	r(h)FSH (unit cost)	58.52
		u(h)FSH (unit cost)	40.00
			45.00
			49.00
		Other hormones (OCP, GnRHa, HCG)	420.00
		Ultrasound (3-4)	700.00
		Consultations	325.00
	Oocyte retrieval	Ultrasound	169.00
		Facility and physician fees	3086.00
	Laboratory	Fertilization (IVF)	2514.50
		Fertilization (ICSI)	3864.50
		Embryo transfer (catheter + disposables)	847.00
		OHSS	1010.00
	Pregnancy determination	HCG	135.00
		Ultrasound	705.00
Frozen		Cryopreservation and embryo preparation	1010.00
		Frozen embryo transfer-facility and physician fees	847.00

r(h)FSH = recombinant human FSH; u(h)FSH = urinary human FSH; OCP = oral contraceptive pill; GnRHa = gonadotrophin-releasing hormone analogues; HCG = human chorionic gonadotrophin; ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome.

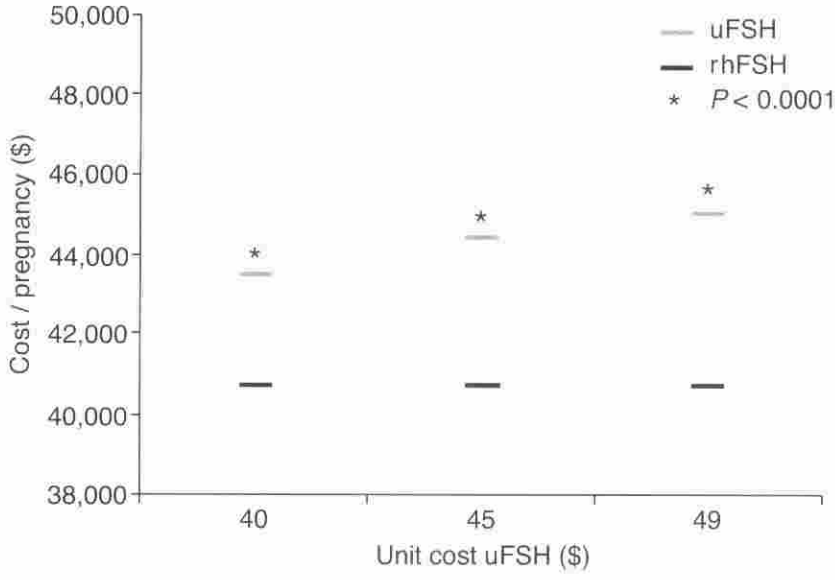

Figure 2. Graphical representation showing that the cost per pregnancy is significantly ($P < 0.0001$) lower with recombinant human FSH (r(h)FSH) than with urinary FSH (uFSH).

$49, the mean costs per successful pregnancy were $43,500, $44,400 and $45,000, respectively. In each case, the cost per successful pregnancy was significantly ($P < 0.0001$) lower with r(h)FSH than with uFSH (**Figure 2**). Similarly, when costs were analysed from an insurer's perspective, the mean cost per successful pregnancy was $28,481 with r(h)FSH, which was significantly lower ($P < 0.0001$) compared with $30,450, $31,080 and $31,500 with uFSH priced at $40, $45 and $49, respectively.

Discussion

The results of this study using a robust Markov modelling technique show that r(h)FSH is consistently more cost-effective than uFSH in assisted reproduction treatment over a wide range of uFSH price scenarios. This improved cost-effectiveness appears to be due primarily to the lower number of cycles required to achieve a successful pregnancy with r(h)FSH than with uFSH. Furthermore, r(h)FSH has been shown to result in a greater number of mature oocytes than uFSH does (Out *et al.*, 1995, 1997; Recombinant Human FSH Study Group, 1995; Fisch *et al.*, 1995; Bergh *et al.*, 1997; Lenton *et al.*, 2000; Frydman *et al.*, 2000; Daya and Gunby, 2001) and thus would be expected to generate more opportunities for subsequent, less expensive, frozen embryo transfers.

The finding that more pregnancies were achieved with r(h)FSH than with uFSH is consistent with those of a previous meta-analysis (Daya and Gunby, 1999). The added value of simulating effectiveness using computer models is that data for three successive cycles can be generated and analysed, an advantage over meta-analyses in which only one treatment cycle can be assessed.

This model was specifically designed to compare the use of r(h)FSH and uFSH in assisted reproduction treatment cycles in the USA. As such, assumptions concerning drug costs and the probabilities of achieving either success or failure for each health state were made based on US data. It is important to emphasize that this model, therefore, cannot be used to compare the costs associated with other drugs, or in other countries, without accounting for differences in efficacy, cost and transition probabilities between treatments. Simply substituting the acquisition costs of other drugs would produce an unreliable estimate of cost-effectiveness. Furthermore, the data used in this study were representative of clinical practice and the economic conditions prevailing in the USA. A study using the same model in the UK also showed that r(h)FSH was more cost-effective than uFSH (Daya *et al.*, 2001), but the difference in cost-effectiveness between the two treatments was less pronounced than in the present study, highlighting the importance of using validated data representative of the country in which the study is performed.

It is possible that the differences in costs associated with r(h)FSH and uFSH might be larger than reported in this study, since indirect costs such as travel expenses and time lost from work were not included in the model. Since fewer cycles were needed in order to achieve a successful pregnancy with r(h)FSH than with uFSH, it is possible that these costs might be reduced to a greater extent with r(h)FSH.

The use of a large Markov cohort and Monte-Carlo techniques allowed a large number of simulations to be performed, with probability estimates at every decision point in the model. As a result, this approach provided more precise estimates of the confidence limits for each outcome than can be achieved with traditional sensitivity analysis, in which a single variable (for example, one mean transition probability) is altered to investigate the impact on outcome measures. Sensitivity analyses usually focus on only a few key variables, resulting in potential selection bias; furthermore, alteration of a single variable does not take into account possible interactions

between variables. It is worth noting that r(h)FSH has also been shown to be more cost-effective than uFSH in studies with less robust and sensitive Markov models (Mantovani *et al.*, 1999; Van Loon *et al.*, 2000).

In conclusion, this study demonstrates that r(h)FSH is more cost-effective than uFSH in assisted reproduction treatment programmes in the USA. The difference was maintained over a range of uFSH prices. This finding highlights the fact that the cost-effectiveness of a drug depends on its clinical efficacy as well as its acquisition cost. The significantly greater cost-effectiveness of r(h)FSH compared with uFSH should be taken into account when making treatment decisions.

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