Article

Costs and outcomes associated with IVF using recombinant FSH

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Abstract

Cost and outcome estimates based on clinical trial data may not reflect usual clinical practice, yet they are often used to inform service provision and budget decisions. To expand understanding of assisted reproduction treatment in clinical practice, an economic evaluation of IVF/intracytoplasmic sperm injection (ICSI) data from a single assisted conception unit (ACU) in England was performed. A total of 1418 IVF/ICSI cycles undertaken there between October 2001 and January 2006 in 1001 women were analysed. The overall live birth rate was 22% (95% CI: 19.7–24.2), with the 30- to 34-year age group achieving the highest rate (28%). The average recombinant FSH (rFSH) dose/cycle prescribed was 1855 IU. Average cost of rFSH/cycle was £646 (SD: £219), and average total cost/cycle was £2932 (SD: £422). Economic data based on clinical trials informing current UK guidance assumes higher doses of rFSH dose/cycle (1750–2625 IU), higher average cost of drugs/cycle (£1179), and higher average total cost/cycle (£3266). While the outcomes in this study matched UK averages, total cost/cycle was lower than those cited in UK guidelines. Utilizing the protocols and (lower) rFSH dosages reported in this study may enable other ACU to provide a greater number of IVF/ICSI cycles to patients within given budgets.

Keywords: *cost, GnRH antagonist, ICSI, IVF, rFSH*

Introduction

Infertility is a condition estimated to affect one in seven couples (14%) in the UK [Human Fertilization and Embryology Authority (HFEA), 2008a]. Ovarian stimulation with a follicle stimulating hormone (FSH) followed by IVF or intracytoplasmic sperm injection (ICSI) is commonly used in assisted reproduction treatment.

Uptake of assisted reproduction in the UK appears to be increasing; the UK HFEA – the independent regulator overseeing safe and appropriate practice in fertility treatment and embryo research – reported approximately 42,000 IVF cycles undertaken in the UK during 2006–2007 compared with 34,000 in 1996–1997 (HFEA, 2008b).

The National Institute for Health and Clinical Excellence (NICE) is a UK body issuing evidence-based guidelines for disease management to the National Health Services (NHS). In 2004, NICE issued guidelines for assessment and treatment of fertility problems (National Collaborating Centre for Women's and Children's Health, 2004). In the guidelines, which were based on clinical trial results and subsequent economic analysis, NICE recommended that NHS should fund up to three cycles of IVF or ICSI (IVF/ICSI) for most women requiring assisted reproduction, finding such treatment to be effective and a cost-effective use of resources.

While clinical trials are the gold standard for establishing efficacy of a treatment, observation and analysis of real-life clinical practice also has great value in elucidating the cost and outcomes associated with treatments. The objective of the current study was to evaluate the utilization, costs and consequences of current assisted reproduction practice, particularly with recombinant FSH (rFSH), in a real-life clinical setting.

Materials and methods

The eligible subjects for this study were all the women who attended a single assisted conception unit (ACU), serving both NHS and private patients in England. The women had received IVF/ICSI between 28 October 2001 (the date from which electronic data collection was initiated) and 1 December 2006 (the date the study started). The clinic database enabled us to identify the fertility treatments that the women received in their treatment cycles whilst preserving anonymity. Assisted reproduction cycles eligible for analysis excluded non-IVF/ICSI treatment (e.g. if intrauterine insemination was used); cycles in which frozen embryo replacement was used, as this procedure does not involve FSH; and cycles for which rFSH prescribing/dispensing data were incomplete or unavailable.

Two sources of drug data were used, prescribed and dispensed. The prescribed dose was that written up in the patient notes and recorded in the ACU dataset, and the dispensed dose was that dispensed by the pharmacy. The pharmacy at the ACU manages the dispensing of rFSH closely to minimize wastage and keep the cost of the drugs to the hospital and patient as low as possible. Normal pharmacy practice is to have the rFSH dispensed in two batches, adjusting the second dispensed dose if the duration of stimulation is unpredictably prolonged due to slow ovarian response. Dosing increases during stimulation are rare.

Costing for clinic procedures was based on an internal financial audit of the ACU undertaken in 2002–2003. The audit comprised a detailed time and motion study and analysis of the majority of ACU procedures [i.e. insemination, counselling sessions, egg collection, embryo transfer, and embryology preparation, consultations (both medical and nursing), blood tests, scans]. Samples of each procedure were timed to obtain an average time of a stage within the IVF/ICSI procedure. During this process, the category of staff employed to undertake the particular stage was verified. The stages were medical consultation (new), medical consultation (follow-up), counselling session, nurse consultation and embryology. Non-staff costs associated with a stage [i.e. blood group testing; screening for HIV, hepatitis B or C, cystic fibrosis, syphilis; karyotype testing; other blood tests; ultrasound scans (baseline and pregnancy); procedure preparation; preparation for egg; egg collection; and preparation for embryo transfer] were also identified. In this audit, the main cost driver of all of the procedures was found to be staff time. The audit findings were utilized and assigned unit costs based on the medical resource use for the different procedures and then calculated an aggregated cost per procedure (**Table 1**). All costs were applied at UK 2007 prices.

It was possible to apply costs to the rFSH (prescribed and dispensed) and also apply costs to the other medications prescribed for each individual procedure and cycle of treatment for each patient. Drug prices were obtained from the British National Formulary (BNF, 2007) to ensure that the results could be generalized; however, it is important to note that UK hospitals often negotiate prices directly with drug companies, and the discounts obtained for the various IVF drugs can be substantial.

Rates of clinical pregnancies per cycle, ongoing pregnancies per cycle and live births were calculated from the clinic records. Using both the procedure and drug costs, it was possible to calculate an overall cost per IVF/ICSI procedure for each cycle, as well as the average cost per clinical pregnancy, ongoing pregnancy and live birth. Using these calculations, the average cost per outcome was determined.

During the study period, the women were treated with various ovulation stimulation protocols, according to need and ACU guidelines at the time. The majority of women received one of three protocols: a 'long' protocol, which starts with a gonadotrophin-releasing hormone (GnRH) analogue on day 21 to suppress the pituitary (normally a 2-week process); a 'short' protocol, which also uses GnRH analogues, which are administered at the start of the cycle; or an antagonist protocol, which uses GnRH antagonists for direct pituitary suppression (but has a shorter total length of treatment than the long protocol). Standard starting doses of rFSH for the three types of protocols was 150 IU/day for women under 35 and 200 IU/day for women 35 and over. The antagonist protocol became a specific focus of the comparative analyses, as use of this protocol was the exception at the start of the study period, but by the end of the study period, it had increased significantly (73% of all cycles given at the ACU). For this reason, it was thought it would be of interest and relevant to present the findings based on this newer protocol alongside those of all protocols combined, in terms of mean outcomes, drug utilization and costs.

For completeness, where a cycle was abandoned after initiation of treatment, a reduced cost (£1509) was allocated based on full costs less costs associated with fertilization and implantation.

Confidence intervals were generated using a non-parametric bootstrapping technique (Briggs *et al.*, 1997).

Results

The final study population comprised 1001 women receiving 1418 treatment cycles. From the 5260 cycles undertaken at the ACU during the study period, the following cycles were excluded: those in which patients received a gonadotrophin for ovarian stimulation other than the rFSH brand Puregon (n = 20), as the number was too small to make a robust comparison between treatments; those in which IVF/ICSI was not received (n = 2414) or frozen embryo replacement was used (n = 486); those in which IVF was not started or was undertaken at another centre (n = 829 cycles); and those for which prescribing and dispensing data were missing or incomplete (n = 93).

The mean age of the women contributing to the analysable data was 35.9 years (range: 22–49 years), with the greatest proportion of patients falling within the 35–39 years of age category (**Table 2**). Where the causes of infertility for each cycle were recorded in the analysable database, 33% were attributable to male factor and 31% to female factor; 15% were unexplained; and 21% had no cause listed or the infertility was due to some other cause.

The study compared (using the chi-squared test) the basic demographics of the final study dataset of 1418 IVF/ICSI cycles used for this analysis and the 232 cycles excluded from the analysis because insufficient data were available (e.g. IVF was never started or there were missing or incomplete prescribing/

dispensing data). The comparison revealed no differences between the two groups with respect to age, which is known to be an important predictor for assisted reproduction outcomes. Statistically significant differences between the groups were found for the cause of infertility, but these were not considered clinically significant.

At the end of the study period, the majority of patients attending the ACU were receiving rFSH as part of an antagonist ovarian stimulation protocol (66%); the long and short protocols comprised an additional 30% (**Table 2**). Mean duration of ovarian stimulation for each cycle was 9.1 days (95% CI 9.0–9.3 days), with oocyte retrieval successfully performed in 91% of cases. Most frequently, two embryos were transferred.

The clinical pregnancy rate was 36.4% (95% CI 33.9–38.9), the ongoing pregnancy rate was 24.4% (95% CI 22.1–26.5), and the live birth rate was 22.0% (95% CI 19.7–24.2) (**Table 3**). The cycles excluded (see above) were not statistically different from the analysed sample in terms of failure to become pregnant or ongoing pregnancy. The influence of age on live birth is illustrated in **Figure 1**, the highest rate of 28% being achieved in the 30–34 year age group.

Table 4 summarizes rFSH usage and the cost per cycle per pregnancy and live birth. The average prescribed rFSH dose per cycle was 1855 IU, while the average dispensed dose per cycle was 1891 IU. The average cost of rFSH per cycle was £646, and the average cost of concomitant medications per cycle was £159. The average cost per cycle for clinic procedures was £2127, and the average total cost per cycle was £2932. The average costs per clinical pregnancy, ongoing pregnancy and live birth were £8058, £12,017 and £13,326 respectively. **Table 5** gives a breakdown of utilization and costs per cycle by age group.

Mean outcomes, drug utilization and costs by the most commonly used assisted reproduction protocol (i.e. antagonist ovarian stimulation) and all protocols combined are shown in **Table 6**. The average total cost of assisted reproduction per patient was £2932 overall and £2967 with the antagonist protocol and £2874 for the other protocols deployed.

Table 1. Cost (£ sterling) per procedure.

Procedure	*IVF*	*IVF + ICSI*	*FER*
Visits and tests	1520	2228	906
Retrieval	212	212	–
Fertilization	53	53	–
Implantation	106	106	95
Total	1891	2599	1001

ICSI = intracytoplasmic sperm injection; FER = frozen embryo replacement.

Table 2. Demographic and treatment data for women receiving IVF/ICSI with pharmacy data (analysable population).

		n *(%)*
Number of women		1001
Number of cycles		1418
Age (years) at time of IVF/ICSI cycles	<30	112 (11)
	30–34	259 (26)
	35–39	384 (38)
	>40	246 (25)
Ovarian-stimulation protocol used	Antagonist	929 (66)
	Long	169 (12)
	Short	249 (18)
	Missing data	61 (4)
	Other	10 (1)

ICSI = intracytoplasmic sperm injection.

Table 3. Pregnancy outcome for analysable IVF/ICSI cycles (*n* = 1418).

Outcome		n	*Percentage of total cycles (95% CI)*
Pregnancy status	Not pregnant	900	63.0
	Missing data	2	0.1
	Clinical pregnancies	516	36.4 (33.9–38.9)
	Ongoing pregnancies	346	24.4 (22.1–26.5)
Pregnancy outcome	Live births	312	22.0 (19.7–24.2)
	Not available[a]	30	2.1
	Still births	4	0.3
	Ectopic pregnancies	10	0.7
	Miscarriages	155	10.9
	Terminations	5	0.4

CI = confidence interval.
[a]Patients lost to follow-up or not having reached their due date at the time of this analysis.
Note: The difference between the ongoing pregnancy rate and live birth rate is accounted for by the stillbirths and patients lost to follow-up or not having reached their due date at the time of this analysis.

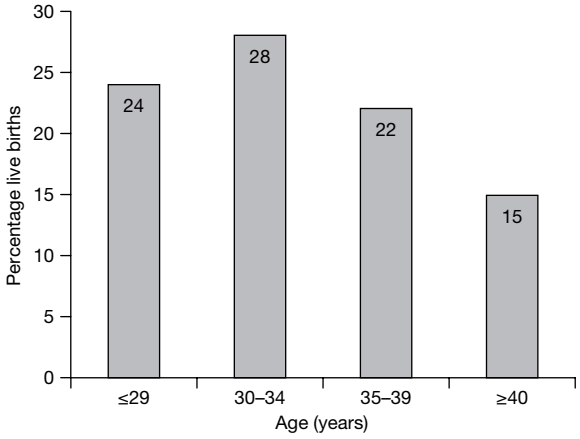

Figure 1. Live birth rates by age of woman at time of cycle.

Table 4. Average recombinant FSH (rFSH) usage and cost per cycle/pregnancy/live birth.

	Mean	*Standard deviation*
Dose prescribed (IU) per cycle	1855	576
Dose dispensed (IU) per cycle	1891	588
Cost[a] per cycle (rFSH)	646	219
Cost[a] per cycle (concomitant medications)	159	122
Cost[a] per cycle (procedure costs)[b]	2127	349
Total cost[a] per cycle	**2932**	422
Cost[a] per clinical pregnancy	8058	
Cost[a] per ongoing pregnancy	12,017	
Cost[a] per live birth	13,326	

[a]All costs in pounds sterling (£).
[b]Data from financial audit of the ACU undertaken in 2002/2003.

Table 5. Mean recombinant FSH (rFSH) usage and cost per cycle by age group.

	Age group (years) *≤29*	*30–34*	*35–39*	*≥40*
Sample size	150	354	553	361
Dose prescribed (IU) per cycle	1481	1726	1844	2154
Dose dispensed (IU) per cycle	1658	1791	1884	2098
Cost[a] of rFSH	576	611	643	716
Cost[a] per cycle (concomitant medications)	174	160	171	133
Cost[a] per cycle (procedure costs)	2251	2155	2125	2050
Total cost[a] per cycle	3001	2926	2939	2899

[a]All costs in pounds sterling (£).

Table 6. Mean outcomes, drug utilization and costs.

	Protocol Antagonist cycles (n = 929)	*All cycles combined[a] (n = 1418)*
Clinical pregnancies (%)	39	36
Ongoing pregnancies (%)	27	24
Live births (%)	24	22
Duration of stimulation (days)	9.32	9.14
Total dose prescribed (IU)	1718	1855
Total dose dispensed (IU)	1815	1891
Total cost per assisted reproduction cycle (£ sterling)	2967	2932

[a]Sixty patients with protocol information missing.

Discussion

The real-life costs and outcomes of assisted reproduction for women treated at a single ACU in England were assessed. Whilst this reflects the case mix and practices at the ACU, interesting differences emerged between the present findings and those based on clinical trials and the associated economic analyses used to inform UK guidance regarding assisted reproduction and its reimbursement. For example, that guidance assumes that the FSH dose per cycle ranges from 1750 to 2625 IU, the cost of drugs per cycle is £1179, and the total cost per cycle of IVF/ICSI is £3266 (National Collaborating Centre for Women's and Children's Health, 2004). These findings are based on observational data from a single centre, but one that rigorously implemented its treatment protocols and standardized practice over the 5-year period from which the data in this study came. The findings showed a lower average rFSH dose per cycle (1855 IU), a lower average cost of rFSH per cycle (£646), and a lower average total cost per cycle of IVF/ICSI (£2932). The live birth rate (22%) from the cycles included in this study, however, was consistent with the UK average of 21.6% (2005 data) (HFEA, 2008).

It is reasonable to think that equivalent outcomes to those in this ACU are potentially achievable in other, similar ACU. The outcomes were achieved with drug utilization and costs below those assumed by NICE. It is possible that by substituting rFSH as used in the protocols in this ACU's clinical practice, there is the potential to reduce the cost per cycle in other centres. The antagonist protocol, with its low-dose rFSH stimulation, shorter duration of treatment, fewer side effects, and lower risk of ovarian hyperstimulation, may enable other ACU to increase the number of fertility treatments within a given budget. This study, however, should be replicated in other UK centres to ensure that the predicted cost savings are reproducible.

The present findings complement those from a large multicentre observational study conducted in Germany (Ludwig *et al.* 2004) analysing 54,487 assisted reproduction cycles (37,991 women) from 74 ACU over a period of 12 months (January to December 2002). In that study, the mean ages of patients in the rFSH and GnRH groups were 32.6 and 33.4 years respectively, and the duration of stimulation was 11.7 days in both groups. The live birth rate was 16.9% (3214 live births out of 19,008 cycles) in the rFSH group compared with 14.5% (837 live births out of 5756 cycles) in the GnRH group, the difference being statistically significant. Overall, more gonadotrophin was required in the GnRH group (2828 IU per cycle) than in the rFSH group (2325 IU per cycle). It is of interest to note that the mean age of the women included in the analysis (35.9 years) was somewhat older than in the German study, yet the live birth rate was higher (22%). This is an important factor to bear in mind when reviewing the results of the analysis, as the success rate of IVF diminishes as patient age increases, which was evident in the analysis.

Two economic evaluations of assisted reproduction undertaken using UK data (Daya *et al.*, 2001; Sykes *et al.*, 2001) report favourable cost–effectiveness outcomes for rFSH compared with non-recombinant FSH for ovarian stimulation in IVF. Two other studies also report favourable cost–effectiveness for non-recombinant FSH compared with rFSH (Lloyd *et al.*, 2003; Wechowski *et al.*, 2007). All four studies present a range of costs for different pregnancy outcomes; however, these cost–effectiveness analyses utilize clinical trial data and stimulation protocols rather than observational data and may not be representative of real life practice.

It was possible to compare the rFSH prescribed and the rFSH dispensed. The amounts were consistent and reflect the careful control of dispensing by the pharmacy team and the local protocols to fine tune dispensing and minimize waste.

The ACU currently utilizes an antagonist protocol with low-dose FSH stimulation in the majority of cases. The resource use and associated costs reported, however, are specific to the clinic's case-mix over the full study period, the shift over time toward predominant use of the antagonist protocol and the individual selection of patients to receive the different stimulation protocols. The long (and ultra-long) protocols in this centre are now only used in a minority of cases, namely those with severe endometriosis and those with previous dyssynchronous follicular response to the antagonist protocol; the short protocol is reserved for predicted poor responders and women over age 40.

A recent meta-analysis of 22 randomized controlled trials involving 3176 patients compared the probability of live birth in patients receiving GnRH agonists and GnRH antagonists for pituitary suppression (Kolibianakis *et al.*, 2006). Antagonists and agonists were equally effective in achieving a live birth (odds ratio 0.86, 95%, CI 0.72–1.02). Subgroup analyses indicated that the result was not affected by type of agonist, type of antagonist, type of protocol, or type of gonadotrophin used.

The outcomes shown in this study (**Table 6**) reflect results from the full study population and the antagonist-protocol sample. Results for the other individual protocols are not presented because of the comparatively low proportion of the use of the long and short protocol samples and the steady shift of preference over time to antagonist protocols, such that it was used in nearly 70% of the cycles by the end of the study period. This change in case mix should be considered when evaluating these results in comparison with those of other ACU.

In addition to the analysis of the cycles of treatment, it would have been ideal to present the costs and consequences of treatment per patient, incorporating costs and outcomes for any frozen embryo replacement (FER) cycles received. This type of analysis would have been desirable to further reflect real-life practice. Unfortunately, the database did not allow us to link individual FER cycles with the initial IVF procedures, so it was not possible to evaluate and include the extra benefit and cost of frozen cycles in this analysis. Despite this, based on the clinic audit data, it was possible to make an estimate of £1101 for the cost of a FER cycle. It would be important to factor the impact of incorporating FER cycles into evaluation of assisted reproduction in further studies.

The costs used in the analysis are 2007 British National Formulary (BNF) prices; however, UK hospitals often negotiate directly with drug companies. Discounts negotiated with hospitals that have significant buying power are not uncommon, and discounts for one or all of the IVF drugs in use can be substantial. To ensure that the results for the analysis described

here can be generalized, standard BNF prices for all drugs were used.

According to the UK National Infertility Awareness Campaign, there continues to be wide variation in the number of cycles funded by the government and little progress toward full implementation of NICE's recommendations on infertility treatment in the UK (Infertility Network UK, 2008). It is likely that cost and access to assisted reproduction contribute to this situation. Although caution must be exercised in the interpretation of the observational data used for this analysis and the results need to be validated in other studies, the present findings may represent a step forward in demonstrating that assisted reproduction can be both effective and achieved at a lower cost than originally predicted by NICE. The UK Government should revisit the affordability of funding recommended levels of IVF/ICSI in light of the better value offered by IVF/ICSI in real-life practice, taking efficient drug-delivery practices into account.

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