Pharmaco-economic aspects of in-vitro fertilization in Italy

L.G. Mantovani¹, A. Belisari and T.D. Szucs

Center of Pharmacoeconomics, Institute of Pharmacological Sciences, University of Milan, Via Balzaretti 9, I-20133, Milan

¹To whom correspondence should be addressed

Given the higher efficacy of follitropin-beta, a new recombinant follicle stimulating hormone (r-FSH), versus urinary-FSH (u-FSH), the present study was carried out to evaluate the cost-effectiveness ratio (CER) of follitropin-beta in comparison with u-FSH in women undergoing in-vitro fertilization (IVF) in Italy. Clinical decision analysis techniques were used to retrospectively model the direct medical costs of women undergoing IVF treatment. Seven Italian experts were interviewed, using a semi-structured questionnaire, in order to adapt the results of all clinical trials to the Italian patterns of care. Three analyses were conducted considering the public, the private sectors and a mixture of them (currently representing the Italian situation). The estimated total cost of IVF treatments varies from 106.9 and 211.7 billion Lire (63.2 and 125.2 million US$) depending on setting and type of treatment. The average CER varies from 21.5 and 37.7 million Lire (12 700 and 22 300 $US) in the different hypotheses considered. The incremental CER varies from 19.2 and 26.0 million Lire (11 300 and 15 400 $US) depending on setting and type of treatment.

Key words: costs/cost-effectiveness analysis/in-vitro fertilization/Italy/recombinant FSH

Introduction

Upwardly spiralling medical costs across Europe as well as the unique burden associated with managing diseases have sensitized health care decision-makers worldwide in both the private and the public sector to the problems of scarce resources and competing interventions. In-vitro fertilization (IVF) was introduced in 1978 and has resulted in thousands of pregnancies and opened a new frontier of research and treatment for the infertile couple (Jennings et al., 1996). Since then the use of these techniques has become more and more widespread, both geographically and quantitatively, now being an important issue for decision makers. Consequently, several economic evaluations have been made to explore feasible as well as efficient ways to implement these procedures (Botes, 1988; Setchell and Howell, 1992; leCotonnec et al., 1993; Hugues, 1994; Ratcliffe, 1994; Visscher, 1994; Bates and Bates, 1996; Collins, 1994; Collins, 1995; Daya, 1995; DeCherney, 1995; Dillner, 1995; Fourie and Gissler et al., 1995; Gocial, 1995; Lambert et al., 1995; Van Voorhis et al., 1995; Ryan and Donaldson, 1996). Until recently, urinary follicle stimulating hormone (u-FSH) products were widely used for the treatment of fertility. Follitropin-beta (Puregon®) is a new recombinant FSH (r-FSH) product which has been studied in several clinical trials (Geurts et al., 1996; Out et al., 1997). Although this compound has been investigated thoroughly on the clinical side, no pharmaeconomic data have been reported so far. Because local treatment patterns may vary considerably, the economic evaluation must be conducted on a national level taking local treatment and costs into account as much as possible. An analysis of cost and consequences of clinical practices on the treatment of infertility in Italy is interesting to both the provider and the consumer. An analysis of the practice of IVF procedures in Italy was conducted as a basis for an economic assessment of the use of u-FSH versus r-FSH.

Materials and methods

Analytical model

Clinical decision analysis techniques were used to retrospectively model the direct medical costs per woman undergoing IVF treatment. A Markov chain model (Briggs and Sculpher, 1998) was used to estimate the clinical and economic outcomes of the two different strategies during three cycles, which are most frequently applied in Italy. This type of model allows configuration of the likely future economic and clinical consequences of different therapeutic alternatives and allows modelling of the mid- and long-term evolution of health states over a specified time period. It provides also an immediate assessment of the economic as well clinical impact of different therapeutic options to society and other relevant subjects (e.g. patients and the national health service). In order to use the results of the clinical trials for the economic analysis in Italy and to obtain local treatment and management pathways, Italian IVF specialists were identified. Seven experts were interviewed, chosen to represent different Italian regions (Lombardia, Toscana, Emilia-Romagna, Lazio, Puglia, Campania, Sicilia) where 63% of the total Italian population (1995) lives and where the IVF treatment is considered to be currently most widely performed on the basis of FSH market data (Organon Italy, personal communication). Experts are also representative of the different geographic areas (north, centre and south), typology of centres (public and private) and originate from regions where an estimated 70 to 90% of women undergoing IVF in Italy are currently being treated. A semi-structured questionnaire was developed and administered to experts during the period June-July 1997. These data sources (clinical trials and expert opinions) together with published literature rendered the necessary data required for the model.

Efficacy data

It has been shown that r-FSH has improved efficacy/effectiveness as compared with u-FSH preparations, e.g. more pregnancies and a
shorter treatment period with a lower total dose of FSH (Out et al., 1995). The results of a recent meta-analysis of three prospective, multicentre, randomized and comparative trials confirm the superiority of r-FSH versus u-FSH (Out et al., 1997). A 5% statistically significant difference was found in the ongoing pregnancy rate at 12 weeks and a 6.4% difference when the cryoprogam was included.

Cost data
Because of the fact that infertility is usually not considered as a disease, according to the classic World Health Organization definition, the current reimbursement practice of IVF procedures in Italy is rather complex. No national health service (NHS) tariff exists for IVF treatment in Italy, although there are proposals made by the Italian Ministry of Health. Therefore, private tariffs have been used as a proxy for the costing of IVF treatment, since 70–90% of the IVF cycles are performed in the private setting. Hence, no average public data on tariffs for the various regions are available. The NHS perspective was only considered for drugs because these are reimbursed by the NHS. With regard to the reimbursement of recombinant FSH it has been assumed that r-FSH (Puregon®) is reimbursed at the same level as u-FSH (Metrodin HP®). Table I gives an overview of the costs per cycle of the private tariffs used in the model. The costs of urinary FSH and recombinant FSH were based on the average number of international units (IU) used in the study of Out et al. (1996). These were 2385 IU of urinary and 2137.5 IU of recombinant FSH. Since urinary FSH is no longer available on the market, the cost of highly purified urinary FSH was incorporated into the model. Although it is likely that urinary FSH and highly purified urinary FSH differ in safety, it cannot be assumed that they are different in efficacy, which is the focus, together with costs, of this analysis (leCotommec et al., 1993; Hugues, 1994; Lambert et al., 1995). Since national tariff codes and real cost data for IVF procedures are not widely available, and differ from region to region, it was necessary to use the private tariffs as a proxy for the public setting. In addition, for the public setting the cost overview from one of the centres was also considered, because it allowed us to employ this in each individual step of the IVF procedure.

Analyses
Three analyses have been conducted from the different perspective of the patients, of the NHS, and of society; the public sector, the private sector, and a mixture of the two (currently reflecting the Italian situation) were also considered. Costs in the private sector were calculated using a weighted average of the number of IVF cycles (all-inclusive) prices provided by experts (Table I). The weighting algorithm was based on the market size of IVF drugs in the seven regions. The amount of IVF drugs sold in the region was calculated as a proportion of total IVF drugs sold in all seven regions. To analyse the cost-effectiveness of r-FSH used for IVF procedures performed in the public sector we used real costs provided by one of the centres (Table II). These costs have been calculated by splitting IVF into single procedures and attributing materials, personnel and structure cost to those procedures. Although this may not represent all public hospitals in Italy, it nonetheless provides an idea of the possible costs in public hospitals. Fattore and Lazzaro (1998) conducted a survey investigating IVF costs in eight Italian IVF centres, which yielded results consistent with those presented in Table II. Finally the cost (and effectiveness) of IVF was calculated according to the current situation in which an estimated average of 80% of IVF treatments are performed in the private sector and 20% in the public sector. Since the number of pregnancies is unlikely to vary depending on the ownership of the centre (public versus private), while it is more likely that costs may be different, we focused on the latter. The average cost to society was calculated using costs calculated as described before and weighting them with the proportion of treatments performed in the public and in the private sector. Average and incremental cost-effectiveness ratio were calculated. The first is defined as the ratio between total cost and total effectiveness, e.g. total cost of IVF treatment using u-FSH divided by the number of pregnancies achievable using u-FSH. Incremental cost-effectiveness ratio is defined as the ratio between the difference in total cost and the difference in total effectiveness, e.g. total cost using r-FSH minus total cost using u-FSH divided by number of pregnancies achievable with r-FSH minus the number of pregnancies achievable with u-FSH. Figures are expressed also in US dollars (exchange rate, 1 $US = 1690 Italian Lire).

Sensitivity analysis
Sensitivity analysis was performed to test the robustness of the model following standard techniques such as one-way and two-way analyses on key parameters (Drummond et al., 1987).

Results

Model
As a result of validating the decision model to the Italian setting, a previously not anticipated option was suggested by the local experts and subsequently added to the model (Figure 1). This included a thawed embryo transfer after resolution of an ovarian hyperstimulation syndrome (OHSS) as stated by the expert panel. This approach, however, occurs

Table I. Weighted private cost for IVF cycle (in million Lire)

<table>
<thead>
<tr>
<th>Region</th>
<th>FSH marketa (IU) Weightb</th>
<th>Range of cost per cyclec</th>
<th>Median value</th>
<th>Median weighted value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lombardia</td>
<td>20 604 300 0.181</td>
<td>5–10</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Emilia-Romagna</td>
<td>7 681 200 0.068</td>
<td>5–20</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Toscana</td>
<td>7 278 825 0.064</td>
<td>5.5</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Lazio</td>
<td>14 436 375 0.127</td>
<td>8–10</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Campania</td>
<td>28 822 575 0.254</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Puglia</td>
<td>14 108 325 0.124</td>
<td>5–6</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Sicilia</td>
<td>20 634 450 0.182</td>
<td>3–9</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>113 566 050 1.000</td>
<td></td>
<td>5.85</td>
<td></td>
</tr>
</tbody>
</table>

IVF, in-vitro fertilization; FSH, follicle-stimulating hormone.

*aSource of market data: Organon Italia S.p.a., personal communication.
*bIU sales in the region/IU sales in the seven regions.
*cSource: experts’ survey.
only rarely. The corresponding transition probabilities for the various branches of the decision tree model are given in Table III.

**Costs**

Results of the questionnaire have allowed quantification of treatment patterns in Italy and derivation of the costs of IVF treatment in Italy. Costs considered in the analyses are listed in Tables I and II. They relate to drugs used in IVF and to procedures normally performed on patients undergoing IVF, as they were described by the panel. The average weighted private cost for IVF treatment (excluding the drugs) was also estimated. This was calculated at around 5.85 million Lire per patient (3400 $US) (Table I).

**Cost-effectiveness**

An incremental cost effectiveness ratio was estimated for the private sector, the public sector, and also for the current situation (Table IV). These were based on the simulation on a time horizon of 1 year of treatment with r-FSH versus u-FSH of a cohort of 10,000 patients undergoing IVF in Italy. This number corresponds, based on the answer of the panel, to the estimated number of women who undergo IVF yearly in Italy. The analysis was limited to the third cycle. The cumulative
**Table III.** Probabilities used in the model

<table>
<thead>
<tr>
<th>Probability of</th>
<th>Puregon (%)</th>
<th>Metrodin HP (%)</th>
<th>Difference (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer</td>
<td>85.5</td>
<td>83.1</td>
<td>2.4</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>Undergoing frozen procedure</td>
<td>63.2</td>
<td>64.7</td>
<td>–1.5</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>Thawed transfer</td>
<td>33.3</td>
<td>26.5</td>
<td>6.8</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>OHSS</td>
<td>3.2</td>
<td>2.0</td>
<td>1.2</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>Pregnancy direct</td>
<td>22.2</td>
<td>18.2</td>
<td>4.0</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>Pregnancy frozen</td>
<td>5.4</td>
<td>2.0</td>
<td>3.4</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>Total pregnancy</td>
<td>27.7</td>
<td>20.4</td>
<td>7.3</td>
<td>Out et al. (1997)</td>
</tr>
<tr>
<td>Pregnancy rate (direct, 12 weeks)</td>
<td>22.9</td>
<td>17.9</td>
<td>5.0</td>
<td>Out et al. (1995)</td>
</tr>
</tbody>
</table>

OHSS, ovarian hyperstimulation syndrome.

*Pregnancy rate after 12 weeks can be used to estimate the delivery rate, since a negligible proportion (1%) of women pregnant at 12 weeks will not reach term (Organon, personal communication). Differences in decimal are attributable to rounding off in efficacy compared to that reported in Out et al. (1995).

**Table IV.** Results

<table>
<thead>
<tr>
<th>Effectiveness (units)</th>
<th>Metrodin HP</th>
<th>Puregon</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>4 966</td>
<td>6 221</td>
<td>1 255</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost (million Lire)</th>
<th>Total cost</th>
<th>Total cost</th>
<th>Incremental cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public sector</td>
<td>106 950</td>
<td>139 590</td>
<td>32 640</td>
</tr>
<tr>
<td>Private sector</td>
<td>187 592</td>
<td>211 713</td>
<td>24 121</td>
</tr>
<tr>
<td>Current situation</td>
<td>171 603</td>
<td>197 113</td>
<td>25 510</td>
</tr>
</tbody>
</table>

**Cost-effectiveness ratios (CER)**

- **Average CER**
  - Public sector: 21.54
  - Private sector: 37.78
- **Incremental CER**
  - Public sector: 26.01
  - Private sector: 19.22

*Current situation (80% private, 20% public)*

- **Average CER**
  - 34.56
- **Incremental CER**
  - 20.33

*Average CER, total cost/number of pregnancies.

Incremental CER, (total cost Puregon® – total cost Metrodin HP®)/(number of pregnancies Puregon® – number of pregnancies Metrodin HP®).

Pregnancy rates, including thawed embryos, on the basis of the model was 62.2% for r-FSH and 49.66% for u-FSH over three cycles, thus leading to an excess of 1255 (6221 versus 4966) pregnancies in the cohort treated with r-FSH. There would be a global 22 457 started IVF cycles in the r-FSH cohort and 24 323 in the u-FSH group. The difference is attributable to the higher pregnancy rate of r-FSH compared to u-FSH, which would limit the number of second and third cycles started in the r-FSH cohort. According to this model the total cost of r-FSH and u-FSH would be 72 and 36.5 billion Lire respectively.

Given the current situation in which an estimated 80% of IVF procedures is performed in the private sector and the remainder in public settings, the total cost was estimated (Table IV) as 197.1 billion Lire (116.6 million US$) for r-FSH and 171.6 billion Lire (101.5 million US$) for u-FSH, with an average cost-effectiveness ratio of 31.6 million Lire (18 700 US$) for r-FSH and 34.5 million Lire (20 400 US$) for

**Figure 2.** (a) Sensitivity analysis, one-way. (b) Sensitivity analysis, two-way.

u-FSH [the incremental cost would be 25.5 billion Lire (15.1 million US$), leading to an incremental cost-effectiveness ratio of 20.3 million Lire (12 000 US$)].

Results for the cases in which all the IVF treatments were performed either in the public sector or in the private sector are similarly presented in Table IV.

**Sensitivity analysis**

To test the robustness of the calculations, a univariate sensitivity analysis was conducted on the most relevant parameters (public sector, NHS perspective). The parameters were therefore varied by ± 20%, e.g. the pregnancy rate (including thawed embryos) of Puregon® (27.7%) was used and multiplied either by 1.2 (= 33.24%) or by 0.8 (= 21.76%). Results are presented in Figure 2a,b together with the two-way sensitivity analysis on both effectiveness and cost on Puregon® (simultaneous 20% increase in effectiveness and decrease in cost; simultaneous 20% decrease in effectiveness and increase in cost). The incremental cost effectiveness ratios were highly sensitive to changes in cost and efficacy/effectiveness of Puregon®.
Discussion

Analyses of costs and outcomes may resolve many issues around IVF, but only when ethical judgments and social values are taken into account. The present data, however, can elucidate the economic implications of in-vitro fertilization and thus inform on the ongoing debate. Efficiency is not, however, the only goal of public health policy. It should be based on efficacy and effectiveness and should be combined with legal as well as social aspects.

Regarding social aspects, there appears to be evidence of value placed in going through IVF, even if the couple remains childless (Ryan, 1996). Unfortunately, only a few such studies have been performed to date and some have given large ranges, depending on how the questions were framed (Neumann and Johannesson, 1994; Ryan, 1996). Results of the present study are in line with the more recent analyses of cost and effects of IVF treatments, although such analyses have been conducted in different countries, with different health-care systems (Collins et al., 1997; Fattore and Lazzaro, 1998; Walter-Hanssen and Rydhstroem, 1998). Previous economic analyses have not addressed the economic benefit of r-FSH versus u-FSH, but rather the overall cost-effectiveness of the IVF procedure itself. The present analysis is, to the best of our knowledge, the first cost-effectiveness analysis of recombinant versus u-FSH in Italy. In spite of significantly higher acquisition costs, r-FSH compares favourably to u-FSH in the present study. It goes without saying that the value of a technology has not only to be assessed on the basis of its price but on its overall impact, in order to avoid misleading conclusions.

The total estimated cost to society according to the current situation would amount to approximately 197.1 million Lire and to 171.6 billion Lire (116.6 and 101.5 million SUS) per year in the r-FSH and in the u-FSH cohort respectively. In addition, the cost of days lost from work and patients’ travel expenses would have to be added to this figure, to capture the overall societal costs. These costs have not been included in the analysis because of the large variability of employment status among women from different centres and because of the large proportion of women referring to centres but coming from other (even very distant) areas characterized by different employment rates. It is reasonable that given the higher efficacy of r-FSH, women would undergo fewer treatments compared to u-FSH, thus leading to a more favourable cost effectiveness ratio for Puregon®. Unfortunately IVF techniques have been excluded from many health-care provision systems, e.g. third party payers, governments and health plans, as infertility is often viewed as a social condition, not a medical condition, and coverage for infertility diagnosis and treatment is often viewed as unnecessary in the bundle of health-care services provided.

It should be pointed out that in general, recombinant technologies have additional advantages, e.g. the possibility of achieving a theoretically unconstrained supply of the active principle, whereas urine-derived technologies have limitations on the availability of raw materials. This study suffers from potential limitations, related to the fact that this analysis is based on an adaptation to Italy of a meta-analysis of clinical trials and of a clinical trial itself. Any statement on how good an adaptation this is must eventually rely on a judgement of the representativeness of experts; about this, it should be acknowledged that every possible effort has been made to choose representative experts and to get valid answers (e.g. consistency of experts’ answers with market data where sought and found). Ideally, future research should favour prospective economic assessments of IVF strategies. This is the first study to investigate IVF in Italy systematically with the tools of medical technology assessment and to draw a picture of the current, indeed confused, reimbursement situation.

Conclusions

Our study shows that beyond its higher effectiveness, r-FSH has a favourable and reasonable cost-effectiveness profile when compared to u-FSH. Despite the higher (more than double) acquisition cost, the total cost of treating IVF patients with r-FSH was estimated to be approximately 13–31% higher, depending on the treatment setting (private versus public). When average cost effectiveness ratios are considered, r-FSH is estimated to perform better than u-FSH in the private setting and in the current situation, while u-FSH had a slightly better profile in the public sector. When incremental costs and effectiveness were taken into account, r-FSH showed reasonable incremental cost-effectiveness ratios between 19.2 and 26 million Lire (11 300 and 15 400 SUS) per ongoing pregnancy, which appeared particularly favourable considering that approximately 98% of these pregnancies will culminate in a newborn baby.

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