NEWS AROUND THE WORLD

Reflections on the Cost-Effectiveness of Recombinant FSH in Assisted Reproduction. The Clinician's Perspective

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Purpose: To analyze the relative cost-effectiveness of recombinant FSH (rFSH) and urinary FSH (uFSH) in assisted reproduction techniques (ART).

Methods: Calculation of the average cost-effectiveness ratio and the incremental cost-effectiveness ratio to compare costs and effects (pregnancy rates) of the two therapeutic options (rFSH and uFSH).

Results: Assuming that the cost of the procedure per ART cycle is between 100,000 pesetas (601 euro) and 150,000 pesetas (901.52 euro), and pricing the GnRH analogues used for pituitary suppression at 35,000 pesetas (210.3 euro), the cost-effectiveness ratio is better for rFSH than for uFSH, implying that the cost per pregnancy is lower when the recombinant preparation is used.

Conclusions: In ART, the use of rFSH is more cost-effective than uFSH.

KEY WORDS: Assisted reproduction; recombinant follicle stimulating hormone; cost effectiveness.

INTRODUCTION

In earlier articles, we discussed the recent introduction of recombinant follicle stimulating hormone

(rFSH) as a therapeutical development of great value for the specialist in reproductive endocrinology in the treatment of infertility (1,2). Figure 1 summarizes the potential advantages of the recombinant gonadotropins, which include both pharmacological and clinical-biological aspects.

For the clinician, there is no doubt that the advantages that recombinant gonadotropins offer the patient fully justify their use. However, for the health-care administrator, the higher unitary cost of rFSH, compared to FSH of urinary origin (uFSH), may overshadow the improvements the newer preparation offers, making it necessary to take into account epidemiological and cost-effectiveness implications.

Since this topic is often debated in scientific forums outside health-care administration, as specialists in the field of assisted reproduction (AR), we would like to offer our analysis of the issue to provide some criteria for clinicians who must make decisions when treating infertility. We begin by establishing a series of background concepts that are necessarily applied when analyzing comparative studies on the use of the different gonadotropins in connection with the assisted reproduction techniques (ART), considering as such in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

BACKGROUND CONCEPTS

The comparison of two types of gonadotropins used to induce the development of multiple follicles in the ART involves comparing their respective profiles for efficacy or effectiveness and safety. However, as explained below, this is not an easy task, as it involves

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Fig. 1. Potential advantages of the recombinant gonadotropins.

analyzing data from the literature that were generated in different studies and at different assisted reproduction centers.

Efficacy. By definition, the best parameter of the efficacy or effectiveness of an FSH preparation should be the number of mature follicles recruited after using a fixed daily dose of the preparation for a fixed period of time (normally in women undergoing pituitary suppression, the ovarian stimulation protocol used in 90% of ART cycles throughout the world) (3). However, with the exception of the first 4–5 days of stimulation, when the dose of FSH administered is usually the same for all subjects participating in a program, the daily dose of FSH varies according to the ovarian response of each patient, gauged by ultrasound determinations and serum estradiol levels. Another complication is interobserver variability when performing ultrasound imaging. This factor adds subjectivity if the same person does not always perform the ultrasound examination in each patient every time. A further confounding factor is associated with the criteria for the administration of human chorionic gonadotropin (hCG), which varies from one ART program to another.

For all of these reasons, the number of oocytes obtained would be the best efficacy parameter to evaluate, since it is the primary objective and the most direct result of ovarian stimulation with gonadotropins and the most easily observed and assessed. Although the ultimate objective of all ART is pregnancy, the pregnancy rate is closely linked to the number of embryos transferred, and this parameter is difficult to compare in dissimilar studies. Furthermore, the maximum permitted number of embryos to be transferred is preestablished in each ART program. Thus, any extra embryos obtained as the result of better follicle recruitment, and a greater number of oocytes obtained thanks to the greater biological potential of either of the gonadotropins compared, would not be reflected in the rate of pregnancies directly obtained as the result of the stimulation cycle. The data to be compared should, therefore, include in the pregnancy rates reported the results obtained after the transfer of cryopreserved embryos, as these constitute the quantitative and direct result of the preceding stimulation with gonadotropins (4,5).

Efficiency. From the clinician's perspective, the efficiency of treatment to stimulate and induce ovulation

is linked to the total dose of the drug administered and the stimulation period needed to obtain the desired effect. In the case of FSH, efficiency is measured by the total number of international unit (IU) administered. Hence, if FSH preparation A is more efficient than preparation B, a lower dose of A would be used (usually for less time).

However, from the perspective of the health-care administrator, the relative "clinical" efficiency of the two FSH preparations may be the reverse if the cost of the IU of FSH is taken into account: if the price of preparation A is significantly higher than that of preparation B, preparation B may seem more efficient in terms of the economic cost, since the total number of IU, multiplied by the unitary cost in Spanish pesetas (1 Euro [€] = 166.386 Spanish pesetas at fixed exchange rate; \$1 U.S. ~175 Spanish pesetas) would mean that preparation A costs more over the long term.

That is why is it essential to link both the efficacy and the efficiency parameters through a cost-effectiveness analysis to be able to draw conclusions that are as exact as possible.

Safety. The assessment of the safety of the gonadotropins used in the ART involves, on the one hand, pharmacological aspects that are discussed in the following section, and on the other, examining the possibility of developing ovarian hyperstimulation syndrome (OHSS). There is no evidence in the literature to suggest that the incidence of OHSS increases with the use of rFSH compared to uFSH. Furthermore, rFSH has been demonstrated to be efficacious and safe for ovulation induction in patients with a history of OHSS (6).

Cost-Effectiveness. A cost-effectiveness analysis provides a way to evaluate a product in economic terms, while simultaneously taking into account not only the costs, but also the results obtained with the program or form of treatment (7,8).

According to pharmacoeconomic practices (7,8), the cost-effectiveness analysis of a drug or form of

therapy must consider all the costs that are relevant. These include direct costs (health care-related costs—the price of the drug, diagnostic tests, medical visits, etc.—as well as non-health care-related costs—transportation to the hospital, social services, etc.), indirect costs (associated with a loss in the patient's wage-earning capacity as the result of working fewer hours), and intangible costs (associated with possible pain and suffering). However, as intangible costs are difficult to quantify, they are usually excluded from the overall economic evaluation of the drug or treatment.

The therapeutical effects (effectiveness or efficacy) of the interventions compared can be evaluated in various ways (epidemiological studies, databases, etc.), although on most occasions relevant information is obtained from clinical trials. The correct measurement of the benefits obtained is extremely important, since the ultimate quality of the study will rest on this factor. For this reason, whenever possible, analytical methods, such as clinical trials, should be used, and when necessary the results of various trials should be combined through a meta-analysis. In addition, it is essential to ensure that the variables selected (the end points) are relevant and representative of the benefits ultimately obtained (7,8).

The comparison between the therapeutical options is made after calculating both the average cost-effectiveness ratio and the incremental cost-effectiveness ratio (Table I). The average cost-effectiveness ratio is easy to calculate, as it represents the coefficient between the total health care-related costs attributable to a given therapeutical option and the efficacy of the option. An incremental analysis is then applied to compare the efficacy of two therapeutical options, for example, A and B. This involves comparing all of the costs and all of the effects obtained with both options.

The average cost-effectiveness analysis implies the relationship between the Cost A/Effectiveness A coefficient, and the Cost B/Effectiveness B coefficient,

Table I. Application of Average and Incremental Cost-Effectiveness to Compare Costs and Effects of Two Therapeutical Options (7)

	Treatment A	Treatment B
Cost-effectiveness	400,000 ptas ^a (2404€) 5 yr of life gained	200,000 ptas (1202€) 4 yr of life gained
Average cost-effectiveness	Cost A/Effectiveness A = 80,000 ptas (480.8€) per yr of life gained	Cost B/Effectiveness B = 50,000 ptas (300.5€) per yr of life gained
Incremental cost-effectiveness of Option A compared to Option B		
	$\frac{\text{Cost A} - \text{Cost B}}{\text{Effectiveness A} - \text{Effectiveness B}} = \frac{400,000 (2404€) - 200,000 (1202€)}{5 - 4} = 200,000 \text{ ptas (1202€) per yr of life gained}$	

^a Pesetas.

by establishing a comparison between the cost per unit of effectiveness of the two options (Table I). In this type of analysis, the two options are not related simultaneously. This will not happen until the incremental analysis is performed. Here, the increment in costs is divided by the increment in effects: Incremental Cost-Effectiveness = (Costs of A – Costs of B)/(Effectiveness of A – Effectiveness of B). Table I shows the differences obtained when these two types of analysis are used. The results should be calculated by using the incremental analysis and should be expressed as the cost of one of the options in terms of additional unitary efficacy compared to the other. In the case shown in the example in Table I, the analysis of averages would indicate that Option B is preferable, since its cost per year of life gained is slightly lower than that for Option A. However, if the incremental analysis is applied, the decision is not so simple. Choosing Option A (the most effective of the two) will depend on whether the decision-maker is willing to pay the additional 200,000 pesetas (1202€) that Option A costs per additional year of life gained compared to Option B.

These are the theoretical concepts that are applied below in our cost-effectiveness analysis of rFSH compared to uFSH in ART.

PHARMACOLOGICAL CHARACTERISTICS

This aspect is the most easily analyzed since, as the recombinant hormones (insulin, growth hormone, gonadotropins, etc.) are obtained with genetic engineering techniques (recombinant DNA), their degree of purity is absolute. This is precisely why they have displaced their counterpart products of biological origin in different medical specialties. A number of articles have demonstrated the possibility of triggering adverse reactions, both locally and systemically (including anaphylactic shock), with the use of urinary gonadotropins, which may contain contaminating proteins (9–14). Another drawback to the use of urinary gonadotropins is that their source of production implicitly implies that the content of bioactive FSH will vary from one batch to another (15).

CLINICAL AND BIOLOGICAL ASPECTS

The greater bioactivity in vivo of rFSH compared to uFSH has been demonstrated in various studies evaluating both types of gonadotropins in anovulatory patients with polycystic ovary syndrome (PCOS).

Characterized by high levels of serum luteinizing hormone (LH) and deficient intraovarian FSH activity, this disease provides a good natural model to evaluate the bioactivity of the gonadotropins. Patients with PCOS present a high “FSH threshold”: in spite of having normal endogenous FSH levels, they are anovulatory. Exogenous FSH is, therefore, necessary to induce follicular development (16). When inducing ovulation in these patients, rFSH has proven to be more efficacious than uFSH, because the total dose of FSH required is significantly lower when the recombinant preparation is used (a lower total dose administered over a shorter period of time) (17–19). In one study (17), the patients were treated with both types of gonadotropins in different cycles, so that each acted as her own control. Because of the heterogeneity of the FSH threshold and other endocrine characteristics in patients with PCOS (16), the use of the same stimulation protocol with different gonadotropin preparations in the same patient appears to provide the most appropriate study design to compare the efficacy of the gonadotropins in ovarian response (follicular development and hormone levels).

The greater biopotency in vivo of rFSH compared to uFSH is also supported by the fact that a lower threshold dose is needed of the recombinant preparation (the dose necessary to initiate follicular development) (17–19). Furthermore, the results of one study have shown that in cycles treated with uFSH, a direct correlation was observed between the LH/FSH ratio (and also basal androstendione) and both the length of treatment and the total dose of FSH used (17). This correlation was not detected with rFSH. On the other hand, in cycles treated with the recombinant hormone, a direct correlation was observed between serum estradiol levels and inhibin A on the day of the hCG injection. This correlation was not observed with uFSH. These findings, emerging from studies comparing both FSH preparations in the same group of patients with PCOS, all point to the superiority of the bioactivity of rFSH (17).

Other authors have also reported a better biopotency for rFSH evidenced in the use of a significantly lower dose of rFSH compared to uFSH, both in patients in a general ART program undergoing pituitary suppression (reviewed in Refs. 5, 20, and 21) and in ovarian stimulation cycles associated with intrauterine insemination (22,23). Two recent studies suggest that the greater biopotency and efficacy of rFSH would also be evident in certain subgroups of patients who are low responders to ovarian stimulation for ART (24,25).

Finally, observational studies indicate that the use of rFSH in the ART is associated with an increase in embryo implantation rates. One study compared two groups of women with overlapping characteristics. They received highly purified urinary FSH (FSH HP) in the first treatment cycle. Even though they had adequate ovarian response, and three or four embryos had been transferred, these patients did not get pregnant in the first cycle and were treated with a second assisted fertilization cycle. Implantation rates were significantly higher in the group of patients who received rFSH in the second ART cycle than in the group stimulated again with FSH HP (26). These findings are further supported by data published in the latest yearly report from the French Registry of the ART (27), based on a total of 37,211 punctures in 1998. Among the most interesting data reported, the Registry indicates that the use of rFSH has become generalized, that there has been a significant reduction in the amount of FSH administered per cycle, and that higher pregnancy rates were achieved with rFSH compared to uFSH (32 vs 28% per cycle), in spite of a significant decrease in the number of embryos transferred. Similarly, in Sweden, Finland, Norway, Denmark, and Iceland, where urinary gonadotropins are not available, an increase in pregnancy rates per cycle was registered after the generalized switch to rFSH and the implementation of a policy to reduce the maximum number of embryos transferred to two (28).

All of the pharmacological and clinical-biological advantages obtained when uFSH is replaced with rFSH imply that the latter provides superior efficacy. However, these advantages may become overshadowed by the unitary cost of the recombinant product, which is 69% higher than the urinary gonadotropins. The only way to establish the relationship between these two parameters is through a cost-effectiveness analysis, as detailed in the following section.

COST-EFFECTIVENESS ANALYSIS OF RECOMBINANT FSH VERSUS URINARY FSH IN ASSISTED FERTILIZATION

In light of the theoretical concepts explained above, to study the cost-effectiveness of the use of rFSH compared to uFSH in ovarian stimulation in the ART, the considerations explained below must all be taken into account. These aspects are all supported in two very

recent articles that study the cost-effectiveness of infertility treatment in the United Kingdom (29) and The Netherlands (30).

The majority of the studies found in the literature took pregnancy as their "end point" to measure efficacy, since the birth of a live baby is the ultimate goal of treatment, from both the medical and the social perspectives. However, as discussed above, the number of oocytes obtained would, in fact, be the parameter most directly related to gonadotropic treatment. Assisted fertilization can be visualized as a sort of obstacle course where your resources diminish with every hurdle cleared: there are fewer oocytes than punctured follicles, fewer fertilized oocytes than total oocytes obtained, fewer developing embryos than fertilized oocytes, and, naturally, fewer fetuses than embryos transferred. It is important, therefore, to begin the race with as many resources as possible. Two important recent studies, which included more than 44,000 cycles each, indicate that the possibility of achieving pregnancy is directly related to the number and the quality of the oocytes and embryos obtained (31,32).

Another important aspect is establishing the cost of treating infertility. Frequently, to simplify calculations, only the cost of the procedure (in this case, the cost of an ART cycle) is used (29). However, it is accepted that the true cost should include the clinic's overheads, the cost of equipment, personnel, etc. Other costs include the labor costs of the couple seeking treatment ("lost" time from work) (30,33–35). Another well-established aspect when calculating the true cost to society of a pregnancy achieved through the ART involves including the costs of failed attempts (canceled cycles and cycles that do not end in gestation even though embryos were transferred) (29,30,33–35). These factors are all included in Markov's statistical model, which is frequently applied to illustrate the treatment of infertility (29,30). This model establishes that each couple seeking treatment can be placed at a specific point along the treatment spectrum during each treatment cycle and after each treatment cycle has been completed (Fig. 2).

Finally, the definition of relative cost-effectiveness used to compare two mutually exclusive types of treatment (such as rFSH and uFSH) is the following (29,30): of the two options to be compared, the option with the lowest expected cost is more cost-effective, unless the incremental cost per each additional pregnancy implicit in the decision to select the more expensive option is lower than the average cost per each pregnancy achieved with the cheapest option.

Fig. 2. The Markov model applied to treatment with IVF/ICSI.

In the case of infertility treatment, this is equivalent to the rule that the option with the lowest average cost per pregnancy is the more cost-effective. Hence, when establishing an available budget, the selection of the more expensive option will imply that fewer couples can be treated. Since the objective is to obtain the maximum number of pregnancies, the selection of the more expensive option will never be cost-effective unless this option produces more pregnancies, in spite of conditioning a reduction in the number of couples treated. This will be the case only if the average cost per pregnancy with this option is lower.

To apply these concepts with specific figures to a comparison of the use of rFSH vs uFSH in IVF/ICSI, it is necessary to establish the parameters that will be chosen to measure both efficacy and efficiency. As stated above, the best way to do this is through a meta-analysis pooling the results of randomized clinical trials exploring the subject. At least six meta-analyses have compared the efficacy and efficiency of rFSH and the urinary preparations of the hormone in connection with the ART (20,21,36–39). Each of these

meta-analyses, in turn, included different studies, chosen because of each one's inclusion criteria and the availability of data at the time of the study. These difference notwithstanding, all of the results of all of the studies point in the same direction: rFSH presents superior efficacy (in terms of the number of both oocytes and pregnancies obtained) and efficiency (in terms of the total average dose used) compared to uFSH. The meta-analyses present differences in pregnancy rates achieved with each treatment, which oscillate between 3.7 and 5% in favor of rFSH (and up to 6.4% if gestations achieved with cryopreserved embryos are included in the calculation). This translates into an average improvement of 15–20% in the results of an ART program. It is beyond the objective of this paper to conduct a critical analysis of the meta-analyses cited; therefore, for the purposes of our calculations, we have selected the meta-analysis that provides the difference in results (3.7%) (39) that is the least favorable to rFSH in terms of efficacy, when clinical pregnancies are taken as the end point. This study did not include pregnancies derived from

cryopreserved embryos. In this meta-analysis (39), the difference in terms of efficiency was -277 IU of FSH in favor of the recombinant preparation.

It should be pointed out that the randomized studies on which these meta-analyses were based almost always included patients with favorable ovarian response profiles (between 18 and 38 years of age, normoovulators, normal body mass index, normal basal FSH). In principle, these features would favor the least effective gonadotropin. However, in spite of this, results were significantly better for rFSH. Furthermore, as explained elsewhere (2), in the first clinical trials conducted to compare rFSH and uFSH in ART, the greater clinical efficiency of rFSH was not reported. This is because in these early trials the recombinant hormone used was presented in vials, while the urinary hormone was presented in ampoules. At a later date, it was established that when the preparation is presented in vials, part of the active product is lost, as it remains in the vial. Currently rFSH is commercialized in ampoules. The inclusion of these clinical trials in the meta-analysis (20,21,36–39) introduces a further negative bias against rFSH.

The cost-effectiveness analysis developed below is, therefore, based on the least favorable scenario for rFSH as presented in the literature available to date. Nevertheless, after analyzing the data and the figures presented here, readers will be able to make their own calculations according to their own criteria.

Calculation of the Prescribing Costs of FSH. The following data must be taken into consideration when calculating prescribing costs (Table II):

- *Average cost of FSH per cycle.* On the basis of the meta-analysis selected for the purposes of our paper (39), the average total number of IU of FSH used in the rFSH cycles was 1990, compared to 2267 for cycles treated with uFSH.
- *Cost of each IU of FSH.* On the basis of prices in force in August 2000, each IU of rFSH cost 68 pesetas (0.41€), compared to 40.1 pesetas (0.24€) for each IU of uFSH (highly purified FSH). The difference is 27.9 pesetas (0.17€).

- *Cost per treatment cycle.* This figure is obtained by multiplying the average number of IU of FSH used by the unitary cost of the FSH [135,320 pesetas (813.29€) in the case of rFSH, compared to 90,907 pesetas (546.36€) for uFSH]. The difference is 44,413 pesetas (266.93€).
- *Cost per pregnancy.* To calculate this cost, it is necessary to take into account the pregnancy rate for each treatment group. According to the meta-analysis cited (39), the rate was 24.7% for the rFSH group and 21% for the uFSH group, or 0.247 and 0.21 pregnancy per cycle, respectively. The cost of the rFSH per cycle [135,320 pesetas (813.29€)] divided by the pregnancy rate per cycle (0.247) gives a cost per pregnancy of 547,854 pesetas (3292.67€). With the same calculation, the cost per pregnancy with uFSH was 432,890 (2601.72€). The difference is 114,964 pesetas (690.95€).
- *Cost per incremental pregnancy.* As explained above, this cost is calculated by the following equation: (total cost for the rFSH group – total cost for the uFSH group)/(pregnancy rate for the rFSH group – pregnancy rate for the uFSH group). If we apply this equation to the costs calculated above, 44,413 pesetas (266.93€)/0.037 pregnancy, we can calculate as 1,200,351 pesetas (7214.25€) the cost of obtaining an “additional” pregnancy in the uFSH group if, rather than receiving the urinary form of the gonadotropin, these patients had received the recombinant form.

As has been exposed above, these calculations represent a simplification of the problem, as they do not take into account the pharmaeconomic concepts discussed above (7,8). To put the problem into a more realistic perspective, it would be necessary to consider at least the total cost of the procedure, in other words, the cost of a complete IVF/ICSI cycle (29,30), since

Table II. Prescribing Cost of Gonadotropins with IVF/ICSI in Pesetas (and Euros)

Parameter	rFSH	uFSH
Average IU/cycle	1990	2267
Cost/IU	68 (0.41€)	40.1 (0.24€)
Cost/cycle	135,320 (813.29€)	90,907 (546.36€)
Cost/pregnancy	547,854 (3292.67€)	432,890 (2601.72€)
Cost/incremental pregnancy	1,200,351 (7214.25€)	

Table III. Calculation of the Cost of One Cycle of IVF/ICSI in Pesetas (and Euros)^a

Parameter	rFSH	uFSH
GnRH analogue	35,000 (210.3€)	35,000 (210.3€)
IVF/ICSI	100,000 (601€)	100,000 (601€)
Gonadotropins	135,320 (813.29€)	90,907 (546.36€)
Total cost/cycle	270,320 (1624.65€)	225,907 (1357.73€)
Cost/pregnancy	1,094,413 (6577.56€)	1,075,748 (6465.38€)
Cost/incremental pregnancy	1,200,351 (7214.25€)	

^a Assuming that the cost of the procedure is 100,000 pesetas (601€).

the administration of gonadotropins represents only one of the many elements comprising the procedure. This is discussed below.

Calculation of the Costs of a Complete ART Cycle. In this calculation (Table III), the (average) cost of treatment with GnRH analogues for pituitary suppression is assumed to be 35,000 pesetas (210.3€) per cycle. The cost of the IVF or ICSI procedure is assumed to be 100,000 pesetas (601€). The total cost of the cycles [(analogue + IVF)/(ICSI + FSH)] is then 270,320 pesetas (1624.65€) with the use of rFSH and 225,907 pesetas (1357.73€) with the use of uFSH. These figures indicate that the cost per pregnancy (cost per cycle divided by pregnancy rate per cycle) is 1,094,413 pesetas (6577.56€) with rFSH and 1,075,748 pesetas (6465.38€) with uFSH.

This means that at a cost of 100,000 pesetas (601€) per cycle of ART, the cost per pregnancy obtained with uFSH is slightly lower. In this light, the cost of each “additional” (incremental) pregnancy that would have been obtained had rFSH been used would be higher than the cost of a pregnancy obtained with uFSH.

Let us now assume that the cost of the ART procedure is 150,000 pesetas (901.52€) and not the 100,000 (601€) used for the calculation in Table III (Table IV). If we make the same calculation, we see that in a figure which is somewhat below 150,000 pesetas (901.52€), the cost of a pregnancy obtained with rFSH is now lower than that of one obtained with uFSH. This dif-

ference is due to the greater efficacy of the recombinant preparation, which, at this point, offsets the unitary cost. Therefore, given the difference in the pregnancy rate achieved, obtaining the same number of pregnancies with uFSH and rFSH would mean that more ART cycles would have to be performed with uFSH. This would involve paying more for the procedures, a cost that would outweigh the difference in the unitary cost between the urinary and the recombinant preparations. For this reason, all calculations based on a cost of somewhat less than 150,000 pesetas (901.52€) for the procedure indicate that the cost per incremental pregnancy obtained with rFSH is lower than the cost of each pregnancy obtained with uFSH. This is because, logically, the cost of each additional pregnancy obtained with rFSH would always be the same [1,200,351 pesetas (7214.25€); see above], since the difference between the total cost of an ART cycle treated with rFSH and that of another treated with uFSH will always be due only to the difference in the price between the two preparations. On the contrary, the cost of each additional pregnancy obtained with uFSH rises in parallel with the cost of the additional ART cycles required to achieve it (see definition and background concepts of the cost-effectiveness analysis).

If the cost of a cycle is assumed to be 400,000 pesetas (2404€) (Table V), the superior cost-effectiveness ratio of rFSH becomes even more pronounced. This is to be stressed considering that the minimal cost of

Table IV. Calculation of the Cost of One Cycle of IVF/ICSI in Pesetas (and Euros)^a

Parameter	rFSH	uFSH
GnRH analogue	35,000 (210.3€)	35,000 (210.3€)
IVF/ICSI	150,000 (901.52€)	150,000 (901.52€)
Gonadotropins	135,320 (813.29€)	90,907 (546.36€)
Total cost/cycle	320,320 (1925.16€)	275,907 (1658.23€)
Cost/pregnancy	1,296,842 (7794.18€)	1,313,843 (7896.36€)
Cost/incremental pregnancy	1,200,351 (7214.25€)	

^a Assuming that the cost of the procedure is 150,000 pesetas (901.52€).

Table V. Calculation of the Cost of One Cycle of IVF/ICSI in Pesetas (and Euros)^a

Parameter	rFSH	uFSH
GnRH analogue	35,000 (210.3€)	35,000 (210.3€)
IVF/ICSI	400,000 (2,404€)	400,000 (2,404€)
Gonadotropins	135,320 (813.29€)	90,907 (546.36€)
Total cost/cycle	570,320 (3427.69€)	525,907 (3160.76€)
Cost/pregnancy	2,308,988 (13,877.30€)	2,504,319 (15,051.26€)
Cost/incremental pregnancy	1,200,351 (7214.25€)	

^a Assuming that the cost of the procedure is 400,000 pesetas (2404€).

an IVF/ICSI cycle (excluding drugs) in Spain is above 400,000 pesetas (2404€).

Application of the Markov Model. As we have seen, the Markov model provides an indispensable tool to perform a cost-effectiveness analysis of any infertility treatment. In our case, it indicates that the cost of repeating the ART cycles in the patients who did not achieve pregnancy after embryo transfer, as well as the cost of repeating a cycle that was canceled, or one in which transfer did not take place, should be added to the costs of using uFSH. Returning to the meta-analysis on which our calculations are based (39), in the group of patients treated with uFSH, there was a difference of 4 points in the cancellation rate compared to the group treated with rFSH (13% for rFSH and 17% for uFSH). This means there were 27% more canceled cycles when the urinary preparation was used.

Selection of the Most Cost-Effective Option Under a Fixed-Budget Regimen. In the definition of cost-effectiveness we established that when choosing between two therapeutical fertility options which are mutually exclusive, the more cost-effective of them should provide a better pregnancy rate under a fixed budget. This aspect is analyzed in Table VI, assuming a budget of 10,000,000 pesetas (60,101.21€).

Supposing that the cost for the procedure is 100,000 pesetas (601€) per cycle, the total cost of the cycle would be 270,320 pesetas (1624.65€) when using rFSH [100,000 pesetas (601€) for the procedure, 35,000 pesetas (210.3€) for the GnRH analogue, and

135,320 pesetas (813.29€) for the rFSH]. At a cost of 270,320 pesetas (1624.65€) per cycle, it would be possible to perform 37 cycles with a fixed budget of 10,000,000 pesetas (60,101.21€). At a pregnancy rate of 24.7%, this means that 9.13 pregnancies would be obtained. If we apply the same calculation for uFSH, 9.29 pregnancies would be obtained.

However, if we make the above calculation assuming that the cost of the procedure is 150,000 pesetas (901.52€), we would obtain a higher number of pregnancies with rFSH than with uFSH. This difference becomes even more pronounced if the calculations are based on a cost per procedure of 400,000 pesetas (2,404€).

CONCLUSIONS

Recombinant FSH presents a greater efficacy or effectiveness than urinary FSH in terms of pregnancy rates per cycle in assisted fertilization. Its efficiency, based on the clinical concept of the total dose of IU of FSH used per cycle, is also better than when uFSH is used. However, if the concept of efficiency is analyzed from the perspective of health-care spending, the higher unitary price of rFSH compared with uFSH makes the latter appear to be more efficient.

Efficacy and efficiency, however, cannot be evaluated independently from costs, and the link between both variables can be established only through an analysis of the cost-effectiveness ratio. This analysis makes it possible to evaluate in economic terms not only the costs, but also the therapeutical results obtained with the different programs or treatment regimes used in a health-care system. In this case, assuming that the cost of the procedure per ART cycle is between 100,000 pesetas (601€) and 150,000 pesetas (901.52€), and pricing the GnRH analogues used for pituitary suppression at 35,000 pesetas (210.3€), the cost-effectiveness ratio is better for rFSH than

Table VI. Cost-Effectiveness Based on a Fixed Budget [10,000,000 Pesetas (ptas) or 60,101.21€] per Cost of Procedure

Cost of IVF/ICSI	No. of pregnancies obtained	
	rFSH	uFSH
100,000 ptas (601€)	9.13	9.29
150,000 ptas (901.52€)	7.71	7.61
400,000 ptas (2404€)	4.33	3.99

for uFSH, implying that the cost per pregnancy is lower when the recombinant preparation is used. Our findings are similar to those reported by other authors (40).

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