

Article

Ovulation induction with urinary FSH or recombinant FSH in polycystic ovary syndrome patients: a prospective randomized analysis of cost-effectiveness



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Abstract

The aim of this prospective, randomized trial was to compare the clinical results and the cost-effectiveness of urinary FSH (uFSH) and recombinant FSH (rFSH) in ovarian stimulation for intrauterine insemination (IUI) cycles in polycystic ovary syndrome (PCOS) patients. One-hundred and seventy PCOS infertile patients undergoing IUI were enrolled, and protocols of ovarian stimulation with uFSH or rFSH were randomly assigned. The total number of cycles performed was 379 (182 and 197, respectively). The main outcome measures were the number of mature follicles, the days of stimulation, the number of ampoules and IU used per cycle, the biochemical/clinical pregnancy rates, the number of multiple pregnancies and the cost-effectiveness. No statistically significant differences were found in the follicular development, length of stimulation, pregnancy rates, delivery rates and multiple pregnancies between the two groups. In the uFSH group, the cost per cycle remained significantly lower ($\text{€}218.51 \pm 88.69$ versus $\text{€}312.22 \pm 118.12$; $P < 0.0001$), even though a significantly higher number of IU of gonadotrophins were used (809.3 ± 271.9 versus 589.1 ± 244.7 ; $P < 0.0001$). The cost-effectiveness (i.e. within a group, the total cost of all cycles divided by no. of clinical pregnancies) was 1729.08 in the uFSH group and 3075.37 in the rFSH group. In conclusion, uFSH and rFSH demonstrated the same effectiveness in ovarian stimulation in IUI cycles in PCOS patients. The urinary preparation is more cost-effective due to the difference of its cost per IU.

Keywords: cost-effectiveness, intrauterine insemination, ovarian stimulation, PCOS, recombinant FSH, urinary FSH

Introduction

Polycystic ovary syndrome (PCOS) is considered to be one of the most common endocrinopathies in women of the reproductive age (Diamanti-Kandarakis *et al.*, 1999). Moreover, it is also the most common cause of anovulatory infertility (Carmina and Lobo, 1999). The main treatments of infertility in PCOS patients are performed by ovarian stimulation with FSH, a reduction in insulin concentration and a decrease in LH levels.

These are considered to be the main points of the therapeutic treatment (Seibel *et al.*, 1984; Jakubowicz and Nestler, 1997; Dale *et al.*, 1998; Homburg, 1998; Nestler *et al.*, 1998; Diamanti-Kandarakis *et al.*, 1999; Yarali and Zeyneloglu, 2004). Clomiphene citrate is often used as first-line treatment in PCOS (Sovino *et al.*, 2002). In case clomiphene citrate treatment is not successful it is generally preceded by direct FSH stimulation (Homburg, 2003). In order to avoid the occurrence of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies,

FSH stimulation is performed with a low-dose protocol (Yarali and Zeyneloglu, 2004).

IVF and intrauterine insemination (IUI) require ovarian stimulation to increase the number of mature oocytes (Guzick *et al.*, 1998; Templeton and Morris, 1998). Human menopausal gonadotrophin (HMG) has been used for ovarian stimulation. Unfortunately, HMG has a low specific activity and contains significant amounts of LH. LH was thought to lead to poor oocyte quality, reduced fertilization rates, lower embryonic viability and early pregnancy loss (Stanger and Yovich, 1985). The development and use of other urine-derived FSH preparations (uFSH) containing smaller quantities of LH resulted in higher pregnancy rates compared with the use of HMG in IVF cycles (Daya *et al.*, 1995).

The development of a new medicinal product containing human recombinant FSH (rFSH) was thought to represent the ultimate solution for ovulation induction, given that rFSH is completely free from LH. Although this presumption was appealing, clinical results in IVF from the use of rFSH were not outstanding. Moreover, some recent trials have shown that the addition of exogenous LH to downregulated rFSH-stimulated cycles, improved implantation rate (Gordon *et al.*, 2001), shortened treatment duration, reduced menotropin consumption and may have decreased the occurrence of side-effects (Filicori *et al.*, 2001). However, there are many important factors to mention in favour of rFSH preparations. These factors include the absence of any other human contaminant protein and the fact that the production is independent of urine collection, ensuring a constant FSH supply and guaranteeing a batch-to-batch consistency.

Aside from the previously mentioned benefits, the production of rFSH has higher medical costs. In fact many trials have been carried out in order to analyse the efficacy and the cost-effectiveness of rFSH in comparison to urinary preparations. Large-scale clinical trials and meta-analysis studies have been performed in order to show the difference between rFSH and uFSH in IVF cycles. (Daya and Gunby *et al.*, 1999; Hoomans *et al.*, 1999; Agrawal *et al.*, 2000; Al-Inany *et al.*, 2003). Moreover, evidence of clinical effectiveness alone is not a sufficient indication to justify the use of a medical product. Therefore, the analysis of relative cost-effectiveness of treatments is becoming increasingly important. The efforts undertaken to create cost-effectiveness models failed to reveal which preparation was associated with a better pregnancy rate and lower costs in IVF cycles. However, it is also important to mention that some studies reported better results when recombinant products were used (Daya *et al.*, 2001; Sykes *et al.*, 2001).

Apart from the fact that IUI is a well-known cost-effective treatment for infertility, no studies have been published concerning a cost-effectiveness evaluation of rFSH versus uFSH in IUI cycles in PCOS patients. A study has already been conducted by the current authors to evaluate the cost-effectiveness of rFSH in comparison to uFSH in IUI cycles in normal infertile patients (Gerli *et al.*, 2004). As far as we know, this is the first trial conducted with the purpose of determining which preparation (between urinary and recombinant FSH) is more cost-effective in IUI cycles in

women suffering from PCOS.

Materials and methods

Patients

PCOS women with a history of at least two years of infertility were recruited in the authors' centres. According to Azziz (2004), diagnostic criteria for PCOS evaluations are: clinical and/or biochemical hyperandrogenism, chronic anovulation and exclusion of related disorders. A diagnostic screening was performed including gynaecological and ultrasound examination, semen analysis, hormonal assessment and hysterosalpingogram. Semen parameters were analysed according to World Health Organization (WHO) criteria (WHO, 1992). The cycles were assessed as ovulatory cycles if serum progesterone concentrations in mid-luteal phase were adequate. Patients with suspected tubaric occlusion during ultrasound examination or hysterosalpingogram underwent laparoscopic examination. Patients who did not present tubal factor, male factor and hypergonadotrophism were previously treated with clomiphene citrate, according to the protocols used in the treatment centres. Those who became clomiphene citrate-resistant or those who did not remain pregnant (within 12 months for patients under 30 years or 6 months for patients over 30 years) were placed in the IUI protocol study.

The study was approved by the local ethics committee. Moreover, all patients signed an informed consent to the procedure following the enrolment.

Study design

A total of 170 patients were assigned to two groups, according to a randomization table. The characteristics of the two groups are shown in **Table 1**. Group A ($n = 82$) was treated with uFSH; Group B ($n = 88$) was treated with rFSH. Protocols of ovarian stimulation were created according to well-known guidelines (Royal College of Obstetricians and Gynaecologists, 1999). The recombinant preparation (Puregon; Organon, the Netherlands) was injected subcutaneously (s.c.) beginning on day 2 of the cycle with a dosage of 50 IU/day. The urinary product (Fostimon, IBSA Farmaceutici Italia) was administered s.c. beginning on the second day of the cycle with 75 IU/day. Ovarian response was assessed on day 6 or 7 of the cycle, and the dosage was adjusted according to the patient's response. If the ovarian response was excessive, the cycle was cancelled. In the case of a single dominant follicle development (poor responder), the patients were warned of the possibility of having a lower likelihood of pregnancy. They were also advised that the risk of multiple pregnancy was extremely low. However, some patients decided to interrupt the cycle. The patients at risk of hyperstimulation syndrome (more than five follicles ≥ 17 mm) were cancelled (excessive responders). In the statistical data all cancelled cycles for excessive response or for patient's decision in the case of development of a single follicle were included.

No plasma hormone concentrations were evaluated since these parameters are not necessary in IUI treatment. Therefore these analyses were not included in the treatment protocol. All patients were given 10,000 IU of human chorionic

Table 1. Demographic characteristics of patients.

	Group A (uFSH)	Group B (rFSH)
Number of patients	82	88
Age (years) (mean \pm SD)	28.6 \pm 2.7	29.1 \pm 2.4
Body mass index (kg/m ²) (mean \pm SD)	23.1 \pm 2.1	23.7 \pm 2.0
Duration of infertility (years) (mean \pm SD)	2.2 \pm 1.4	2.3 \pm 1.3

No statistical differences were found between groups, thus *P*-values are not shown.

gonadotrophin (HCG) (Profasi HP; Serono Pharmaceuticals) i.m. when the largest follicle reached a diameter of at least 18 mm. A single IUI was performed 32–40 h after the injection of HCG. No luteal support treatment was given to the patients.

A pregnancy test was given if menstruation did not occur within two weeks of insemination.

End-points

Main outcome measures were: number of follicles \geq 17 mm, days of stimulation, number of ampoules and IU used per cycle, biochemical and clinical pregnancy rates, costs per cycle, and cost-effectiveness. The multiple pregnancies obtained, spontaneous abortions, cases of OHSS and cancelled cycles were counted.

Clinical results

A biochemical pregnancy was defined as a small and transient increase in β -HCG concentrations. A clinical pregnancy was determined by the visualization of an embryo with cardiac activity at 6–7 weeks of pregnancy.

Spontaneous abortion was classified as the loss of the pregnancy between the fifth and twelfth week of gestation.

Cost analysis

The cost of a single ampoule of uFSH and rFSH was examined during the study according to the Italian Formulary (L'Informatore Farmaceutico, 2001) (€20.11 and €26.45, respectively). The cost per cycle was calculated by multiplying the cost of a single IU with the mean number of IU used per cycle.

The cost-effectiveness was calculated by multiplying the cost per cycle by the total number of cycles performed in each group, then dividing the result for the number of clinical pregnancies obtained in the group during the trial.

Statistical methods

Given that almost all variables in the analysis of the data showed a non-normal distribution (in the Shapiro–Wilk test and normal probability plots), the non parametric Mann-Whitney U test was

used to analyse the continuous variables and Fisher's exact test and the χ^2 test were used for categorical variables.

The significance level was set at $P < 0.05$. The results were described in terms of mean \pm standard deviation (SD) and confidence intervals (CI), in order to facilitate comparison of the data with those of the literature. All data analyses were carried out with SPSS release 10.1.1 for Windows (SPSS Inc., Chicago, USA, 1999).

Results

A total of 379 cycles (in 170 patients) were included in the study. Before beginning the stimulation protocol, two patients in Group A and three patients in Group B requested to be withdrawn from one of the cycles for personal reasons. Therefore these five cycles were not considered. Both groups (182 and 197 cycles respectively in the uFSH group and the rFSH group) were comparable in demographic characteristics and duration of infertility (**Table 1**).

Clinical results did not reveal significant differences between the two groups (see **Table 2**). Twenty-nine cycles were cancelled: 13 in the uFSH group (11 due to the risk of hyperstimulation and 2 for poor response) and 16 in the rFSH group (15 for risk of hyperstimulation and 1 for poor response). Follicular development was comparable in the two groups. No statistically significant differences were found in the number of gonadotrophin ampoules administered and in the days of stimulation. In the rFSH group, there was a tendency to have a longer stimulation period and additionally a higher number of FSH ampoules were used. A slightly higher (not significant) pregnancy rate (12.6% versus 11.2%) was obtained with the use of rFSH. No differences were found in the number of spontaneous abortions between the two groups (13.0% in group A and 15.0% in group B), and the number of multiple pregnancies (1.6% in group A and 1.5% in group B). No OHSS were recorded.

The data related to costs are shown in **Table 3**. A significantly higher number ($P < 0.0001$) of IU of FSH were used in the uFSH group (809.3 \pm 271.9; 95% CI 721.1–930.5 versus 589.1 \pm 244.7; 95% CI 544.7–675.8), with a significantly lower cost ($P < 0.0001$) per cycle (€218.51 \pm

Table 2. Clinical results.

	Group A (uFSH)	Group B (rFSH)
Follicles >17 mm (mean \pm SD)	2.3 \pm 1.5	2.4 \pm 1.7
Days of stimulation (mean \pm SD)	10.2 \pm 2.1	9.8 \pm 1.9
Number of ampoules per cycle (mean \pm SD)	11.3 \pm 4.2	10.8 \pm 4.9
Biochemical pregnancy rate (%)	2/182 (1.1)	3/197 (1.5)
Clinical pregnancy rate (%)	22/197 (11.2)	23/182 (12.6)
Spontaneous abortion (%)	3/23 (13.0)	3/20 (15.0)
Multiple pregnancies (%)	3/182 (1.6)	3/197 (1.5)
Cancelled cycles (%)	13/182 (7.1)	16/197 (8.1)

No statistical differences were found between groups, thus *P*-values are not shown.

Table 3. Cost-effectiveness analysis.

	Group A (uFSH)	Group B (rFSH)	Difference ^a
Cost per ampoule (€)	20.11	26.45	6.34
Cost per IU (€)	0.27	0.53	0.26
Number of IU per cycle (mean \pm SD)	809.3 \pm 271.9 ^c (721.1–930.5)	589.1 \pm 244.7 ^c (544.7–675.8)	–220.2
Cost per cycle (€)	218.51 \pm 88.69 ^c (152.6–270.4)	312.22 \pm 118.12 ^c (215.3–375.8)	93.71
Cost of all cycles (€)	39 768.82	61 507.34	21 738.52
Cost-effectiveness (€) ^b	1 729.08	3 075.37	1346.28

Values are means or means \pm SD (in parenthesis 95% CI).

^arFSH – uFSH.

^bCalculated by dividing the total cost of all the cycle performed in the group by the number of clinical pregnancies obtained in the same group.

^c*P* < 0.0001 (uFSH group versus rFSH group).

88.69; 95% CI 152.6–270.4 versus €312.22 \pm 118.12; 95% CI 215.3–375.8). The cost-effectiveness was €1729.08 in the uFSH group and €3075.37 in the rFSH group.

Discussion

During the last decade the production of recombinant FSH has been considered to be a turning point in endocrine research, particularly in the field of human reproduction. Urinary preparations of gonadotrophins have been progressively replaced by the new biotechnological products which completely lack of any LH activity and other human protein. These compounds contaminate the urinary preparations. However, it must be stressed that the highly purified FSH has proved to be a safe and efficient preparation in ovarian stimulation (Gerli *et al.*, 1999).

Having more purified and scientifically advanced products available on the market does not necessarily mean that better results can be achieved in terms of efficacy. For this reason, several studies have been carried out to determine whether rFSH was able to improve IVF outcomes compared with those obtained using urinary products.

The higher medical costs of the recombinant products motivated many researchers to carry out numerous trials in order to explore the efficacy and the relative cost-effectiveness of alternative treatments in IVF cycles (Ola *et al.*, 2001; Silverberg *et al.*, 2002). The efforts undertaken to perform meta-analysis and to create cost-effectiveness models failed to reveal which preparation was associated with a better pregnancy rate and with lower costs in IVF cycles. However, it is important to acknowledge that recombinant products showed a tendency to give better results (Daya *et al.*, 2001; Ola *et al.*, 2001).

Intrauterine insemination has been considered as the first-line treatment in patients aged under 37 years, with a short duration of infertility and no severe male factor or tubal factor. Several studies have been performed to assess the efficacy and analyse the cost-effectiveness of the treatment. Results have demonstrated that although IVF tended to be more effective on a per-cycle basis than IUI, the latter had a higher cumulative pregnancy rate at the end of the programmed treatment cycles in idiopathic subfertility and male subfertility, because of the lower drop-out rate (Goverde *et al.*, 2000). Moreover a meta-analysis showed that ovarian stimulation with gonadotrophins in IUI cycles has a better probability of conception than IUI alone (Hughes, 1997).

This is the first trial that analyses clinical results and cost-effectiveness of different FSH preparations used in IUI cycles in PCOS patients. In this study the pregnancy rates were similar in the two groups of patients, which led to the decision to analyse the cost-benefit in each group.

This study could be easily criticised since different numbers of IU of FSH were used according to the different types of FSH (50 for rFSH and 75 for uFSH). The recombinant preparation was administered in lower concentration for two reasons: a supposedly higher efficacy and bioactivity of the product (Out et al., 1995), and the drug availability in Italy (50 and 100 IU per ampoule). On the other hand administration of a single vial of 50 IU was preferred instead of running the risk of hyperstimulation syndrome and a higher multiple pregnancy rate.

Two outcome measures have been considered as reliable markers of drug bioactivity: the number of mature follicles and the cancellation rate, the latter being the expression of an excessive or a poor response. Similar results in terms of these two parameters were obtained in both groups (means of 2.3 ± 1.5 and 2.4 ± 1.7 mature follicles for Groups A and B respectively). This indicates that the pharmacological stimulation of the ovaries was similar and comparable in both study groups. There were no differences in the efficiency of the treatments, since there were similar biochemical and clinical pregnancy rates in the two groups.

The number of stimulation days and the number of ampoules used were not statistically different. On the contrary, the mean number of IU administered to the patients, as shown in **Table 3**, were significantly higher in the uFSH group. As previously mentioned, this group received a higher daily dosage of FSH. Although such data should allow us to come to the conclusion that a higher cost per cycle (and per pregnancy) is connected to the use of uFSH, it is counterbalanced by the lower per IU price of uFSH in comparison to the recombinant formulation.

Silverberg and colleagues (Silverberg et al., 2002) recently compared the cost-effectiveness of rFSH and uFSH in IVF cycles. They concluded that the economic effectiveness of a drug depends less on its costs and rather more on the clinical outcomes associated with its use. The results of the present study are strictly in contrast with this statement: a highly significant difference was found in favour of the urinary product, which is mainly due to the lower cost of this product. The possibility cannot be excluded that the conclusion reached by Silverberg may be applied to IVF cycles but may not be valid for ovulation induction in IUI cycles.

It must also be remembered that aside from pregnancy or delivery rates, the main outcome measures of the studies performed in IVF cycles were the number of growing follicles, the number of oocytes retrieved and the number of embryos obtained. The higher the values were, the better the efficacy of the drug was. In ovulation induction for IUI cycles where no pituitary down-regulation protocols are used, the goal of the stimulation is different. The aim is to obtain no fewer than two and no more than four mature oocytes. A stronger stimulation could either result in a multiple pregnancy or at worst, in hyperstimulation (Farhi et al., 1996). Therefore, the different results obtained in the analysis of the cost-effectiveness of the

two FSH compounds is explained by the diverse perspective in the evaluation of the outcomes of ovarian stimulation, together with the diverse methodology in obtaining these results.

Numerous studies concerning the potential improvement of IVF outcomes using rFSH versus uFSH have been published, whereas few data comparing the urinary and recombinant products in ovulation induction are available (Yarali et al., 1999; Gleicher and Karande, 2000).

Yarali and colleagues (Yarali et al., 1999) prospectively compared the efficacy and safety of recombinant and urinary products for ovulation induction in patients with clomiphene citrate-resistant, normogonadotrophic, and chronic anovulation. The main outcome measures of this study were the cumulative ovulation and pregnancy rates, the total amount of gonadotrophin used throughout the stimulation and follicular development. No differences were found between the two treatment groups (Yarali et al., 1999). In contrast, a large cohort study in unselected patients revealed a possible detrimental effect of the FSH preparation compared with preparations containing HMG (Gleicher and Karande, 2000).

Taking into account clinical outcome measures, it is difficult to achieve statistically significant results due to the limited number of cycles analysed and the low value of pregnancy rates. These are considered to be the only two clinically relevant parameters in ovulation induction or IUI cycles. Hence it is extremely important to assess the cost of each pregnancy obtained with both treatment options. In consequence it is important to suggest the use of the more cost-effective drug. In this study it has been demonstrated that the cost per cycle and the cost per pregnancy were 44% and 36% respectively higher when the recombinant products were used. Additionally the total amount of IUI used in the rFSH group was lower in comparison to the uFSH one (21.2% less than in the uFSH group).

The results of this study have demonstrated that the use of a more expensive recombinant product does not seem cost-effective in protocols of ovulation induction in IUI cycles in PCOS patients.

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