Recombinant versus urinary follicle-stimulating hormone in intrauterine insemination cycles: a prospective, randomized analysis of cost effectiveness

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Objective: To compare the clinical results and the cost effectiveness of urinary FSH and recombinant FSH in ovarian stimulation for IUI cycles.

Design: Prospective, randomized trial.

Setting: University Hospital, Perugia, and A.G.UN.CO. Obstetrics and Gynaecology Centre, Rome, Italy.

Patient(s): IUI cycles were performed in 67 infertile patients.

Intervention(s): Protocols of ovarian stimulation with urinary FSH or recombinant FSH were randomly assigned, for a total of 138 cycles performed (67 and 71, respectively).

Main Outcome Measure(s): Number of mature follicles, days of stimulation, number of ampules, and IU used per cycle, biochemical/clinical pregnancy rates and cost-effectiveness ratio.

Result(s): Follicular development, length of stimulation, pregnancy and delivery rates were not statistically different. Although in the urinary FSH group a significantly higher number of IU of gonadotropins were used (815.5 vs. 596.0), the cost per cycle remained significantly lower (220.73 vs. 318.50).

The cost-effectiveness ratio was €1,848.61 in the urinary FSH group and €2,512.61 in the recombinant FSH group.

Conclusion(s): Urinary FSH and recombinant FSH are both effective in ovarian stimulation in IUI cycles. The urinary preparation is more cost effective due to the difference of its cost per IU. (Fertil Steril 2004;83: 573–8. ©2004 by American Society for Reproductive Medicine.)

Key Words: Intrauterine insemination, ovarian stimulation, recombinant FSH, urinary FSH, cost effectiveness

Infertility is a pathology that affects one of seven couples worldwide (1). There have been numerous guidelines issued for the effective treatment of infertility. At present, assisted reproduction technologies (ART) are proven to be safe and effective.

In vitro fertilization and IUI require ovarian stimulation to increase the number of mature oocytes and subsequently increase the chances for a successful treatment (2, 3).

Human menopausal gonadotropin has been used for ovarian stimulation. Unfortunately, it has a low specific activity and contains significant amounts of LH, which was thought to lead to poor oocyte quality, reduced fertilization rates, lower embryonic viability, and early pregnancy loss (4). The development of other urine-derived FSH preparations, with significantly reduced quantities of LH, has resulted in higher pregnancy rates compared to the use of hMG in IVF cycles (5). We already demonstrated in previous works the similar efficacy of two products containing highly purified urinary FSH (obtained with two different methodologies) in two groups of patients (6).

The introduction of human recombinant FSH in the market was thought to represent the ultimate solution in ovulation induction, given that it is completely free of LH. Notwithstanding this attractive premise, clinical IVF results using recombinant FSH were not so outstanding. Recent trials have shown that the addition...
of exogenous LH to down-regulated FSH-stimulated cycles improved implantation rate (7), shortened treatment duration, reduced menotropins consumption, and might have decreased the occurrence of side effects (8).

Recombinant human FSH preparations, which are completely lacking of any LH activity and extraneous human protein, have numerous advantages. These advantages consist of being independent from urine collection, ensuring a constant FSH supply, and guaranteeing a batch-to-batch consistency. Aside from these evident advantages, such products had higher medical costs. As a result many trials were carried out to analyze the efficacy and the cost effectiveness of recombinant FSH compared to urinary preparations. Large-scale clinical trials and meta-analysis studies comparing recombinant FSH and urinary FSH in IVF cycles have been performed to demonstrate the better efficacy of one treatment compared to the other (9–12).

Moreover, evidence of clinical effectiveness alone is not a sufficient indication to justify the use of a new medical product. Therefore, the analysis of cost effectiveness 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, although it is also important to mention that a tendency to better results was obtained with recombinant products (13, 14).

Although IUI is a well-known cost-effective treatment for infertility, no studies have been published on the cost effectiveness of recombinant FSH vs. urinary FSH in IUI cycles. 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.

**MATERIALS AND METHODS**

**Patients**

Women with a history of infertility were recruited for this study between March 2000 and December 2002. Diagnostic screenings included gynecologic and ultrasound examination, semen analysis, hormonal assessment, and hysterosalpingogram. Semen parameters were analyzed according to World Health Organization criteria (15). The ovulatory cycles were in midluteal phase as assessed by serum P levels. Patients suspected of having tubal occlusion at ultrasound examination or hysterosalpingogram underwent laparoscopic examination. Exclusion criteria were tubal factor, male factor infertility not suitable for IUI (<10 million motile sperm in the ejaculate) (16), and hypergonadotropism. Inclusion criteria were ovulatory factor (polycystic ovary syndrome [PCOS], clomiphene resistant, normogonadotropic anovulation), endometriosis (stage I or II), mild male factor infertility, and unexplained infertility. The characteristics of the patients are presented in Table 1.

All patients gave written informed consent to the procedure. The study was approved by the local Ethics Committee.

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**TABLE 1**

Demographic characteristics of patients.

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>32</td>
</tr>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>31.7 ± 3.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²) (mean ± SD)</td>
<td>23.2 ± 2.2</td>
</tr>
<tr>
<td>Duration of infertility (years) (mean ± SD)</td>
<td>2.8 ± 1.3</td>
</tr>
</tbody>
</table>

**Note:** No statistical differences were found between groups, thus P values (P<0.05) are not shown.

SD = standard deviation.


**Study Design**

A total of 67 patients were assigned to two groups, according to a randomization table, one treated with urinary FSH (n = 32; group A), the other with recombinant FSH (n = 35; group B). Protocols of ovarian stimulation were followed according to well-known guidelines (17). The recombinant preparation (Pur- egon, Organon, Ireland) was injected SC starting on day 2 of the cycle with a dosage of 50 IU/day. The urinary product (Fostimon, AMSA, Italy) was administered SC 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 response of the patient. Cycles were cancelled depending on the poor or excessive ovarian response. The patient was warned of the possibility of a lower pregnancy rate in case she developed a single dominant follicle (poor responders); patients with monofollicular growth were also advised that the risk of multiple pregnancy was negligible. As a result, some patients stopped the procedure. The patients at risk of ovarian hyperstimulation syndrome (OHSS; more than 5 follicles ≥17 mm) were discontinued (excessive responders). The data from all cancelled cycles because of poor or excessive response or because of the patient’s decision in case of the development of a single follicle were included in the statistical data.

Evaluation of the plasma hormone level was not performed because these parameters are not necessary to undergo IUI treatment; therefore, they were not listed in the treatment protocol. When the largest follicle reached a diameter of at least 18 mm, all patients were given 10,000 IU of IM hCG (Profasi HP; Serono Pharmaceuticals, Italy). A single IUI was performed 32–40 hours after the injection of hCG. No luteal support was given to the patients.

If menstruation did not occur within 2 weeks of the insemination, a pregnancy test was given.

**End Points**

Main outcome measures were number of follicles ≥17 mm, days of stimulation, number of ampules and IU used per cycle, biochemical and clinical pregnancy rates (PR), costs per cycle, and cost-effectiveness ratio. Single and multiple
pregnancies, spontaneous abortions, cases of OHSS, and cancelled cycles were all counted.

All end points underwent statistical comparison.

Clinical Results
A biochemical pregnancy was defined as a small and transitory increase in β-hCG levels. 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 12th week of gestation.

Cost Analysis
We examined the cost of a single ampule of urinary FSH and recombinant FSH during the study according to the Italian Formulary, 2001 Edition (€20.11 and €26.45, respectively). The cost per cycle was calculated multiplying the cost of a single IU with the mean number of IU used per cycle.

The cost-effectiveness ratio was calculated 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
Almost all variables in the analysis of the data showed a non-normal distribution using the Shapiro-Wilk test and normal probability plots. Consequently, we used the non-parametric Mann-Whitney U test to analyze continuous variables and the Fisher’s exact test and $\chi^2$ test for categorical variables.

The significance level was set at $P<.05$. To facilitate comparison of data with those from other studies, the results were described in terms of mean ± standard deviation and confidence intervals (CI). All data analyses were carried out by using SPSS release 10.1.1 for Windows (SPSS Inc., Chicago, IL).

RESULTS
A total of 140 cycles (in 67 patients) was included in the study. A patient in each group requested to be withdrawn from one of the cycles for personal reasons before starting the stimulation protocol. These two cycles were not considered. Both groups (67 and 71 cycles, respectively, in the urinary FSH group and the recombinant FSH group) were comparable in demographic and infertility characteristics (Table 2). The main cause of infertility was unexplained in almost half of the treated patients (17 in the urinary FSH group and 17 in the recombinant FSH group). Ten couples included in the study (4 in the urinary FSH group and 6 in the recombinant FSH group) presented with male factor infertility. These men were comparable in terms of total motile sperm in the ejaculate (>10 million in each case) and of sperm morphology (which was normal).

The clinical results did not show any significant difference (Table 3). Nine cycles were cancelled: 4 in the urinary FSH group (1 due to the risk of hyperstimulation and 3 for poor response) and 5 in the recombinant FSH group (1 for risk of hyperstimulation and 4 for poor response). The follicular development was comparable in the two groups. No statistically significant difference was found in the number of ampules of gonadotropin administered and in the days of stimulation, although in the recombinant FSH group there was a tendency to have a longer stimulation and to use a higher number of FSH ampules. A slightly higher (not significant) pregnancy rate (12.7% vs. 11.9%) was obtained with the use of recombinant FSH. No difference was found in number of spontaneous abortions between the two groups. No OHSS cases or multiple pregnancies were recorded.

Data related to the costs are shown in Table 4. A significantly higher number ($P<.0001$) of IU of FSH have been used in the urinary FSH group (815.5 ± 284.9; 95% confidence interval [CI] 711.3–924.8 vs. 596.0 ± 235.8; 95% CI 565.7–680.8), with a significantly lower cost ($P<.0001$) per cycle (220.73 ± 94.7; 95% CI 165.7–278.4 vs. 318.50 ± 26.45 €).

### Table 2
Characteristics of infertility in the two groups of treatment.

<table>
<thead>
<tr>
<th></th>
<th>No. of women</th>
<th>No. of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td></td>
<td>(n = 32)</td>
<td>(n = 35)</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td></td>
<td>(n = 67)</td>
<td>(n = 71)</td>
</tr>
<tr>
<td>Ovulatory factor (%)$^a$</td>
<td>5 (15.6)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Endometriosis (%)</td>
<td>6 (18.8)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Male factor (%)</td>
<td>4 (12.5)</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Unexplained (%)</td>
<td>17 (53.1)</td>
<td>17 (48.6)</td>
</tr>
</tbody>
</table>

Note: No statistical differences were found between groups, thus $P$ values ($P<.05$) are not shown.

$^a$PCO = clomiphene-resistant; anovulatory/normogonadotropic.


### Table 3
Clinical results.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles &gt;17 mm (mean ± SD)</td>
<td>2.6 ± 1.7</td>
<td>2.9 ± 1.4</td>
</tr>
<tr>
<td>Days of stimulation (mean ± SD)</td>
<td>9.2 ± 2.1</td>
<td>10.0 ± 1.9</td>
</tr>
<tr>
<td>No. of ampules per cycle (mean ± SD)</td>
<td>10.9 ± 3.6</td>
<td>11.9 ± 4.1</td>
</tr>
<tr>
<td>Biochemical PR (%)</td>
<td>1/67 (1.5)</td>
<td>1/71 (1.4)</td>
</tr>
<tr>
<td>Clinical PR (%)</td>
<td>6/67 (11.9)</td>
<td>7/71 (12.7)</td>
</tr>
<tr>
<td>Spontaneous abortion (%)</td>
<td>1/8 (12.5)</td>
<td>1/9 (11.1)</td>
</tr>
<tr>
<td>Cancelled cycles (%)</td>
<td>4/67 (6.0)</td>
<td>5/71 (7.0)</td>
</tr>
</tbody>
</table>

Note: No statistical differences were found between groups, thus $P$ values are not shown.

SD = standard deviation; PR = pregnancy rate.

During the past decade the production of the recombinant FSH has been considered as a milestone in the endocrine research, particularly in the field of human reproduction. The urinary preparations of gonadotropins have been progressively replaced by biotechnological products, which completely lack LH activity and other human proteins. These compounds contaminated the urinary preparations. However, we must stress that the highly purified FSH has been previously proved to be a safe and efficient preparation in ovarian stimulation (6).

Having more purified and scientifically more advanced products available on the market does not mean achieving better results in terms of efficacy. As a result several studies have been carried out to determine whether recombinant FSH was able to improve IVF outcomes compared to the rates obtained using urinary products.

The higher medical costs of the recombinant products motivated many researchers to conduct numerous trials and explore the efficacy and relative cost effectiveness of alternative treatments in IVF cycles (18, 19). The meta-analyses and 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 mention that recombinant products showed a tendency to have better results (13, 18).

Intrauterine insemination has been considered as the first-line treatment in patients less than 37 years of age with a short duration of infertility and no severe male factor infertility or tubal factor. Several studies have been performed to assess the efficacy and analyze the cost effectiveness of the treatment. Results 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 (20). Moreover a meta-analysis showed that ovarian stimulation with gonadotropins in IUI cycles has a better probability of conception than IUI alone (21).

This is the first trial that analyzes the clinical results and cost effectiveness of different FSH preparations used in IUI cycles. In this study the pregnancy rates were similar in the two groups of patients and therefore we decided to analyze the cost/benefit ratio in each group.

This study could raise criticisms concerning the different number of IU of FSH used (50 for recombinant FSH and 75 for urinary FSH). The recombinant preparation was administered at a lower concentration for two reasons: supposedly a higher efficacy and bioactivity of the product (22) and the drug availability in Italy (50 and 100 IU per ampules). On the other hand, we preferred to administer a single vial of 50 IU instead of running the risk of OHSS and multiple pregnancies.

Two outcome measures are 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 (a mean of 2.6 ± 1.7 and 2.9 ± 1.4 mature follicles). 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, as there were similar biochemical and clinical pregnancy rates in the two groups.

The number of days of stimulation and the number of ampules used were not statistically different, but the mean number of IU administered to the patients, as shown in Table 4, were significantly higher in the urinary FSH 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

| TABLE 4 |
| Cost-effectiveness analysis. |
| :---: | :---: | :---: |
| **Group A** | **Group B** | **Difference** |
| Cost per ampule (€) | 20.11 | 26.45 | 6.34 |
| Cost per IU (€) | 0.27 | 0.53 | 0.26 |
| No. of IU per cycle (mean ± SD) | 815.5 ± 284.9 (711.3–924.8) | 596.0 ± 253.8 (565.7–680.8) | −219.5 |
| Cost per cycle (€) | 220.73 ± 94.72 (165.7–278.4) | 318.50 ± 125.21 (225.6–369.1) | 97.77 |
| Cost of all cycle (€) | 14,788.91 | 22,613.50 | 7,824.59 |
| Cost-effectiveness ratio (€) | 1,848.61 | 2,512.61 | 664.00 |

*Note: Values are means or means ± standard deviation (in parenthesis 95% confidence intervals).*

*Recombinant FSH – urinary FSH.*

*Calculated dividing the total cost of all the cycle performed in the group for the number of clinical pregnancy obtained in the same group.

*P<.0001 (urinary FSH group vs. recombinant FSH group).*
connected to the use of urinary FSH, this is counterbalanced by the lower per IU price of urinary FSH in comparison to the recombinant formulation.

Silverberg et al. (19) recently compared the cost effectiveness of recombinant FSH and urinary FSH in IVF cycles. They concluded that the economic effectiveness of a drug depends less on its costs but rather on the clinical outcomes associated with its use. Our results are strictly in contrast with this statement: we obtained a highly significant difference in favor of the urinary product, which is mainly due to the lower cost of this type of product. We cannot exclude the fact that the conclusion reached by Silverberg et al.(19) may be applied to IVF cycles and may not be valid for ovulation induction in IUI cycles.

We also have to keep in mind that, other than the pregnancy or delivery rates, the main outcome measures of the studies performed in IVF cycles were the number of growing follicles, the number of the oocytes retrieved, and the number of embryos obtained. The higher were those values, the better was the efficacy of the drug. The goal of the stimulation changes when ovulation induction is performed for IUI and no down-regulation protocols are used. We want to obtain 2–4 mature oocytes, not more. A stronger stimulation could result in a multiple pregnancy or, at worst, in the onset of OHSS (23). Therefore, this perspective in the evaluation of the outcomes of the ovarian stimulation, as well as the different methodology, could explain the results obtained in the analysis of the cost effectiveness of the two FSH compounds.

Numerous studies have been published concerning the potential improvement of IVF outcomes using recombinant FSH vs. urinary FSH, whereas few data comparing the urinary and recombinant products in ovulation induction are available (24, 25).

Yarali et al. (25) prospectively compared efficacy and safety of recombinant and urinary products for ovulation induction in patients with clomiphene citrate (CC)-resistant, normogonadotropic, chronic anovulation. The main outcome measures of this study were the cumulative ovulation and pregnancy rates, the total amount of gonadotropin used throughout the stimulation, and the follicular development. No differences were found between the two treatment groups (25). In contrast, a large cohort study in unselected patients revealed a possible detrimental effect of the FSH preparation compared to those containing hMG (24).

Taking into account clinical outcome measures, it is difficult to achieve statistically significant results because of the limited number of cycles analyzed and the low value of the pregnancy rates. These are considered to be the only two clinically relevant parameters in ovulation induction or IUI cycles. It is therefore extremely important to assess the cost of each pregnancy obtained with both treatment options and in consequence, it is important to suggest the use of the more cost-effective drug. In this study we demonstrated that the cost per cycle and the cost per pregnancy were 44% and 36%, respectively, higher when the recombinant products were used, although the total amount of IU used in the recombinant FSH group was lower in comparison to the recombinant FSH one (27% less than in the urinary FSH group).

The results of this study demonstrated that the use of a more expensive recombinant product does not seem cost effective in protocols of ovulation induction in IUI cycles. The limited number of patients is not sufficient to draw final conclusions and more prospective randomized studies are needed to eventually confirm such results.

Acknowledgment: The authors thank Suzette Paolella for her support in (English) translation and language assistance.

References