Comparison of different gonadotrophin preparations in intrauterine insemination cycles for the treatment of unexplained infertility: a prospective, randomized study

A.Demirol¹,³ and T.Gurgan¹,²

¹Clinic Women Health, Infertility and IVF Center and ²Department of Obstetrics and Gynecology, Reproductive Endocrinology and IVF Unit, Hacettepe University, Ankara, Turkey
³To whom correspondence should be addressed at: Clinic Women Health, Infertility and IVF Center, Cankaya caddesi, 20/3, Cankaya, Ankara, Turkey. E-mail: ademirol@gmail.com

BACKGROUND: A comparison of the effectiveness of different gonadotrophin preparations in intrauterine insemination (IUI) cycles for patients with unexplained infertility was performed. METHODS: Two hundred and forty-one patients were prospectively randomized using computer-generated random numbers into three groups: 81 in the Follicitropin α (Group I), 80 in the urinary FSH (uFSH) (Group II) and 80 in the hMG (Group III). The primary outcome was clinical pregnancy rate with duration of stimulation, total gonadotrophin dose, number of dominant follicles, clinical pregnancy rate, multiple pregnancy, miscarriage rate and ovarian hyperstimulation syndrome (OHSS) rate being secondary outcomes. RESULTS: Clinical pregnancy rate was significantly higher in the rFSH group (25.9% in Follicitropin α, 13.8% in uFSH and 12.5% in HMG groups; \(P = 0.04\)). There was no significant difference in terms of duration of stimulation, but mean FSH dose consumed per cycle was significantly lower in the recombinant FSH (rFSH) group compared with others (825 IU in Follicitropin α, 1107 IU in uFSH and 1197 IU in HMG groups; \(P = 0.001\)). The number of follicles ≥16 mm diameter was significantly higher in the rFSH group compared with the uFSH and HMG groups (2.6 in Follicitropin α, 1.3 in uFSH and 1.4 in HMG groups; \(P = 0.001\)). CONCLUSION: rFSH may result in a better outcome in IUI cycles for unexplained infertility.

Key words: gonadotrophin/IUI/ovarian stimulation/recombinant FSH/unexplained infertility

Introduction

Ovarian stimulation improves the cycle fecundity rate in part by increasing the number of follicles available for fertilization and correcting subtle, unpredictable ovulatory dysfunction. Combined with intrauterine insemination (IUI), ovarian stimulation is recommended for many causes of infertility with patent tubes (Hughes, 1997; Hecht and Magoon, 1998; Guzick et al., 1999). Various hormonal treatment protocols have been used for ovarian stimulation, including clomiphene citrate and hMG, alone or in combination (Nuojua-Huttunen et al., 1997). Several factors can account for the improvement in cycle fecundity with stimulated IUI therapy, regardless of the apparent aetiology of infertility; the number and concentration of sperm in the upper genital tract are increased, and simultaneously several oocytes are made available.

Currently, because most patients undergoing IUI also receive ovarian stimulation, the main concern is the efficacy of the agent used for stimulation. There is still a controversy on whether gonadotrophin stimulation with or without IUI results in higher pregnancy rates than clomiphene stimulation or no stimulation (Tredway et al., 1990; Matorras et al., 1997; Guzick et al., 1999; Ecochard et al., 2000; Dankert et al., 2005). Several studies suggest that IUI cycles with ovarian stimulation improves the probability of conception compared with ovulation induction alone in unexplained infertility (Hughes, 1997; Zeyneloglu et al., 1998).

Until recombinant human FSH [r(h)FSH] has been recently marketed (Olijve et al., 1996; Shoham and Insler, 1996), all available human FSH pharmaceutical preparations were made from post-menopausal urine extracts. Recombinant FSH (rFSH) preparations, which are completely lacking of any LH activity and extraneous human protein, have numerous advantages.

The comparison of different gonadotrophin preparations was performed in some studies for IVF cycles (Out et al., 1995; Bergh et al., 1997; Brinsden et al., 2000; Harlin et al., 2000). However, there is little data in IUI cycles. In a prospective randomized study, urinary FSH (uFSH) and rFSH were compared in IUI cycles (Matorras et al., 2000; Isaza et al., 2003; Gerli et al., 2004). But, prospective randomized comparison of rFSH, uFSH and hMG has not been performed in IUI cycles up to now. As far as we know, our study is the first comparing three different gonadotrophin preparations in IUI cycles.
Materials and methods

Two hundred and forty-one patients with unexplained infertility were enrolled in this study. Patients were recruited between May 2000 and May 2004 and included in the study if they satisfied the following criteria: (i) history of primary infertility of >2 years, (ii) woman’s age between 20 and 40 years, (iii) documentation of normal ovulatory cycles, (iv) patent tubes have been shown by hysterosalpingography (HSG) or laparoscopy (LJS) and (v) normal sperm count and motility according to the World Health Organization criteria (World Health Organization, 1992) and normal morphology according to the Kruger’s criteria (Kruger et al., 1988). Exclusion criteria are as follows: (i) previous assisted reproduction technology (ART) cycle, (ii) previous controlled ovarian stimulation (COS)-IUI cycle and (iii) history of pelvic surgery.

The primary outcome measure was clinical pregnancy rate. The hypothesis is that rFSH results in a different clinical pregnancy rate IUI cycles for unexplained infertility than that in highly purified uFSH or hMG.

This study was designed to have sufficient power to detect an absolute difference (rFSH) of 15% in the clinical pregnancy rate. The clinical pregnancy rate of 10% with IUI + COS was expected for one luteal difference (rFSH) of 15% in the clinical pregnancy rate. The unexplained infertility than that in highly purified uFSH or hMG.

Analysis is that rFSH results in a different clinical pregnancy rate IUI cycles for

mean BMI and number of patients with BMI <25 kg/m2 among the groups. There was no difference according to the mean BMI and number of patients with BMI <25 kg/m2 and ≥25 kg/m2 among the groups.

Results

With regard to the ovarian cycle parameters, there was no significant difference in terms of duration of stimulation, but mean gonadotrophin dose consumed per cycle was significantly lower in the rFSH group than uFSH and HMG groups (825 IU in Follitropin α, 1107 IU in uFSH and 1197 IU in HMG groups; P < 0.05).

The number of follicles ≥16 mm diameter was significantly higher in rFSH group compared with the uFSH and HMG groups (2.1 in Follitropin α, 1.3 in uFSH and 1.4 in HMG groups; P = 0.001), and likewise, E2 concentration on the day of HCG was significantly higher in rFSH group (464 pg/ml in Follitropin α, 395 pg/ml in uFSH and 455 pg/ml in HMG groups; P = 0.001). There was no difference among the groups with respect to the endometrial thickness on the HCG day.

Clinical pregnancy rate was significantly high in rFSH group (25.9% in Follitropin α, 13.8% in uFSH and 12.5% in HMG groups; P = 0.04).

75 IU of gonadotrophins if the patient’s BMI was <25 kg/m² and with 150 IU if the patient’s BMI was ≥25 kg/m² with daily injections. Stimulation of the cycles was monitored by serum estradiol (E₂) level and transvaginal sonography, and gonadotrophin doses were adjusted individually. hCG, 10 000 IU (Profasi, Serono), was given on the day which one or more follicles of ≥16 mm diameter. Patients with decreasing E₂ levels or more than three follicles of ≥16 mm, on the day of HCG, the cycle was cancelled. A single insemination per cycle was performed at 36 h after HCG administration. Sperm preparation was performed with PureSperm (Dogan Medikal, Istanbul, Turkey). A prepared sperm volume of 0.3–0.4 ml was used for insemination. There were no significant differences in semen characteristics of three groups. Only one cycle per patient was performed.

Serum samples were obtained 14 days after hCG administration for progesterone and βhCG levels. Clinical pregnancy was documented by TV-US, 6 weeks after the IUI.

All groups were comparable (Table I) with regard to the age and duration of infertility, and all patients had primary infertility. There was no difference according to the mean BMI and number of patients with BMI <25 kg/m² and ≥25 kg/m² among the groups.

Statistical analysis was performed by the Yates corrected chi-square, Student’s t-test, one-way analysis of variance (ANOVA) and Fisher’s exact tests with SPSS software, version 10.0 for windows. Statistical significance was set at P < 0.05.

Institutional review board approval was obtained for prospective randomized controlled study, and this study was not supported financially.

<table>
<thead>
<tr>
<th>Table I. Patients characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Mean duration of infertility (years)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
</tr>
<tr>
<td>Number of patients with BMI ≥25</td>
</tr>
<tr>
<td>Number of patients with BMI &lt;25</td>
</tr>
</tbody>
</table>

NS, non-significant; rFSH, recombinant FSH; uFSH, urinary FSH. P > 0.05.

Figure 1. CONSORT statement flow diagram.
There was no significant difference according to the multiple pregnancy, miscarriage rate and ovarian hyperstimulation syndrome (OHSS) among the groups.

Cycle outcomes are summarized in Table II.

### Discussion

The combination of COS and IUI has gained acceptance as a treatment for various fertility disorders. The rationale of this approach is based on the assumption that the likelihood of conception will increase if multiple fertilizable oocytes can be recruited in a treatment cycle and if the motile spermatozoa can be introduced directly into the uterine cavity to bypass the cervical mucus barrier and be placed closer to the oocytes (Allen et al., 1985).

Stimulated IUI cycle is less expensive and invasive than other ARTs, which is as an advantage of this type of therapy. Treatment regimens, insemination methods and indications have all undergone significant changes during time. The overall success of IUI across different studies varies with pregnancy rates ranging from as low as 5 to as high as 66% (Hannoun et al., 1998). Many of these controversies may stem from differences in treatment groups, diagnostic criteria, techniques used, age of the cohort, cause of infertility and the number of treatment cycles.

Ovulation induction with gonadotrophin significantly improves the probability of conception in couples with unexplained infertility, particularly when associated with IUI (Zikopoulos et al., 1993; Hughes, 1997; Cohlen et al., 1998; Zeyneloglu et al., 1998; Guzick et al., 1999). In the meta-analysis by the European Society for Human Reproduction and Embryology (ESHRE), the effects of IUI and FSH treatment in patients with unexplained infertility were similar: each treatment significantly increased the likelihood of conception approximately 2-fold (The ESHRE Capri Workshop, 1996a,b). In the systematic review of Hughes, when compared with untreated cycles, the average level of fecundity is more than 2-fold higher in a cycle with either treatment and approximately 5-fold higher when both treatments are combined in unexplained infertility (Hughes, 1997).

Considering the IVF cycles, r(h)FSH is more effective than hMG in some reports (Daya et al., 1995; Out et al., 1997). However, in Cochrane reviews of IVF trials, pregnancy and live birth rates with (rFSH) were not significantly better than hMG (Van Wely et al., 2003). Similarly, a prospective randomized study revealed that a standard daily dose of 100 IU of rFSH is more effective than uFSH in women undergoing IUI treatment because a more symmetric response is obtained and, in the rFSH group, a significantly lower dose of FSH was as compared with the uFSH group (Isaza et al., 2003).

There has been a controversy on the effect of ovarian stimulation on multiple pregnancy. It was suggested that in the absence of any randomized trial showing a clinical benefit over natural cycle IUI for patients with unexplained infertility, gonadotrophin treatment might not be recommended (Cohlen et al., 2005). In contrast, the review by Fauser and co-workers reported that the very nature of ovarian stimulation—with or without IUI—enhances the risk of multiple pregnancy (e.g. two or more babies) (Fauser et al., 2005). However, in a recent retrospective cohort study, it was stated that in ovulation induction for unexplained non-conception, induction of more than one follicle did not improve the ongoing pregnancy rate but increased the risk of multiple pregnancies. Therefore, to reduce the number of multiple pregnancies, in all IUI cycles for unexplained non-conception, monofollicular growth was suggested (van Rumst et al., 2006).

In another recent study, it was found that the application of a mild hyperstimulation protocol as an alternative to a standard hyperstimulation protocol for IUI did not result in higher pregnancy rates than IUI in the natural cycle, while at the same time multiple pregnancies could not be avoided. Therefore, the authors suggested that there was no place for the use of gonadotrophins in IUI treatment (Goverde et al., 2005). According to above collection of data, there is still uncertainty about the effect of ovarian stimulation on pregnancy rate and multiple pregnancies. Therefore the choice of use of gonadotrophin is an authority based, and the best gonadotrophin regimen that achieves the highest pregnancy rates in IUI cycles is also controversial.

In this study, we used ovulation induction with IUI in the treatment of unexplained infertility on the basis of the controversial current literature. As far as we know, this study is the first in which different gonadotrophin preparations were compared in a prospective randomized manner. However, previous randomized trials are not in line with the results of this study. In the trial of Gerli, the only difference found was that less ampoules FSH were used. There were no differences in clinical outcomes or duration of stimulation (Gerli et al., 2004).
another trial, hMG was compared with rFSH in IUI-COS cycles. In this trial hMG administration was associated with lower treatment duration, gonadotrophin dose and cost. Clinical outcomes where comparable (Filicori et al., 2003). In contrast, in our study, rFSH administration was significantly associated with lower gonadotrophin dose, higher number of follicles and pregnancy rates. However the limited size in all groups, the low power value and the $P$ value of clinical pregnancy rate close to significance are all the limitations of our study.

In this study, the pregnancy rates observed in the hMG and uFSH groups (12.5 versus 13.8%) were lower than that in the rFSH group (25.9%). However, a 10–20% clinical pregnancy rates per cycle is regarded as acceptable range for all aetologies (Allen et al., 1985; Ombelet et al., 1995).

In spite of the limitations of our study, the results of this study may suggest an increased efficacy of rFSH over uFSH and HMG in terms of pregnancy rate. The reason for this higher effectiveness of rFSH may be related to higher mean number of dominant follicle in this group. Furthermore, mean total dose per cycle was significantly lower in rFSH group. To confirm our results, more randomized prospective studies including high number of women should be planned.

References

Bergh C, Howles CM, Borg K, Hamberger L, Josefsson B, Nilsson L and Wicklund M (1997) Recombinant human follicular stimulating hormone (r-hFSH; Gonal-F) versus highly purified urinary FSH (Metrodin HP); results of a randomized comparative study in women undergoing assisted reproductive techniques. Hum Reprod 12,2133–2139.


Submitted on January 30, 2006; resubmitted on May 13, 2006; accepted on July 24, 2006