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A prospective randomized noninferiority study comparing recombinant FSH and highly purified menotropin in intrauterine insemination cycles in couples with unexplained infertility and/or mild-moderate male factor

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Objective: To demonstrate the noninferiority of highly purified menotropin (HP-hMG) compared with recombinant FSH (rFSH) regarding clinical pregnancy rate (PR) in intrauterine insemination (IUI) cycles.
Design: Prospective randomized noninferiority trial.
Setting: Unit of physiopathology of human reproduction, university hospital.
Patient(s): Five hundred twenty-three patients with unexplained infertility or mild male infertility undergoing controlled ovarian hyperstimulation for IUI.
Intervention(s): Patients were randomized for treatment with rFSH (262 patients) or HP-hMG (261 patients). Insemination was performed 34–36 hours after hCG injection.
Main Outcome Measure(s): The primary outcome was clinical pregnancy rate (PR). The secondary outcome was the number of interrupted cycles for high risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy.
Result(s): The clinical PR was 19.7% (95% confidence interval [CI] 15.3%–25.1%) in the HP-hMG group and 21.4% (95% CI 16.9%–26.8%) in the rFSH group [absolute difference −1.7% (95% CI −8.6%–5.2%)]; therefore, the noninferiority was demonstrated. The number of interrupted cycles for OHSS risk and multiple pregnancy was significanty higher in the rFSH group, 8.4% (95% CI 5.6%–12.4%) than in the HP-hMG group 1.2% (95% CI 0.4%–3.3%) [absolute difference −7.27% (95% CI −11.3 to −3.7)].
Conclusion(s): HP-hMG is not inferior compared with rFSH regarding clinical PR. (Fertil Steril® 2011;95:689–94. ©2011 by American Society for Reproductive Medicine.)

Key Words: HP-hMG, infertility, IUI, ovulation induction, rFSH

Intrauterine insemination (IUI) associated with ovarian stimulation is the first treatment option for couples with unexplained or moderate-to-mild male infertility (1–5).

Various factors might influence the outcome of IUI. These include: type of subfertility, women's age, semen quality, timing of insemination, premature luteinization, and ovarian stimulation protocol (6, 7). The overall success of IUI across different studies regarding pregnancy rate ranges from as low as 4% to as high as 40% (8, 9).

Several hormonal treatment protocols are described in the literature for ovarian stimulation: gonadotropins, antiestrogens, and aromatase inhibitor. However, there is not agreement regarding the best treatment to be used. It is important to emphasize that the majority of published data compares different gonadotropin preparations in intracytoplasmic sperm injection (ICSI) or in vitro fertilization (IVF) cycles (10, 11). Few studies are present in the literature (12–14) regarding the IUI procedure.

Our study compared two different gonadotropin preparations, recombinant FSH (rFSH) and highly purified menotropin (HP-hMG), for ovarian stimulation/IUI cycles for couples with unexplained infertility or mild male factor.

This study was set up as a noninferiority trial, in which the primary outcome was the clinical pregnancy rate (PR). A noninferiority trial is appropriate when a new intervention has fewer adverse effects and/or lower costs, and one might accept a little less benefit that with the standard intervention (rFSH in this case) to gain the advantage in adverse effects or costs. It is well established that the overall costs of stimulated cycles are reduced using HP-hMG compared with rFSH in ICSI or IVF cycles (15).

The aim of our study was to evaluate whether HP-hMG is a noninferior treatment, compared with rFSH, regarding obtained clinical PR in couples with unexplained infertility or mild-moderate male factor that undergo IUI. In addition, the secondary end point was the prevalence of multiple pregnancy, miscarriage, and the number of interrupted cycles for high risk of ovarian hyperstimulation syndrome (OHSS).

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MATERIALS AND METHODS

Study Population

Five hundred fifty consecutive infertile women aged 30–40 years were recruited between January 2008 and December 2009 at the Institute of Physiopathology of Human Reproduction of the Policlinico Gemelli, Rome.

The eligibility criteria were: women in good health; aged <41 years; regular ovulatory menstrual cycles; body mass index (BMI) ≤26 kg/m^2; bilateral tubal patency; normal or moderate-to-mild male infertility, according to World Health Organization criteria; and normal day 3 hormonal pattern: FSH (2.5–11 mIU/mL), LH (2.5–15 mUI/mL), E_2 (30–100 pg/mL), PRL (3.5–26.5 ng/mL), A (0.40–3 ng/mL), T (0.20–0.60 ng/mL), SHBG (25–100 nmol/L), free androgen index (FAI) <5, DHEAS (800–3,000 ng/mL), 17OH-P (0.2–1.2 ng/mL), and cortisol (80–220 ng/mL). The exclusion criteria were: mono/bilateral closed tubes; severe male factor, represented by a total motile sperm count of <1 million after semen preparation; polycystic ovarian syndrome or any systemic disease or endocrine or metabolic abnormalities; endometriosis; pelvic inflammatory disease; malformation of sexual organs; malignancies; and breast pathology incompatible with gonadotropin stimulation.

Women were enrolled in this study only for one cycle of treatment. Each of the participants gave her informed consent, after having been informed on all aspects of the study and in particular about the risks of ovarian hyperstimulation and multiple pregnancy.

Intervention

Two hundred sixty-two patients were treated with rFSH (follitropin alpha; Gonal-f; Merck Serono, Geneva, Switzerland), and two hundred sixty-one patients were treated with HP-hMG (Meropur; Ferring Pharmaceuticals, Copenhagen, Denmark). Both gonadotropin preparations were used subcutaneously.

Ovarian stimulation cycles were started on the third day of menstruation, after basal ultrasound examination and hormonal assay. The starting gonadotropin dose used was 75 UI if the woman's age was ≤35 years and 150 UI if the woman's age was >35 years. The drug dose was adjusted according to the individual follicular response. Follicular development was monitored by ultrasound and by E_2 levels. A single intramuscular injection of hCG (Gonasi; Serono; 10,000 IU) was administered in the presence of ≥1 follicle ≥17 mm.

hCG was not administered if >3 large follicles ≥17 mm, >4 follicles ≥16 mm, and/or E_2 >1,500 pg/mL, to minimize the risk of multiple pregnancy and/or OHSS.

A single IUI was performed 34–36 hours after hCG injection. A gradient technique with Percoll (Irvine Scientific, Irvine, CA) was used for semen preparation. The sperm suspension, in a volume of 0.35 mL, was kept at room temperature until transfer into the uterine cavity, which was performed within 15 minutes. Ovulation was confirmed by progesterone and ultrasound.

A serum β-hCG test was performed 15–20 days after hCG administration. Clinical pregnancy was documented by transvaginal ultrasound 6 weeks after the IUI. Miscarriage was defined as a loss of a pregnancy before the 13th week of gestation.

The Institutional Board of the Department of Obstetrics and Gynecology approved the plan of work and informed consent was obtained from each patient.

Objective

The aim of this study was to evaluate the noninferiority of HP-hMG compared with rFSH regarding clinical PR in IUI cycles for patients with unexplained infertility or mild-moderate male factor. The noninferiority margin was set at 9%, because this threshold was considered to indicate important differences based on clinical judgement from standard day-to-day practice in our center. Moreover, we would like to determine whether both treatments were equivalent regarding multiple pregnancies, miscarriages, and interrupted cycles for high risk of OHSS.

Outcomes

The primary efficacy end point was the clinical PR. The major secondary end points were cycle cancellation for risk of OHSS, multiple pregnancy, and miscarriage.

The other secondary end points were length of stimulation, total gonadotropin dose, numbers of midsize follicles and dominant follicles, E_2 levels on hCG day, endometrial thickness, and *P* levels on the midluteal phase.

Sample Size

Our sample size calculation was based on the primary outcome. Because it was a noninferiority trial, this study was designed to exclude an actual difference between HP-hMG and rFSH of >9% (the noninferiority margin) regarding a previously reported clinical trial evaluating clinical PR (26%) in IUI cycles stimulated with rFSH (14). The chosen noninferiority margin corresponds to preservation of 17% of the minimum efficacy of HP-hMG. On the basis of this threshold, 500 events would be necessary for 80% power with a one-sided type I error of .05. To face possible missing data or dropout in the follow-up, we aimed to recruit 275 patients per group, 550 in total.

Randomization

Five hundred twenty-three consecutive eligible subjects, who accepted to participate to the study, were randomly assigned to one of the two treatment groups by giving them a code number from a computer generated randomization list, in order of enrollment. To guarantee the concealment of allocation, a staff member who was not directly involved in the study was in possession of the randomization list; in this way, after receiving information from the physician recruiting the women, the staff member followed his own randomization list when allocating each patient. Both the patient and the gynecologists were informed of the assigned treatment.

Statistical Methods

The main principle of our analysis was noninferiority; we hypothesized that there would be no difference between treatments in clinical PR. Noninferiority of HP-hMG was accepted if the lower bound of the two-sided 95% confidence interval (CI) around the estimated difference, in proportion of patients reaching pregnancy was above −9%.

Primary and major secondary end points within each treatment arm are presented as absolute number and percentage with corresponding two-sided normal-approximation 95% CI. The results are summarized comparatively as differences between the two arms with a 95% CI for each comparison made (16). Baseline characteristics of patients and clinical parameters during gonadotropin stimulation are presented as means with SD.

Comparisons between the two groups for the other secondary outcomes were made with Student *t* test (or Mann-Whitney test when the requirements for *t* test were violated) for continuous variables and with the χ^2 test for nominal variables. The significance level was set at $P<.05$.

RESULTS

All recruited women were screened for eligibility, and 550 of these were included in the study (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. No significant difference existed between the two groups regarding age, BMI, hormone levels, and sperm quality.

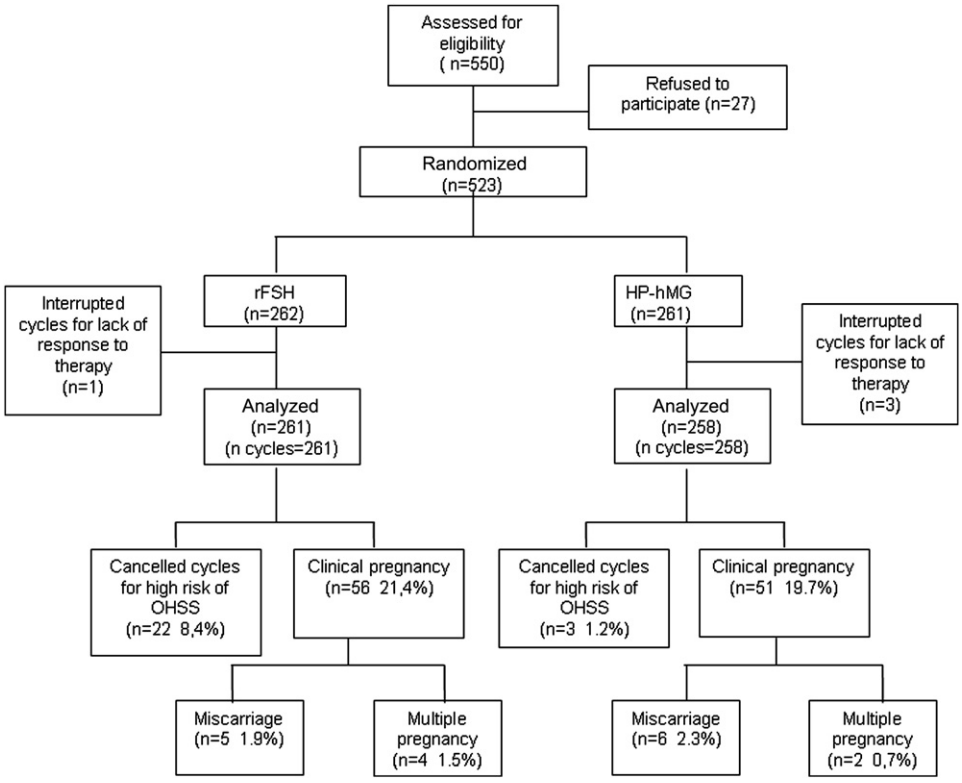
In particular, 262 patients underwent one cycle of ovarian stimulation with rFSH and 261 with HP-hMG. There were three interrupted cycles for lack of response to therapy in the HP-hMG group and 1 in the rFSH group.

We obtained 51 clinical pregnancies in the 258 HP-hMG cycles (19.7%, 95% CI 15.3–25.1) and 56 in the 261 rFSH cycles (21.4%, 95% CI 16.9–26.8); the noninferiority of HP-hMG to rFSH was demonstrated based on the values of the lower 95% CI limits for the absolute differences between arms (being <−9%), as shown in Table 2.

There were six cases of miscarriage with HP-hMG (2.3%, 95% CI 1.1–4.9) and five with rFSH (1.9%, 95% CI 0.8–4.3); multiple pregnancy was observed in two HP-hMG–treated patients (0.7%, 95% CI 0.2–2.8) and four rFSH (1.5%, 95% CI 0.6–3.9). All of them were twin pregnancies. This study was not sufficiently powered to

FIGURE 1

Flow diagram. There were three cycles interrupted for lack of response to therapy in the highly purified menotropin (HP-hMG) group and one in the recombinant FSH (rFSH) group. There were 51 clinical pregnancies in the 258 HP-hMG cycles (19.7%) and 56 in the 261 rFSH cycles (21.4%). There were six cases of miscarriage with HP-hMG (2.3%) and five with rFSH (1.9%), and two cases of multiple pregnancy in the HP-hMG group (0.7%) and four in the rFSH group (1.5%). The canceled cycles for high risk of OHSS were 22 (8.4%) in the rFSH group and 3 (1.2%) in the HP-hMG group. No case of extrauterine pregnancy was observed.



Sagnella. Randomized trial: rFSH vs HP-hMG. Fertil Steril 2011.

exclude an actual difference between treatments regarding multiple pregnancy and miscarriage. No case of extrauterine pregnancy was observed.

Regarding the characteristics and response to stimulation of pregnant patients, there were no significant difference between the two groups regarding: infertility causes (unexplained infertility 92.3% in HP-hMG and 84.6% in rFSH; male factor 7.7% in HP-hMG and 15.4% in rFSH); FSH on day 3 (8.3 ± 0.84 in HP-hMG and 8.1 ± 1.47 in rFSH); E_2 on day 3 (59.8 ± 35.67 in HP-hMG and 46.7 ± 9.45 in rFSH); and endometrial thickness on the hCG day (8.13 ± 0.63 in HP-hMG and 8.7 ± 0.58 in rFSH). Interestingly the only significant differences were: mean patient age (37.2 ± 1.2 years in HP-hMG and 32 ± 2.1 years in rFSH group; $P<.05$); E_2 levels (551.75 ± 240.06 in HP-hMG and 833.19 ± 385.8 in rFSH group; $P=.004$); and the number of follicles >17 mm on the hCG day (1.15 ± 0.38 in HP-hMG and 1.7 ± 0.63 in rFSH group; $P=.01$).

Regarding the major secondary end point, the number of interrupted cycles for OHSS risk was significantly higher in the rFSH group [8.4% (95% CI 5.6–12.4)] compared with the HP-hMG group [1.2% (95% CI 0.4–3.3; Table 2)].

No significant difference were observed regarding mean gonadotropin dose and length of stimulation between the two treatments. Regarding follicular development, there was a significantly lower average number of intermediate-size follicles (14–16 mm) at the end of stimulation in the HP-hMG group (0.73 ± 1.00 in HP-hMG and 1.96 ± 1.54 in rFSH; $P=.001$); furthermore, the number of follicles ≥17 mm was significantly higher in rFSH cycles (1.27 ± 0.45 in HP-hMG and 1.69 ± 0.84 in rFSH; $P=.03$; Table 3).

Development of one dominant follicle (≥17 mm) without intermediate-size follicles was achieved for 42.3% in the HP-hMG cycles versus 11.5% in the rFSH cycles ($P=.03$). On the hCG day, E_2 levels were significantly higher in the rFSH group compared with HP-hMG (833.19 ± 385.80 pg/mL and 551.75 ± 240.06 pg/mL, respectively; $P=.004$). No significant difference in endometrial thickness were observed. Higher *P* levels were observed in the rFSH cycles (37.77 ± 26.22 ng/mL in rFSH and 23.52 ± 13.39 ng/mL in HP-hMG; $P=.02$) (Table 3).

DISCUSSION

This prospective randomized noninferiority study demonstrated that HP-hMG preparation is noninferior to a r-FSH preparation regarding clinical PR.

Several studies have analyzed the efficacy of different gonadotropin treatments in the IVF and ICSI cycles, but only a few authors

TABLE 1

Baseline characteristics of patients.

Characteristic	rFSH group	HP-hMG group	*P* value
Age (y)	35.38 ± 3.09	35 ± 2.98	NS
Duration of infertility (mo)	36 ± 17.95	35 ± 18.2	NS
BMI (kg/m^2)	21.9 ± 2.2	22.4 ± 1.9	NS
Indication			
Male factor (%)	19.1	20.3	NS
Unexplained (%)	80.9	79.7	NS
Male age (y)	38.1 ± 4.7	39 ± 3.2	NS
Spermiogram characteristics with male factor			
Concentration (/mL)	1,9800,000 ± 4,750,000	18,655,000 ± 5,962,000	NS
Motility (%)	48 ± 11.4	45 ± 9.7	NS
Morphology (%)	30 ± 8.4	26 ± 9.9	NS
Spermiogram characteristics with unexplained infertility			
Concentration (/mL)	41,444,000 ± 15,780,614	54,221,700 ± 12,795,400	NS
Motility (%)	50 ± 11.4	52.7 ± 12	NS
Morphology (%)	35 ± 6.9	38 ± 8.2	NS
Mean baseline hormone values			
FSH (mUI/mL)	7.47 ± 1.55	7.75 ± 1.76	NS
E_2 (pg/mL)	44.40 ± 13.95	48.93 ± 20.00	NS
PRL (ng/mL)	16.7 ± 5.67	19.2 ± 7.8	NS
LH day 3 (mUI/mL)	4.2 ± 0.92	5.4 ± 1.3	NS
A (ng/mL)	1.38 ± 0.52	1.68 ± 0.9	NS
Free androgen index	1.38 ± 0.58	1.56 ± 0.72	NS
Glucose (mg/dL)	73.78 ± 5.22	75.91 ± 6	NS
Insulin (μgUI/mL)	5.73 ± 1.42	6.2 ± 2.5	NS
Antral follicle count	9.2 ± 2.1	9.9 ± 2.1	NS

Note: Data are expressed as mean ± SD. Statistical analysis was performed by Student *t* test for continuous variables and by χ^2 test for nominal variables. The significance level was set at $P<.05$. BMI = body mass index; HP-hMG = highly purified menotropin; NS = not significant; rFSH = recombinant FSH.

Sagnella. Randomized trial: rFSH vs HP-hMG. Fertil Steril 2011.

have focused on IUI cycles (14, 17). As far as we know, our study is the first randomized noninferiority study comparing two different gonadotropin formulations in IUI cycles.

In this investigation, different effects on follicle recruitment and circulating E_2 concentrations were observed at the end of ovarian stimulation cycles, despite the administration of a similar dose of two preparations, equally calibrated for FSH bioactivity (IU). Bi/multifollicular development was significantly higher in the rFSH cycles, contributing to the significantly higher estradiol concentration compared with HP-hMG cycles. In contrast, the development of a single dominant follicle without intermediate-size follicles was significantly higher in the HP-hMG cycles.

The lower number of follicles obtained in HP-hMG cycles could reflect an LH effect during the follicular phase; the gonadotropin might induce follicular atresia. The same effect has also been observed in IVF and ICSI cycles comparing HP-hMG and rFSH (18, 19). It is known that FSH and LH have two different roles in the development of follicles. FSH promotes the growth of all follicles, and LH facilitates selective follicular growth (20, 21). Exposure to the hCG activity present in the HP-hMG preparation from the beginning of stimulation might explain the different effects on follicular growth and selection that we observed. Smitz et al. (22) found higher androgen concentrations in the HP-hMG group compared with rFSH. It is reasonable to believe that the shift in favor

TABLE 2

Primary and major secondary outcome measures.

	HP-hMG, % (95% CI)	rFSH, % (95% CI)	Absolute difference (95% CI)
Clinical PR	19.7 (15.3 to 25.1)	21.4 (16.9 to 26.8)	−1.7 (−8.6 to 5.2)
Interrupted cycles for high risk of OHSS rate	1.2 (0.4 to 3.3)	8.4 (5.6 to 12.4)	−7.27 (−11.3 to −3.7)
Miscarriage rate	2.3 (1.1 to 4.9)	1.9 (0.8 to 4.3)	0.4 (−2.3 to 3.3)
Multiple pregnancy rate	0.7 (0.2 to 2.8)	1.5 (0.6 to 3.9)	−0.7 (−3.2 to 0.2)

Note: Noninferiority of HP-hMG was accepted if the lower bound of the two-sided 95% CI around the estimated difference, in proportion of patients reaching pregnancy, was ≥9%. CI = confidence interval; OHSS = ovarian hyperstimulation syndrome; PR = pregnancy rate; other abbreviations as in Table 1.

Sagnella. Randomized trial: rFSH vs HP-hMG. Fertil Steril 2011.

TABLE 3

Clinical parameters during gonadotropin stimulation.

Parameter	HP-hMG	rFSH	*P* value
Dose total for cycles (UI)	672.12 ± 219.92	742.79 ± 317.14	NS
Days of stimulation	7.08 ± 1.49	7.27 ± 1.99	NS
FSH on day 3 (mUI/mL)	7.75 ± 1.76	7.47 ± 1.55	NS
E_2 on day 3 (pg/mL)	48.93 ± 20.00	44.40 ± 13.95	NS
Endometrial thickness on hCG day (mm)	8.82 ± 1.51	9.23 ± 1.46	NS
Follicles of 14–16 mm on hCG day	0.73 ± 1.00	1.96 ± 1.54	.001
Follicles ≥17 mm on hCG day	1.27 ± 0.45	1.69 ± 0.84	.03
E_2 on hCG day (pg/mL)	551.75 ± 240.06	833.19 ± 385.80	.004
Endometrial thickness in midluteal phase (mm)	10.56 ± 2.24	9.96 ± 1.94	NS
P in midluteal phase (ng/mL)	23.52 ± 13.39	37.77 ± 26.22	.02

Note: Data are expressed as mean ± SD. Statistical analysis was performed by Student *t* test (or Mann-Whitney test when the requirements for *t* test were violated). The significance level was set at $P<.05$. Abbreviations as in Table 1.

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of hCG-induced androgens could lead to a more selective follicle growth (21).

The present study also demonstrated higher *P* levels in rFSH cycles, probably explained by two mechanisms: the more obvious one represented by the higher number of ovulating follicles producing E_2 and consequently more *P*. A second hypothesis could be justified by the possible following intraovarian mechanism: LH/hCG might inhibit transforming growth factor (TGF) β, which in turn suppresses 17 α-hydroxylase; thus, the lack of the TGF-β suppressive action might induce the enzymatic conversion of a greater amount of *P* in androgens. The consequent result is a lower *P* level in HP-hMG cycles (23, 24).

In the present study, despite significant differences between the two treatment groups regarding number of dominant follicles and hormonal environment, the endometrial thickness and the clinical pregnancy rate were similar between the two groups. Our results are in agreement with the evidence deriving from studies conducted by several authors in assisted reproductive technology cycles.

Platteau et al. found higher PR in women undergoing IVF when HP-hMG was used compared with rFSH. Conversely, no difference was observed among ICSI patients (25), suggesting a possible positive effect of HP-hMG on cumulus oophorus function. According to Smitz et al. (22), we could hypothesize that exogenous LH/hCG activity might positively influence oocyte quality and development. This observation could explain the benefit regarding PR for those normo-ovulatory women with unexplained infertility who achieved pregnancy even though they developed a monofollicular response.

Interesting data in the present study concern the different mean age of pregnant patients. Mean age of pregnant patients was higher in the HP-hMG group compared with the rFSH group. This observation led us to hypothesize that, in older women, the addition of LH/hCG activity could positively affect oocyte quality and steroidogenesis. This hypothesis is supported by data demonstrating that in poor responders, superimposing rLH on rFSH improves outcome data (26, 27).

Finally, because one of the main challenges for clinicians involved in ovulation induction is controlled ovarian hyperstimulation cycle cancellation, another end point of our work was to evaluate the frequency of interrupted cycles for high risk of OHSS and multiple pregnancy. We observed that the number of interrupted cycles was higher in the rFSH group; therefore, HP-hMG treatment might besafer in women who tend to a multifollicular response.

In conclusion, considering the primary outcome—clinical PR—HP-hMG preparation is noninferior to rFSH. Nevertheless, in our opinion, in IUI cycles the choice of the best treatment to use should take into consideration the characteristics of each patient, such as age and tendency to hyperstimulation. In particular, young patients might benefit from the use of rFSH, whereas in patients aged over 35 years, the association of the LH/hCG component with rFSH seems to be more appropriate. Further studies need to be performed to confirm this hypothesis.

REFERENCES

1. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Human Reprod 1997;12:1865–72.
2. Cohlen BJ. Should we continue performing intrauterine insemination in the year 2004? Gynecol Obstet Invest 2005;59:3–13.
3. Zikopoulos K, West CP, Thong PW, Kacser EM, Morrison J, Wu FC. Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility. Hum Reprod 1993;8:563–7.
4. Zeyneloglu HB, Arici A, Olive DL, Duleba AJ. Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis. Fertil Steril 1998;69:486–91.
5. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. National Cooperative Reproductive Medicine Network. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. N Engl J Med 1999;340:177–83.
6. Costello MF. Systematic review of treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. Aust N Z J Obstet Gynaecol 2004;44:93–102.
7. Cunha-Filho JS, Kadoch J, Righini C, Fanchin R, Frydman R, Olivennes F. Premature LH and progesterone rise in intrauterine insemination cycles: analysis of related factors. Reprod Biomed Online 2003;7:194–9.
8. Karlström PO, Bergh T, Lundkvist O. A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate. Fertil Steril 1993;59:554–9.
9. Fanchin R, Olivennes F, Righini C, Hazout A, Schwab B, Frydman R. A new system for fallopian tube sperm perfusion leads to pregnancy rates twice as high as standard intrauterine insemination. Fertil Steril 1995;64:505–10.
10. Kilani Z, Dakkak A, Ghunaim S, Cognini GE, Tabarelli C, Parmegiani L, et al. A prospective, randomized, controlled trial comparing highly purified hMG with recombinant FSH in women undergoing ICSI: ovarian response and clinical outcomes. Hum Reprod 2003;18:1194–9.
11. Al-Inany HG, Abou-Setta AM, Aboulghar MA, Mansour RT, Serour GI. Efficacy and safety of human

menopausal gonadotrophins versus recombinant FSH: a meta-analysis. Reprod Biomed Online 2008;16:81–8.
12. Balasch J, Ballesca JL, Pimentel C, Creus M, Fabregues F, Vanrell JA. Late low-dose pure follicle stimulating hormone for ovarian stimulation in intra-uterine insemination cycles. Hum Reprod 1994;9:1863–6.
13. Matorras R, Recio V, Corcóstegui B, Rodríguez-Escudero FJ. Recombinant human FSH versus highly purified urinary FSH: a randomized study inintrauterine insemination with husbands" spermatozoa. Hum Reprod 2000;15:1231–4.
14. Demirol A, Gurgan T. Comparison of different gonadotrophin preparations in intrauterine insemination cycles for the treatment of unexplained infertility: a prospective, randomized study. Hum Reprod 2007;22:97–100.
15. Wechowski J, Connolly M, Schneider D, McEwan P, Kennedy R. Cost-saving treatment strategies in in vitro fertilization: a combined economic evaluation of two large randomized clinical trials comparing highly purified human menopausal gonadotropin and recombinant follicle-stimulating hormone alpha. Fertil Steril 2009;91: 1067–76.
16. Altman DG, Doré CJ. Baseline comparisons in randomized clinical trials. Stat Med 1991;10: 797–9.
17. Filicori M, Cognini GE, Pocognoli P, Tabarelli C, Ferlini F, Perri T, et al. Comparison of controlled ovarian stimulation with human menopausal gonadotropin or recombinant follicle-stimulating hormone. Fertil Steril 2003;80:390–7.
18. Bosch E, Vidal C, Labarta E, Simon C, Remohi J, Pellicer A. Highly purified hMG versus recombinant FSH in ovarian hyperstimulation with GnRH antagonists—a randomized study. Hum Reprod 2008;23: 2346–51.
19. Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod 2006;21:3217–27.
20. Platteau P, Andersen AN, Balen A, Devroey P, Sorensen P, Helmgaard L, et al. Similar ovulation rates, but different follicular development with highly purified menotrophin compared with recombinant FSH in WHO group II anovulatory infertility: a randomized controlled study. Hum Reprod 2006;21: 1798–804.
21. Loumaye E, Engrand P, Shoham Z, Hillier SG, Baird DT. Clinical evidence for an LH "ceiling" effect induced by administration of recombinant human LH during the late follicular phase of stimulated cycles in World Health Organization type I and type II anovulation. Hum Reprod 2003;18: 314–22.
22. Smitz J, Andersen AN, Devroey P, Arce JC. Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant in IVF patients. Hum Reprod 2007;22:676–87.
23. Hernandez ER, Hurwitz A, Payne DW, Dharmarajan AM, Purchio AF, Adashi EY. Transforming growth factor-β1 inhibits ovarian androgen production: gene expression, cellular localization, mechanism(s), and site(s) of action. Endocrinology 1990;127:2804–11.
24. Fournet N, Weitsman SR, Zachow RJ, Magoffin DA. Transforming growth factor-β inhibits ovarian 17 α-hydroxylase activity by direct noncompetitive mechanism. Endocrinology 1996;137:166–74.
25. Platteau P, Smitz J, Albano C, Sorensen P, Arce JC, Devroey P. Exogenous luteinizing hormone activity may influence the treatment outcome in in vitro fertilization but not in intracytoplasmic sperm injection cycles. Fertil Steril 2004;81:1401–4.
26. Lisi F, Rinaldi L, Fishel S, Lisi R, Pepe G, Picconeri MG, et al. Use of recombinant FSH and recombinant LH in multiple follicular stimulation for IVF: a preliminary study. Reprod Biomed Online 2001;3:190–4.
27. Ferraretti AP, Gianaroli L, Magli MC, d'Angelo A, Farfalli V, Montanaro N. Exogenous luteinizing hormone in controlled ovarian hyperstimulation for assisted reproduction techniques. Fertil Steril 2004;82:1521–6.