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Effectiveness of HP-hMG versus r-FSH in patients undergoing IVF/ICSI cycles with moderate male-factor infertility

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Aim: The aim of this case-control study was to compare the efficacy of highly purified human menopausal gonadotropin (HP-hMG) versus recombinant follicle stimulating hormone (r-FSH) treatments following gonadotropin-releasing hormone (GnRH) agonist suppression in patients undergoing intracytoplasmic sperm injection (ICSI) with moderate male-factor infertility in terms of oocyte and embryo quality and clinical pregnancy outcomes.

Materials and methods: A total of 240 infertile women were treated with HP-hMG (HP-hMG group, n = 120 patients) or r-FSH (r-FSH group, n = 120 patients) following GnRH agonist suppression (long regimen). Inclusion criteria for the study groups were infertility due to moderate oligoasthenoteratospermia with no associated female infertility factor, fewer than 2 previous assisted reproductive technology cycles, and female patients with ages between 19 and 35 years, normal basal FSH, regular ovulatory cycles, and body mass index below 30 kg/m^2.

Results: Treatment durations and gonadotropin doses were similar in both groups. Cycle cancellation rates, clinical pregnancy and miscarriage rates, total and metaphase II oocytes retrieved, fertilization rate, and number of embryos transferred were all similar in both groups. The clinical pregnancy rates were 45.9% (n = 50/109) in the r-FSH group and 40.4% (n = 44/109) in the HP-hMG group.

Conclusion: HP-hMG is as effective as r-FSH in terms of oocyte and embryo quality and clinical pregnancy outcomes in patients undergoing ICSI with moderate male-factor infertility.

Key words: Male-factor infertility, ICSI, highly purified hMG, recombinant FSH, GnRH agonist

1. Introduction

In recent years, induction of ovulation has shown major advances, with multiple products becoming commercially available, while the focus of ovarian stimulation has shifted from trying to obtain the maximum possible number of oocytes to trying to obtain an adequate cohort of good-quality embryos, i.e. from quantity to quality (1). Urinary products include human menopausal gonadotropins (hMG), urinary FSH (uFSH), and human chorionic gonadotropin (hCG). More recently, recombinant preparations such as recombinant-FSH (r-FSH) and recombinant luteinizing hormone (rLH) have entered the market. Finally, highly purified (HP)-hMG, in which the purification process allows its administration via the subcutaneous route, is the latest addition to this family of infertility drugs. HP-hMG and r-FSH have been widely and successfully used for ovarian stimulation in infertile women undergoing treatment for in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and embryo transfer.

It is well known that the quantitative aspects can be modulated by the doses of gonadotropins, the type of gonadotropin used, and by the endocrine environment associated with stimulation (2–5). Randomized controlled trials comparing gonadotropin preparations have primarily focused on clinical aspects and have been designed to evaluate the number of oocytes retrieved or, to a lesser extent, pregnancy rates.

Several studies comparing the outcome of r-FSH and hMG have been reported, most of which were performed in women undergoing pituitary downregulation with a GnRH agonist long protocol (6–13). Recent metaanalyses

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have demonstrated that hMG was not inferior to r-FSH with regard to pregnancy and live birth rates (14,15). Van Wely et al. found a borderline significant difference of a 5% higher clinical pregnancy rate in women stimulated with menotropins (27%) compared with r-FSH (22%) (16). The authors further noted that additional large randomized trials were needed to precisely estimate any difference between menotropins and r-FSH. Recently, it was confirmed that a better outcome in terms of the live birth rate was obtained when HP-hMG was used for ovarian stimulation as compared with r-FSH in the GnRH agonist long protocol (17).

The aim of the present case-control study was to compare the efficacy of HP-hMG, which combines FSH and human chorionic gonadotropin-driven LH activities, versus r-FSH alone in patients undergoing ICSI with moderate male-factor infertility with a focus on oocyte and embryo quality and IVF treatment outcome.

2. Materials and methods

A total of 240 infertile women were treated with HP-hMG (HP-hMG group, n = 120 patients) or r-FSH (r-FSH group, n = 120 patients) following GnRH agonist suppression (long regimen).

Inclusion criteria for the study groups were infertility due to moderate oligoasthenoteratospermia with no associated female infertility factor and fewer than 2 previous assisted reproductive technology. An oligoasthenoteratospermic patient was defined as having sperm concentration between 5×10^6/mL and 20×10^6/mL (18).

Patients were selected if they met all the following inclusion criteria: women with good physical and mental health; aged 19–35 years; regular menstrual cycles ranging from 21 to 35 days; body mass index of <30 kg/m^2; normal basal serum FSH (1–12 IU/L) and estradiol (E2) (≤75 pg/mL) levels determined on day 3 of the cycle previous to controlled ovarian stimulation; a uterus consistent with expected normal function; presence of both ovaries and no evidence of abnormality; and no adnexal pathology as assessed by transvaginal ultrasound.

The exclusion criteria were: history of recurrent pregnancy loss; any significant systemic disease, endocrine, or metabolic disorder; concomitant medication interfering with the purposes of the study; and use of any ovulation induction drug within 1 month before inclusion in the study. Patients with polycystic ovary syndrome, stage III/IV endometriosis, or partners with severe male-factor infertility requiring ICSI were not included in the study. Likewise, poor responders (previous cycles with >20 days of gonadotropin stimulation, cancellation due to limited follicular response, or <4 follicles of 15 mm) and patients with a previous IVF cycle with unsuccessful fertilization were excluded from participation.

The primary endpoint was the clinical pregnancy rate per patient and secondary outcome endpoints were the number of cumulus–oocyte complexes retrieved, the number of metaphase II oocytes obtained, fertilization rate and serum E2 levels, and endometrial thickness on the day of hCG administration. We also compared pregnancy loss (including biochemical pregnancies, miscarriages, and ectopic pregnancies), implantation rate, and ovarian hyperstimulation syndrome (OHSS) rate.

Patients underwent controlled ovarian hyperstimulation following downregulation with a GnRH agonist in a long protocol for women undergoing IVF. All patients received an identical type and dose of concomitant fertility treatments, i.e. GnRH agonist for downregulation, hCG for triggering final maturation, and progesterone for luteal support. Treatment with GnRH-a (daily subcutaneous injections of 0.1 mg triptorelin acetate [Decapeptyl, Ferring Pharmaceuticals GmbH]) was started in the midluteal phase of the menstrual cycle and continued until the day of hCG injection. Ovarian stimulation was started with highly purified hMG (Merional, IBSA) or recombinant FSH (follitropin-alpha, GONAL-f, Serono; or follitropin-beta, Puregon, Organon) on the third day of menstrual bleeding after the pituitary desensitization (serum E2 of <50 pg/mL) in the absence of an ovarian cyst (diameter of >2 cm). If such a cyst appeared persistent during the GnRH-a treatment and E2 levels did not drop below 50 pg/mL within 2 weeks after the menstrual bleeding, the patient were excluded from the study.

The starting dose of HP-hMG or r-FSH was 225 IU for the first 5 days, followed by individual adjustments according to the patient's follicular response. Choriongonadotrophin-alpha, 250 μg subcutaneously (Ovitrelle, Serono), was administered to induce final follicular maturation within 1 day of observing 3 or more follicles of 17 mm in diameter. Oocyte retrieval took place 36 ± 1 h after hCG administration. Oocytes were cultured individually (1 oocyte per well or per droplet), from the time of retrieval until the assessment on day 3, allowing for continued individual assessment of each oocyte/embryo. Transfer of 1–3 embryos fulfilling at least the minimum-quality criteria was done on day 2 or 3 after oocyte retrieval. Vaginal progesterone gel at 90 mg/day (Crinone 8%, Serono) for luteal support was given from the day of embryo transfer until confirmation of clinical pregnancy (5–6 weeks after embryo transfer) or negative serum hCG test (13–15 days after embryo transfer).

Implantation rate is defined as the total number of gestational sacs in the study divided by the total number of embryos transferred in the study. Clinical pregnancy rate was defined as the presence of a gestational sac with a positive heartbeat 4–5 weeks after the embryo transfer.

2.1. Statistical evaluation

Data were expressed as mean ± standard deviation (SD). Normality of distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Between-group differences of normally distributed continuous variables were assessed with parametric statistics (Student's t-test), while nonparametric statistics (Mann–Whitney rank sum test) were employed when the normality test was not passed. Between-group differences in noncontinuous variables were assessed with the chi-square method with Yates' correction, if needed.

3. Results

Demographic and baseline hormonal profile characteristics of the study participants were similar in both groups (Table 1).

Out of 240 patients initially recruited for the study, 8 did not reach the oocyte retrieval procedure [5 patients receiving r-FSH (4.2%) and 3 receiving HP-hMG (2.5%); P = 0.87]. Four patients (4.1%) had treatment cancelled because of low response and 4 patients (3.8%) had treatment cancelled for being at risk of OHSS in both groups. Cycle cancellation rates were not significantly different.

Ovarian stimulation outcomes are presented in Table 2. Treatment durations and gonadotropin doses were similar in both groups.

In Table 3, parameters of oocyte retrieval and of retrieved oocytes are presented. Total and metaphase II oocytes retrieved, fertilization rate, total number of grade 1 embryos on day 3, and number of embryos transferred were all similar in both groups. The rate of mature oocytes relative to the total number of oocytes retrieved, the embryo cleavage rate, and the rate of grade 1 embryos relative to the number of fertilized oocytes were also similar. In 2 out of the 115 patients receiving r-FSH (1.7%) and 3 out of the 117 patients receiving HP-hMG (2.6%), fertilization failure occurred (P = 0.87). Embryo transfers were cancelled for 4 patients (3.5%) receiving r-FSH and in 5 patients (4.4%) receiving HP-hMG because of the low embryo quality in both groups. Cycle cancellation rates were not significantly different.

Implantation rate, clinical pregnancy, pregnancy loss, and live birth rates are presented in Table 4. No significant differences were observed between the groups.

Table 1. Demographic characteristics and baseline hormonal profiles of the participants.

Baseline parameters	r-FSH (n = 120)	HP-hMG (n = 120)	P-value
Age (years)	28.1 ± 3.3	28.2 ± 2.8	0.91
Body mass index (kg/m^2)	24.2 ± 1.5	23.9 ± 1.7	0.87
Basal FSH (IU/L)	6.2 ± 1.8	6.8 + 1.6	0.74
Basal E2 (pg/mL)	39.4 ± 23.3	39.5 ± 22.3	0.77
TSH (mU/L)	1.8 ± 0.8	1.9 ± 1.1	0.86
Antral follicle count (2–10 mm)	15.9 ± 3.9	15.2 ± 4.1	0.67

Values are expressed as mean ± SD. r-FSH, recombinant FSH; HP-hMG, highly purified hMG; E2, estradiol; TSH, thyroid-stimulating hormone.

Table 2. Ovarian stimulation outcome.

	r-FSH (n = 120)	HP-hMG (n = 120)	P-value
Total gonadotropin dose (IU)	2096 ± 923	2481 ±994	0.14
Duration of stimulation (days)	8.4 ± 1.6	8.8 ± 1.5	0.31
Peak estradiol (pg/mL)	2292 ± 965	2444 ± 978	0.12
Endometrial thickness (mm)	11.2 ± 4.3	10.7 ± 4	0.23

Values are expressed as mean ± SD.

Table 3. Parameters of oocyte retrieval and of retrieved oocytes.

	r-FSH (n = 115)	HP-hMG (n = 117)	P-value
Total number of oocytes collected	11.4 ± 8.1	10.3 ± 6.0	0.71
Number of metaphase II	8.7 ± 6.0	7.8 ± 4.0	0.43
Metaphase II/total number of oocytes (%)	75.5 ± 20.8	70.1 ± 18.4	0.12
Number of fertilized oocytes	6.1 ± 3.4	5.1 ± 3.7	0.21
Fertilization rate (%)	68.9 ± 22.3	72.8 ± 26.4	0.35
Number of grade 1 embryos	3.5 ± 2.5	3.4 ± 2.7	0.32
Grade 1 embryos/number of fertilized oocytes (%)	52.6 ± 26	59 ± 22	0.26
Number of transferred embryos	2.6 ± 0.7	2.3 ± 0.6	0.08

Values are expressed as mean ± SD. Fertilization rates are expressed as the mean of [number of zygotes per cycle/ number of oocytes per cycle] ± SD for all cycles in which oocytes were retrieved.

Table 4. Results of cycle outcomes/embryo transfer.

	r-FSH n = 109	HP-hMG n = 109	P-value
Implantation rate (%)	36.2	38	0.88
Positive hCG (%)	52.3 (57/109)	53.2 (58/109)	0.99
Clinical pregnancy (%)	40.4 (44/109)	45.9 (50/109)	0.49
Pregnancy loss (%)	16 (7/44)	16 (8/50)	0.79
Ectopic pregnancy (%)	-	2 (1/50)	0.95
Live birth rate (%)	32.1 (35/109)	37.6 (41/109)	0.48

4. Discussion

At present, different gonadotropin preparations are used in pituitary-suppressed women who are undergoing controlled ovarian stimulation for IVF procedures. Several randomized, prospective trials, comparing the effect of FSH alone and hMG preparations in IVF by using a long GnRH-a protocol, have shown that severe suppression of serum LH levels (1 IU/L) may occur in about half of the FSH-treated subjects (19). Although follicular growth can be induced by FSH in the total absence of LH, the resulting follicles have developmental deficiencies such as abnormally low production of E2 and an inability to luteinize and rupture in response to hCG stimulus (20–23). Optimal follicular development is therefore also dependent on a minimal exposure to LH or the LH threshold.

In metaanalyses of the effectiveness of hMG and r-FSH in IVF-ICSI cycles, it became evident that hMG treatment resulted in a higher clinical pregnancy rate and in higher ongoing pregnancy and live birth rates than did r-FSH, but the latter difference was of borderline significance (16). However, the heterogeneous pituitary suppression regimens and the flexible gonadotropin dosages used in those studies limited the potential for discriminating the features of these 2 gonadotropin preparations. The importance of using a similar gonadotropin dose was confirmed by Van Wely et al. in that report (16). The present clinical study represents a comprehensive and systematic evaluation of oocyte and embryo quality and pregnancy outcome in patients undergoing ovarian stimulation with 2 different gonadotropin preparations, following a similar stimulation protocol and a similar starting gonadotropin dose.

In a study of Hompes et al. (13) at an equal dose, HP-hMG displayed a milder stimulation pattern, reflected in a higher cancellation rate as a result of poor ovarian response. Despite the lower number of oocytes retrieved, HP-hMG

treatment resulted in a similar ongoing pregnancy rate per started cycle and in a slightly higher ongoing pregnancy rate per transfer (not reaching statistical significance) as compared with r-FSH. In 2 large studies that compared HP-hMG and r-FSH in a long downregulation protocol for ICSI, the OHSS incidences were similar in both treatment groups (10,11). In those studies, however, the dosage could be individually adjusted after 5 days of treatment. Another recent study (24) that compared HP-hMG and r-FSH for ovulation induction demonstrated that the LH activity in HP-hMG induces a more modulated folliculogenesis that is associated with a lower risk of excessive ovarian response and an ovulation rate similar to that obtained with r-FSH. In the present study no statistically significant or clinically relevant differences were found between the 2 treatment groups for any of the clinical endpoints. Comparable follicular development and E2 levels were obtained during stimulation with HP-hMG and r-FSH. Cancellation rates were similar for both groups because of low response or risk of OHSS.

The results of the current study do not demonstrate significant differences with respect to oocyte and embryo quality or clinical parameters with HP-hMG versus r-FSH in patients whose indication for assisted reproduction was the moderate male factor. The rate of mature oocytes relative to the total number of oocytes retrieved, the embryo cleavage rate, and the rate of grade 1 embryos relative to the number of fertilized oocytes were also similar. However, little is known about the quality of the oocytes retrieved and their developmental potential. Limited data from randomized controlled trials are available in the clinical area regarding the impact of LH activity on embryo quality; however, a recent study (25) reported a higher incidence of grade 1 and 2 embryos when supplementing LH activity to FSH stimulation in women undergoing a long agonist protocol. The mechanisms for the improved oocyte/embryo quality in IVF cycles after exposure to exogenous LH activity are not fully understood, but it has been hypothesized that it could materialize through cumulus cells upon exposure to LH activity during stimulation (26). Recent gene expression data supported this concept and provided some molecular evidence for a mediation of the cumulus cells in embryo development (27).

The clinical pregnancy and live birth rates were slightly higher in HP-hMG treated patients, but the differences did not reach a statistically significant level. The results of our trial are very similar to the results of Van Wely et al. (16) and recent trials comparing HP-hMG with r-FSH in IVF (10,11). A higher ongoing pregnancy rate with HP-hMG compared with FSH was found, but it did not reach statistical significance. Another recent study (9) did use a fixed gonadotropin dosage (150 IU/day). However, because a small number of patients was used (50 patients in each group), no statistically significant difference was found in reproductive outcomes. It is important to perform more studies to confirm the same results when comparing HP-hMG with r-FSH.

Westergaard et al. (28) compared the effectiveness of hMG with r-FSH in ovarian stimulation protocols in IVF or ICSI treatment of infertility in normogonadotropic women in a recent metaanalysis. There was no evidence of a difference between hMG and r-FSH in ongoing pregnancy/live birth per woman (OR: 1.27; 95% CI: 0.98 to 1.64). Furthermore, there was no clear difference in any of the secondary outcomes, although the clinical pregnancy rate per woman was of borderline significance in favor of hMG (summary OR: 1.28; 95% CI: 1.00 to 1.64). The authors concluded that additional large randomized trials are needed to estimate the difference between hMG and r-FSH more precisely. Such trials should preferably 1) use a consistent long GnRH-a protocol, 2) use a fixed dose of gonadotropin to prevent potentially subjective decisions of the clinician in dosing, and 3) take live birth as the primary endpoint. They suggested that at this moment in time, however, in prescribing gonadotropins for ovarian hyperstimulation in IVF, one should use the least expensive medication. The present study used a consistent long GnRH-a protocol, used a fixed dose of gonadotropin, and used live birth rate as the primary endpoint. The only limitation of the present study might be the small number of patients. The significance of the different pharmacodynamic profiles of these 2 gonadotropins to the reproductive outcome should be further investigated by even efficacy trials or by other metaanalyses.

In conclusion, we compared the efficacy of HP-hMG versus r-FSH treatments following GnRH agonist suppression in patients undergoing ICSI with moderate male-factor infertility in a prospective randomized, controlled trial. We found HP-hMG to be as effective as r-FSH in terms of oocyte and embryo quality and clinical pregnancy outcomes.

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