A Randomized, Double-Blind, Multicenter Study Comparing a Starting Dose of 100 IU or 200 IU of Recombinant Follicle Stimulating Hormone (Puregon®) in Women Undergoing Controlled Ovarian Hyperstimulation for IVF Treatment

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Purpose: To compare the efficiency and efficacy of two starting doses of recombinant FSH (follitropin- β , Puregon) in women undergoing IVF treatment.

Methods: This prospective, randomized, double-blind, multicentric ($N = 6$) study included 192 women undergoing IVF using the long protocol of GnRH agonist who received either 100 IU or 200 IU of r-FSH per day. Gonadotropin dose adjustment was allowed after day 4 of stimulation.

Results: The average (SD) number of oocytes retrieved was 10.9 (5.4) and 12.2 (5.6) in the 100 IU and 200 IU group respectively ($p = 0.067$). The total doses of Puregon administered were 1887 IU and 2559 IU in the 100 IU and 200 IU group respectively. The number of transferable embryos, and the rates of pregnancies, cancelled cycles, miscarriages and adverse events including OHSS were comparable between the two groups.

Conclusions: Women undergoing IVF have similar outcomes whether recombinant FSH is commenced in a dose of 100 IU or 200 IU for the first 4 days of stimulation.

KEY WORDS: Gonadotropins; IVF; ovarian stimulation; recombinant.

INTRODUCTION

The pregnancy rate following in vitro fertilization (IVF) treatment is related to the numbers of mature oocytes retrieved and fertilized, since this allows for a choice of multiple good quality embryos for transfer (1). Consequently, ovarian stimulation with go-

nadotropins is used in order to achieve a multifollicular ovarian response and an increased number of oocytes retrieved during IVF (2).

However, the use of gonadotropins represents a certain cost and their administration may be associated with a number of side effects including nausea, abdominal bloating, breast tenderness, mood-swings,

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and potentially, ovarian hyperstimulation syndrome (OHSS) (3). Furthermore, there is concern about using a larger amount of gonadotropins than required because of the potential morbidity associated with OHSS. Accordingly, there has been an increasing recognition of the need to reduce the amount of gonadotropins administered for ovarian stimulation to the minimum necessary to achieve a satisfactory treatment outcome (4).

Gonadotropins for ovarian stimulation may be administered in a variety of dosing regimens. The same starting dose may be used for all women, or the starting dose can be individualized based on predictors of ovarian response such as female age, early follicular phase serum FSH concentration (5), ultrasonographic criteria (3,6,7) and previous follicular response to ovarian stimulation. Subsequently, the dose may be held constant throughout stimulation, increased or decreased in a fixed manner, or titrated according to the ovarian response. The ovarian response may be assessed through ultrasonographic follicular tracking with or without measurement of the serum estradiol concentration. However, the choice of particular starting doses and dosing regimens is generally based on empirical data and experience of the ART-specialist rather than on well-designed controlled studies.

In the past few years, two preparations of recombinant follicle stimulating hormone (r-FSH) have been developed, namely, follitropin- α (Gonal-F, Serono Laboratories, Geneva, Switzerland) and follitropin- β (Puregon, Organon Laboratories, Oss, The Netherlands). A number of randomized controlled trials suggest that, compared with urinary derived FSH (u-FSH), recombinant preparations are more potent and generally result in increased numbers of oocytes collected, transferable embryos, and pregnancy rates (8–10). A recent study also suggests that the two recombinant preparations are equally efficacious (11).

The availability of follitropin- β (Puregon) in 50 and 100 IU ampules allows for the study of novel dosing regimens. Recent multicenter, randomized-controlled trials have examined the effectiveness of fixed doses of follitropin- β in 100 versus 200 IU (12,13), and 150 versus 250 IU (14) regimens. However, the dose of follitropin- β was held constant throughout ovarian stimulation in these trials. There is consequently a need for a randomized controlled study, using r-FSH in low dose regimens, but allowing for adjustment of the dose during stimulation to simulate the conditions in actual clinical practice.

The aim of this study is to compare the efficiency and efficacy of a starting dose of 100 IU versus 200 IU of follitropin- β (Puregon) maintained during the first 4 days of ovarian stimulation in pituitary-suppressed women undergoing IVF treatment.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, group-comparative, double-blind, multicenter study (six centers in Canada) to investigate the efficacy and efficiency of a starting dose of 100 IU or 200 IU of follitropin- β (Puregon) in pituitary suppressed infertile women undergoing controlled ovarian hyperstimulation for IVF. The aim was to include 200 patients (100 in each treatment group). The Ethics Committees of the individual study centers approved the study and each subject gave written informed consent before participating in the study.

Selection of Patients

Inclusion criteria were at least 18 and at most 39 years of age at the time of screening; cause of infertility potentially treatable by IVF or ICSI; normal ovulatory cycles with a mean cycle length of between 24 and 35 days; good physical and mental health; body mass index (BMI) between 18 and 29 kg/m²; normal early follicular phase (day 2–4) serum FSH concentration.

Exclusion criteria were infertility caused by endocrine abnormalities such as hyperprolactinaemia, polycystic ovarian syndrome, absence of ovarian function; previous ovarian stimulation cycles in which less than three oocytes were retrieved; chronic cardiovascular, hepatic, renal or pulmonary disease; either current or previous (within 12 months) alcohol or drug abuse; administration of any investigational drugs within 3 months prior to screening.

Study Drugs and Procedures

Subjects were administered a long protocol of GnRH agonist in which GnRH agonist was administered daily, commencing either from the first day of the menstrual period or the midluteal phase of the preceding menstrual cycle. In both cases, GnRH agonist was continued until pituitary suppression was achieved as shown by a serum estradiol (E2) level

<200 pmol/L. Any licensed GnRH-agonist was allowed except the intra-muscular depot preparations. Once pituitary suppression was achieved, two ampoules of either 50 IU or 100 IU of Puregon, dissolved in one ampoule of solvent, were administered as a fixed, daily subcutaneous dose for a minimum of 4 days. Following this, ultrasound assessments with or without serum estradiol measurements were used to evaluate individual patient responses and dose adjustments were made, if necessary.

Gonadotropin treatment was continued until at least three follicles with mean diameters ≥ 17 mm developed, when human chorionic gonadotropin (5000–10,000 IU) was administered to achieve final oocyte maturation. Oocyte retrieval was performed and fertilization achieved by IVF or intracytoplasmic sperm injection (ICSI). A maximum of three embryos were transferred and progesterone supplementation was given for luteal support.

Puregon (recombinant FSH) was supplied in 50 and 100 IU ampoules as lyophilized spheres. The two different dosage ampoules appeared identical. The composition of Puregon included recombinant FSH (Org 32489, follitropin- β), sucrose, sodium citrate, polysorbate 20 and hydrochloric acid/sodium hydroxide 0.1 N.

Randomization

Eligible subjects were randomized by receiving a subject number from a randomization list corresponding with patient boxes in which the medication was kept. The randomization was carried out in blocks of four according to random numbers generated by the computer. The ampoules used in the study were individually numbered for each subject. After allocation of subject code number, each subject used medications with the same code number throughout the study. The investigator had no knowledge regarding the treatment assigned therefore the study was performed as a double-blind trial. After day 4 of stimulation, the r-FSH dose was adjusted if deemed necessary but the initial Puregon dose received was not revealed. The treatment cycle was no longer, from that point forward, assessor or patient blind.

Efficacy and Safety Variables

The primary efficacy variables were the numbers of oocytes retrieved and the total dose of r-FSH administered. Secondary variables included the num-

ber of follicles ≥ 15 mm, serum estradiol (E2), and follicle-stimulating hormone (FSH) levels on the day of HCG administration and the number of transferable embryos. In addition the rate of ongoing pregnancy (>12 weeks gestation) was compared between the groups. Safety measures included adverse events, hormone determinations, vital signs, and physical examination.

Statistical Methods

The primary intent of this study was to assess the efficacy and efficiency of the starting dose of 100 IU and 200 IU follitropin- β as measured by *numbers of oocytes retrieved* and *total dose of follitropin- β administered*. The null hypothesis of interest was that there was no difference between the two treatment groups with reference to these two primary efficacy variables. For the primary and secondary variables of interest, a two-way analysis of variance (ANOVA) was performed. The standard ANOVA model included *center*, *treatment group*, and *treatment group-by-center* terms.

A significant *treatment group-by-center* interaction ($p \leq 0.10$) indicates some degree of inconsistency in treatment effect across centres. If this were detected, descriptive statistics would be used to summarize the inconsistencies. If the interaction term was not significant, then the term was ignored and the main analysis was based on a reduced model consisting of *center* and *treatment group* terms. Hypothesis testing between the two treatment groups in the reduced model was performed at the 5% level. If the assumption of a normal distribution was not valid, ranked ANOVA was performed. Hormone measurements were converted to a logarithmic scale prior to analysis by the ANOVA model. Analysis was performed on an intention-to-treat basis. All patients who received at least one dose of the study drug were included. All analyses were performed by SAS Version 8.0.

Sample Size Calculation

The two primary efficacy parameters were the *numbers of oocytes retrieved* and the *total dose of follitropin- β administered*. Assuming a standard deviation (SD) of 6.4 oocytes, and values of $\alpha = 0.05$ and $\beta = 0.80$, a sample size of 100 subjects per treatment group (total = 200 patients) was required to detect a statistically significant difference of 2.5 oocytes between the two treatment groups. The total sample

size of 200 subjects also allowed for detecting a statistically significant difference of 180 IU r-FSH between the two treatment groups, assuming a SD of 450 IU for the *total dose of r-FSH administered*.

RESULTS

A total of 192 patients (97 in the 100 IU group and 95 in the 200 IU group) were enrolled and randomized into the study. The numbers of patients randomized per center were 12, 27, 40, 39, 13, and 61, respectively. The recruitment period for the trial was extended in an attempt to reach the targeted 200 subjects. In order to keep within project timelines the study was ended with 192 patients recruited. One-hundred and ninety one patients received the minimum 4 days of follitropin- β treatment, 188 patients underwent oocyte retrieval (95 and 93 in the 100 IU and 200 IU group, respectively), and 185 patients completed the study as per study termination record (7 and 3 in the 100 IU and 200 IU group, respectively). In both treatment arms the cancellation rate was very low (5 and 8 in the 100 IU and 200 IU group, respectively).

Both groups had comparable demographic and infertility characteristics (see Table I). The average duration of infertility was 5 years and the average age 33 years (range 25–40 years).

Number of Oocytes Retrieved

The average number of oocytes retrieved was 12.2 in the 200 IU group (SD = 5.6, range: 2–27) versus 10.9 (SD = 5.4, range: 2–30) in the 100 IU group (see Table II). The median number was 11 oocytes in the

200 IU dose group and 10 oocytes in the 100 IU group. The mean numbers of oocytes retrieved in the six study centers ranged from 10.2 to 13.8 in the 200 IU group and 8.8 to 12.1 in the 100 IU group. There was no significant variation in the treatment effects across centers ($p = 0.750$, interaction term). A reduced model excluding the interaction term was fitted. Based on the reduced model, a nonsignificant difference was detected between the two treatment groups ($p = 0.067$).

Daily Dose and Duration of r-FSH Treatment

Total exposure to Puregon in the 100 IU group was 1887 IU compared to 2559 IU in the 200 IU group (see Table II). The summary statistics for daily dose show considerable variability across the six centers ($p = 0.079$, interaction term). Statistical analysis of the difference in total units used between the treatment groups therefore could not be performed. Patients in the 100 IU group received on average, 148 IU daily, while in the 200 IU group, the daily dose was 239 IU per day.

The average duration of treatment was 11 days. Patients in the 100 IU group were on Puregon treatment an average of 2 days longer compared with patients in the 200 IU dose group (13 days vs. 11 days respectively).

Number of Follicles ≥ 15 mm

The average number of follicles ≥ 15 mm was 8.3 (SD = 4.4, range 0–27) in the 200 IU group compared to 7.7 (SD = 4.1, range 0–26) in the 100 IU group ($p = 0.324$) (see Table III).

No significant *treatment-by-center* interaction was observed.

Table I. Demographics and Infertility Characteristics

Characteristic	100 IU ($n = 97$)	200 IU ($n = 95$)
Mean age (years, SD)	33.3 (3.1)	33.4 (3.3)
Mean weight (kg, SD)	61.7 (8.8)	60.9 (8.1)
Mean height (cm, SD)	162 (6.4)	162 (6.2)
Mean cycle length (days, SD)	28.6 (2.4)	28.1 (2.2)
Duration of infertility (years, SD)	4.7 (3.2)	4.8 (2.3)
Number of women with primary infertility (%)	78 (80%)	72 (76%)
Number of women with cause of infertility ^a		
Tubal	39 (40%)	48 (51%)
Male infertility	32 (33%)	33 (35%)
Endometriosis	12 (12%)	6 (6%)
Other	6 (6%)	6 (6%)
Unknown	1 (1%)	0

^aPercentage is based on the number of patients in each treatment group. More than one cause of infertility may be listed.

Table II. Results for Primary Parameters

	Treatment group [mean (SD)]		p-Value	
	100 IU	200 IU	Treatment-by-center ^a	Treatment ^b
Total dose of Puregon administered (IU)	1887 (823)	2559 (1075)	0.079	—
Number of oocytes retrieved	10.9 (5.4)	12.2 (5.6)	0.750	0.067

Note. Results are mean (SD).

^ap-Value associated with “Treatment-by-center” interaction term in an ANOVA model containing Treatment, Center, and Treatment-by-center terms.

^bp-Value associated with “Treatment” term in an ANOVA model containing Treatment and Center terms. This p-value is reported only if the treatment-by-center interaction term in the full model is not significant, i.e. treatment-by-center $p \geq 0.10$ (see text).

Serum Estradiol Concentrations

The mean serum estradiol levels on the day of hCG administration in the 200 IU group were comparable with those in the 100 IU group, 7390 pmol/L versus 6341 pmol/L respectively.

Number of Transferable Embryos

The mean number of transferable embryos was 7.2 (SD = 4.4, range 0–23) in the 200 IU group and 6.7 (SD = 3.9, range 0–20) in the 100 IU group ($P = 0.36$) (see Table III). The numbers of embryos transferred and cryopreserved were also comparable in the two treatment groups (see Table III).

Treatment Cycle Summary

Ninety-three percent of all patients completed the treatment cycle. The cycle was cancelled prior to embryo transfer in 13 patients (5 in the 100 IU group and 8 in the 200 IU group). Seven of the cycle cancellations were because of *failed fertilization* (2 cycles in

100 IU group vs. 5 in the 200 IU group). Three cancellations were the result of *poor ovarian response* (1 cycle in the 100 IU group vs. 2 in the 200 IU group). The remaining three cancellations were due to *premature luteinizing hormone surge*, *increased risk for ovarian hyperstimulation syndrome* (one cycle in the 100 IU group), and *other reasons* (development of endometrial polyps). The ongoing pregnancy rates per cycle initiated (ITT population) were 27% ($N = 26$) and 24% ($N = 23$) in the 100 IU and 200 IU groups respectively ($P = 0.68$). Three miscarriages, two in the 100 IU group and one in the 200 IU group, were reported. In addition, three ectopic pregnancies were observed (one in the 100 IU and two in the 200 IU group).

Safety Results

Seven serious adverse events were reported, three in the 100 IU group (all in one patient) and four in four women in the 200 IU group. The patient

Table III. Results for Secondary Parameters

	Treatment group		p-Value	
	100 IU	200 IU	Treatment-by-center ^a	Treatment ^b
Follicles ≥ 11 mm	12.0 (6.0)	13.0 (5.6)	0.900	0.131
Follicles ≥ 13 mm	10.1 (5.0)	11.1 (4.9)	0.853	0.225
Follicles ≥ 15 mm	7.7 (4.1)	8.3 (4.4)	0.898	0.404
Follicles ≥ 17 mm	5.1 (3.1)	5.7 (3.6)	0.718	0.414
Mature oocytes	9.4 (5.0)	10.5 (5.0)	0.724	0.088
Embryos obtained	6.7 (3.9)	7.2 (4.4)	0.735	0.357
Embryos transferred	2.7 (0.9)	2.7 (0.7)	0.266	0.850
Embryos frozen	1.8 (3.2)	2.0 (3.1)	0.943	0.481
Pregnancy rate per cycle commenced	27%	24%		

Note. Results are mean (SD) unless otherwise stated.

^ap-Value associated with “Treatment-by-center” interaction term in an ANOVA model containing Treatment, Center, and Treatment-by-center terms.

^bp-Value associated with “Treatment” term in an ANOVA model containing Treatment and Center terms. This p-value is reported only if the treatment-by-center interaction term in the full model is not significant, i.e. treatment-by-center $p \geq 0.10$ (see text).

with three serious adverse events in the 100 IU group developed 1) severe OHSS requiring intravenous rehydration and paracentesis, 2) abdominal pain, and 3) an ovarian abscess requiring treatment by salpingo-oophorectomy. The four women with reported serious adverse events in the 200 IU group had 1) a ruptured ectopic pregnancy requiring salpingectomy, 2) moderate OHSS, 3) pelvic pain, and 4) ovarian torsion requiring laparoscopic salpingo-oophorectomy, respectively. Headache, abdominal pain, dysmenorrhoea and ovarian hyperstimulation syndrome were the most frequently reported non-serious adverse events. These events were observed in 3% of the study population. Ovarian hyperstimulation syndrome (all gradations) was reported in six patients (3%), of which only one case was severe OHSS. There were four women in the 100 IU group (moderate OHSS in two and severe in one) and two in the 200 IU group (both moderate OHSS) ($p = 0.683$; Fishers exact test). Seven (4%) patients reported injection site inflammation, pain or reaction.

DISCUSSION

The increased bioavailability of r-FSH compared to urinary derived products, and the availability of follitropin- β (Puregon) in 50 and 100 IU ampules, has allowed us the opportunity of examining the efficacy of a lower starting dose (100 IU) than is generally used for ovarian stimulation for IVF. The results of this study indicate that women undergoing controlled ovarian stimulation who received 100 IU of follitropin- β (Puregon) for the first 4 days of treatment, followed by dose adjustment, have a borderline significant decrease in the number of oocytes retrieved (10.9 vs. 12.2) compared with those who received 200 IU. Although the duration of treatment was prolonged by an average of 2 days in the 100 IU group the average total amount of follitropin- β used was less compared with the high-dose group, 1887 IU and 2559 IU respectively.

Secondary outcome analysis indicates that the two groups had similar rates of transferable embryos (6.7 vs. 7.2 for 100 vs. 200 IU), ongoing pregnancies per cycle initiated (27% vs. 24% for 100 vs. 200 IU), cancelled cycles, miscarriages and adverse events, including OHSS.

These findings are clinically important as gonadotropin treatment regimens have classically been based on empiric evidence rather than well-designed randomized-controlled trials. The current results

suggest that milder ovarian stimulation does not significantly alter important outcome variables, while potentially reducing expense and the risk associated with treatment complications. This is in keeping with recent literature, which suggests that for many women there exists a gonadotropin dose above which increases in the dose of medication will not improve outcome but may increase the risk for complications (12).

Four multicenter randomized trials have compared the efficacy of fixed doses of follitropin- β (Puregon) in 100 versus 200 IU (12,13), and 150 versus 250 IU regimens (14). In women aged 30–33 years who received 250 IU Puregon throughout ovarian stimulation, there was an increased number of oocytes collected, 14.8, compared to women who received 150 IU throughout, 10.6 (14). Pregnancy rates were comparable between the two dose groups. However, in women over 33 years of age, there was no increase in the number of oocytes retrieved in the group who had been stimulated with a 250 IU gonadotropin dose.

Out and colleagues (12,13) examined the efficacy of a fixed dose of 100 IU or 200 IU of Puregon in two multicenter trials and demonstrated that the higher dose was associated with significantly more oocytes retrieved. However, the pregnancy rates per cycle commenced were similar and the higher dose was associated with more cases of OHSS.

The results of these studies suggest that a lower fixed dose of follitropin- β (Puregon) reduces both the number of oocytes retrieved (especially in younger women) and the total dose of gonadotropin used, without reducing the pregnancy rate per cycle commenced. This is in spite of a higher number of cancelled cycles, due to poor ovarian response, with a fixed dose of 100 IU per day (12,13).

In the current study, the low-dose group started on the same dose (100 IU) of Puregon as the studies described above but produced an average 10.9 oocytes compared with 6.2 (12) and 5.7 (13) in the aforementioned trials. In the two fixed-dose 100 IU versus 200 IU studies, the cancellation rates due to poor ovarian response in the 100 IU group were 15% and 24% compared to 1% (one patient) in the present study. The much lower cancellation rate for poor response was presumably in part due to the dose adjustment allowed. There was also a dose-response relationship since the low-dose group had a borderline significant reduction in the numbers of oocytes retrieved (10.9 vs. 12.2) compared with the high-dose group. However, since the numbers of transferable

embryos and pregnancy rates were similar between the two groups, there would appear to be little advantage to initiate stimulation using a higher dose of gonadotropins.

Empirically, most centers start with the administration of either 150 or 225 IU of FSH daily. It has not been firmly established whether increasing the daily dose during stimulation yields a better result. The only prospective randomized controlled trial showed that doubling the administered dose in patients with a low response after 5 days of 225 IU human menopausal gonadotropin (hMG) did not result in a higher number of oocytes retrieved compared with patients treated with a fixed dose of hMG (15). The results of the present study suggest that a dose increase improves the outcome (in terms of numbers of oocytes retrieved) since compared to the previous fixed dose trials using 100 IU follitropin- β (Puregon), an average four to five extra oocytes were retrieved. However, to test this hypothesis, a trial in which patients with a suboptimal follicular response are randomized to either continue with the same gonadotropin dose or undergo dose increase will have to be performed.

A recent randomized study compared fixed doses of 150 IU or 200 IU of Puregon for the first four days of stimulation in 300 women with a normal early follicular phase serum FSH concentration <8.5 IU/L (16). As found in our study, women in the low dose Puregon group used significantly less total amounts of follitropin- β and had fewer oocytes retrieved although pregnancy rates were similar between the groups. Our study extends these observations in that we commenced at an even lower starting dose of 100 IU per day.

If a higher dose resulted in greater number of transferable embryos, a potential advantage would be more embryos available for cryopreservation or extended culture to the blastocyst stage. It has been shown in the past that, with a good embryo cryopreservation program, the augmentation in pregnancy rates achieved by replacing frozen-thawed embryos can be clinically relevant (17). The numbers of embryos available for transfer in the two treatment groups in the present study were similar. This is a further illustration of the apparent lack of advantage in commencing with a higher dose regimen of 200 IU compared with 100 IU per day.

A number of studies have attempted to identify prognostic markers for a poor ovarian response to gonadotropin stimulation. Possible markers include female age, early follicular serum FSH (18), estradiol

and inhibin B concentrations (19), and ultrasonographic parameters including ovarian volume (20), antral follicle count (21), and peak ovarian stromal blood flow velocity (7). Further work is required on selecting stimulation protocols and appropriate starting doses of gonadotropins for women identified to be at increased risk of poor ovarian response. The inclusion and exclusion criteria for the present study aimed to reduce the chance of including study patients at increased risk of poor response to ovarian stimulation (age <40 years, normal early follicular phase serum FSH, normal BMI, no previous IVF cycle with <3 oocytes retrieved). Study patients were predicted to be normoresponders, and in keeping with recent reports (12), our data suggest these women have a threshold for optimal follicular development with gonadotropin stimulation.

In conclusion, our data suggest that women undergoing ovarian stimulation for IVF have similar outcomes whether recombinant FSH is commenced in a dose of 100 IU or 200 IU for the first 4 days of stimulation followed by dose adjustment, as necessary. Although a starting dose of 100 IU resulted in a small decrease in oocytes retrieved and an average of 2 extra days of stimulation, about 700 IU less of r-FSH were used per cycle. The study patients were not considered to be at high risk for poor response to gonadotropin stimulation and were representative of the general IVF population. Our findings lend experimental weight to the increasing desire for, and move towards, less aggressive ovarian stimulation protocols. Reducing the total gonadotropin dose benefits the patient through financial savings and a likely reduction in the side effects of gonadotropin stimulation.

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