A Group-Comparative, Randomized, Double-Blind Comparison of the Efficacy and Efficiency of Two Fixed Daily Dose Regimens (100- and 200-IU) of Recombinant Follicle Stimulating Hormone (rFSH, Puregon®) in Asian Women Undergoing Ovarian Stimulation for IVF/ICSI

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Purpose: To compare the efficacy, efficiency and safety of a fixed daily dose of recombinant FSH (Puregon®) of a 100- and 200-IU regimen in Asian women undergoing ovarian stimulation for IVF/ICSI.

Methods: This was a prospective, randomized, double-blind, multicenter ($n = 9$) study. Prior to the start of rFSH, all women were pretreated with a gonadotropin releasing hormone agonist (GnRH-a) for pituitary downregulation.

Results: A total of 330 women were treated with rFSH: 163 subjects with 100 IU and 167 subjects with 200 IU. In the 200 IU treatment group, significantly more oocytes were retrieved compared to the 100 IU group (9.6 vs. 5.0 oocytes, $p < 0.001$). The total dose rFSH needed to develop at least three follicles with a diameter of ≥ 17 mm was significantly lower in the 100 IU treatment group (1194 vs. 2034 IU, $p < 0.001$). Although more cycle cancellations were seen in the 100 IU group (24 vs. 13%), the ongoing pregnancy rate per started cycle was comparable between both groups (16.6% in the 100 IU group vs. 15.0% in the 200 IU group).

Conclusions: The use of a 100 IU fixed dose is less effective in terms of the number of oocytes retrieved and the higher cancellation rate, but more efficient as indicated by a lower total recombinant FSH dose needed.

KEY WORDS: Dosing; ICSI; IVF; Puregon®; recombinant FSH.

INTRODUCTION

For many years now there has been a debate on the best gonadotropin starting dose for ovarian stimulation before in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

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Principally two different dosing approaches are currently employed: the so-called step-up protocol predominantly employed in Europe and the step-down regimen often used in Northern America. With the step-up regimen most clinics start either with 150 or 225 IU daily for at least the first four treatment days after which the dose is adapted according to the individual ovarian response. Both starting doses induce serum FSH levels that are sufficient to stimulate multiple follicular growth.

The discussion on the most optimal gonadotropin starting dose for IVF/ICSI will also depend on the individual clinic's objectives. A sufficient number of oocytes should be obtained to assure a good number of embryos for an optimal chance of pregnancy directly following fresh embryo transfer. The routine use of embryo cryopreservation and frozen embryo transfer cycles will augment the need for the number of oocytes obtained. However, profound ovarian stimulation in order to obtain as many oocytes and embryos as possible for fresh and frozen transfer cycles introduces specific risks, such as ovarian hyperstimulation syndrome (OHSS). Therefore, it is difficult to indicate the optimal number of oocytes needed for optimal chances of pregnancy.

The introduction of rFSH, given its higher potency compared with urinary FSH (uFSH) (1) and its availability in lower presentation forms allows for lower dosing regimens. As yet, a number of trials have been undertaken, all showing that lower starting doses of rFSH are efficacious. Observational studies have led to the conclusion that starting doses of 100-IU rFSH can work, provided that it is selected for the appropriate type of patients (2). Recently, double-blind comparisons have been performed of fixed daily dosages of 100 and 200 IU rFSH (3,4). Significantly more oocytes were retrieved in the high-dose group but the clinical pregnancy rates were not different.

So far, no clinical experience has been obtained on the best rFSH dosing regimen in Asian women. Especially since in Asian countries women generally have a lower body weight we wanted to compare the efficacy and efficiency of the 100- and 200-IU fixed dose regimens of rFSH with the aim to provide a scientific basis on the best rFSH dose in Asian women.

MATERIAL AND METHODS

Study Design

The study was designed as a randomized, group-comparative, double-blind, multicenter investigation

comparing a fixed daily dose of 100 or 200 IU of recombinant FSH (follitropin beta, Puregon®). The objective of the study was to assess the efficacy and efficiency of these dosing regimens in downregulated women undergoing ovarian stimulation prior to IVF or ICSI. The study was performed between December 1997 and July 1999 and involved nine study centers in Hong Kong ($n = 2$), India ($n = 3$), Singapore ($n = 1$), and Thailand ($n = 3$). The aim was to include, in each study center, 300 subjects, 150 in each treatment group. The ethics committees of the individual study centers approved the study protocol and each subject had given her written informed consent before participation in the study. The study was conducted in compliance with the current revision of the Declaration of Helsinki, and according to the European Community note on Good Clinical Practice for trials on medicinal products in the European Community (5) and local regulatory requirements.

Selection of Subjects

Inclusion criteria were that subjects had to be at least 18 and at most 39 years of age at the time of screening, having a cause of infertility suitable for IVF or ICSI. All subjects had to have normal ovulatory cycles with a mean length of between 24 and 35 days, a good physical and mental health, and a body mass index between 18 and 29 kg/m².

Subjects were excluded if they suffered from infertility caused by endocrine abnormalities such as hyperprolactinemia, polycystic ovarian syndrome and absence of ovarian function, or previous assisted reproduction in which fewer than three oocytes were retrieved. They were also excluded in case of previous hospitalization due to severe ovarian hyperstimulation syndrome, if they suffered from chronic cardiovascular, hepatic, renal, or pulmonary disease, had a history of (within 12 months) or currently indulged in abuse of alcohol or drugs, or had used investigational drugs within 3 months before screening. When all of the inclusion and none of the exclusion criteria were met, the subject was considered to be eligible.

Study Drugs and Study Procedures

Pretreatment with a gonadotropin releasing hormone agonist (GnRH-a) for pituitary downregulation was started either on the first day of the menstrual cycle or in the midluteal phase (locally purchased intranasal buserelin 0.5–1.0 mg/day in 8 centers and s.c. leuporelin 0.5 mg/day in 1 center). Recombinant FSH [batch nos. CP 096011 and CP 097122

(50 IU); CP 096053, CP 096219, and CP 097123 (100 IU), Puregon, Org 32489, NV Organon, Oss, The Netherlands] was supplied as lyophilized spheres (lysospheres) in ampoules containing 50- or 100-IU FSH in vivo bioactivity. For s.c. injection, lysospheres were reconstituted with 1 mL of solvent (0.45% NaCl for injection, 1 mL per ampoule). Human chorionic gonadotropin (batch no. CP 097151, Pregnyl; NV Organon) in doses of 5000 IU per ampoule was supplied for induction of ovulation. For i.m. injection of hCG, two ampoules were reconstituted with 1 mL of solvent (0.9% NaCl for injection, 1 mL per ampoule).

During the admission visit demographic and other subject characteristics were obtained. In addition, medical and gynecological history was reviewed, a physical examination including a gynecological examination was performed, ultrasound scanning (USS) was performed to exclude ovarian abnormalities, serum hormone concentrations (FSH, in the early follicular phase, and prolactin) were determined and clinical laboratory tests (hematology, blood biochemistry) were performed. During GnRH agonist pretreatment, estradiol levels were measured to confirm downregulation. All general medical, biochemical, and hematological measurements were performed according to the routine procedures of the individual study centers. Eligible subjects were randomized to one of the two starting-dose groups by means of a computer-generated randomization list using random numbers.

When downregulation with GnRH agonist was achieved (i.e., serum E_2 levels <200 pmol/L) treatment with rFSH was started and continued until at least three follicles of ≥ 17 mm in diameter had developed (as assessed by transvaginal ultrasound scanning) for a maximum period of 3 weeks. Human chorionic gonadotropin (10,000 IU) was administered to induce ovulation, and after oocyte retrieval a maximum of three embryos was replaced. Luteal support was given according to the preference of the treatment center.

Study Endpoints

The following efficacy and efficiency variables were recorded according to the routine methodology of each individual study center: number of oocytes retrieved, total dose of gonadotropin administered, ongoing pregnancy rate, the number of follicles ≥ 15 mm at day of hCG administration, and the number of transferable embryos. In addition, serum concentrations of E_2 , P, FSH, and LH were measured

on the day of hCG injection using locally applied assays. The number of oocytes retrieved per age category was also analyzed.

At each visit the subjects were asked whether they had experienced any adverse events. If present, the intensity of the ovarian hyperstimulation syndrome (OHSS) was graded as mild, moderate, or severe according to the pre-determined criteria.

Statistical Analysis

The analyses were performed on subjects who received at least one injection of study medication. All statistical tests were two-sided and an assigned significance level of 0.05 was used. Descriptive methods were used to compare the groups at baseline.

For nondichotomous data a two-sided 95% confidence interval (CI) was calculated for the overall treatment difference using the Cochran method stratified for center (6). The model contained main effect treatment and center. The treatment mean was adjusted for center. The treatment-center interaction was also tested.

In addition, a Wilcoxon rank sum test stratified for center was applied. In case the Wilcoxon rank sum test confirmed the Cochran's results, the Cochran approach was discussed, otherwise both results were mentioned.

For dichotomous data a two-sided 95% CI for the overall treatment difference was calculated on the basis of a Cochran-Mantel-Haenszel approach (7). If a subject did not have oocyte retrieval, then the number of oocytes, the number of embryos, etc. was set to 0 and the pregnancy outcome was set negative.

RESULTS

Study Population

Table I shows the demographic and infertility characteristics, which were comparable for both groups. Tubal factor was the most frequent cause of infertility reported in both groups, followed by male infertility. The mean duration of infertility was approximately 5 years in the 100-IU group and approximately 6 years in the 200-IU group. All women were downregulated at the start of rFSH treatment (estradiol <200 pmol/L). The mean estradiol concentrations prior to FSH treatment were 84.6 and 78.8 pmol/L in the 100- and 200-IU group, respectively. The corresponding FSH concentrations were 3.8 versus 3.5 IU/L and the LH concentration was 4.9 IU/L in both groups, respectively.

Table I. Demographics and Infertility Characteristics

Characteristic	100 IU (<i>n</i> = 163)	200 IU (<i>n</i> = 167)
Mean age, years	31.6 (3.6) ^a	32.1 (3.8)
Mean weight, kg	54.7 (8.1)	55.3 (7.5)
Mean height, cm	156.9 (6.0)	157.4 (5.9)
Mean body mass index, kg/m ²	22.2 (2.9)	22.3 (2.9)
Median cycle length, days	29.2 (2.2)	28.9 (2.0)
Number of subjects with cause of infertility as		
Tubal	67	69
Male infertility	56	60
Endometriosis	23	26
Unknown	31	32
Mixture of causes	4	6
Mean duration of infertility, years	5.2 (2.8)	5.9 (3.5)

^a Values in parentheses are standard deviations.

In total, 330 subjects from nine study centers were randomized to receive either the 100-IU (*n* = 163) or the 200-IU dose rFSH (*n* = 167). The number of subjects treated per center ranged from 22 to 45. All subjects started Puregon treatment. Pregnyl (hCG) was given to 297 subjects. In 10 subjects (3% in the 100-IU and 2% in the 200-IU group), the hCG injection was not followed by an oocyte pickup. In 285 subjects (79% in the 100-IU and 92% in the 200-IU group), oocytes were retrieved and treated by IVF or ICSI. Eventually, 269 subjects (76% in the 100-IU and 86% in the 200-IU group) had an embryo transfer.

Primary Endpoints

Results on the primary efficacy and efficiency endpoints in both dose regimen groups are presented in Tables II and III.

Significantly more oocytes were retrieved in the 200-IU group (9.6 vs. 5.0, *p* < 0.001). However, the total dose used was considerably lower in the 100-IU group (1194 vs. 2034 IU, *p* < 0.001). For both parameters, these differences were consistently found in each study center, although statistically significant interaction (*p* < 0.01 for oocytes and *p* = 0.02 for rFSH dose) still seemed to exist between treatment and center for both parameters.

Secondary Endpoints

Results on the main secondary variables are given in Table IV. In the high-dose group, more follicles ≥ 13 mm, ≥ 15 mm, ≥ 17 mm, and ≥ 19 mm on the day of hCG injection were found. The mean number of follicles ≥ 15 mm was 7.8 in the 200-IU group and 5.9 in the 100-IU group (*p* < 0.001). Endocrinological parameters measured on the day of hCG injection showed significantly higher values in the 200-IU group for serum estradiol (6649 vs. 4568 pmol/L, *p* < 0.001), serum FSH (11.7 vs. 6.8 U/L, *p* < 0.001) and serum progesterone (2.1 vs. 1.5 nmol/L, *p* < 0.001). However, across the centers the mean hormone levels per treatment group differed. A significant (*p* < 0.05) interaction between treatment and center was found for E₂ and FSH. Serum LH concentrations did not differ (2.4 U/L in both groups).

On average, the treatment length was nearly 2 days longer in the 100-IU group (12.8 days) as compared with the 200-IU group (11.0 days).

In the 100-IU group 58% of women received conventional IVF and 42% received ICSI. In the 200-IU group the percentages were 53 and 47% for

Table II. Mean Number of Oocytes Retrieved Per Cycle Started

Center	Recombinant FSH				100-IU minus 200-IU treatment group			
	100 IU		200 IU					
	<i>n</i>	Mean	<i>n</i>	Mean	Estimate of difference	SE ^a	95% CI ^b	Test for interaction
1	15	4.3	15	6.1	−1.7	2.18		
2	20	7.6	20	17.4	−9.9	2.72		
3	20	3.1	20	10.2	−7.2	2.12		
4	20	7.8	20	21.6	−13.8	2.37		
5	20	5.4	20	11.9	−6.5	1.73		
6	23	5.0	22	12.4	−7.5	2.10		
7	18	5.9	20	10.4	−4.5	2.22		
8	10	6.8	12	10.8	−3.9	2.83		
9	17	4.1	18	5.4	−1.3	0.98		
Total ^c	163	5.0	167	9.6	−4.6	0.61	−5.8 to −3.4 (<i>p</i> < 0.001)	<i>p</i> < 0.01

Note. FSH: follicle stimulating hormone.

^a Standard error of estimate.

^b CI: confidence interval.

^c Mean adjusted for center.

Table III. Mean Total Dose (IU) of Recombinant FSH Used Per Cycle Started

Center	Recombinant FSH				100-IU minus 200-IU treatment group			
	100 IU		200 IU		Estimate of difference	SE ^a	95% CI ^b	Test for interaction
	<i>n</i>	Mean	<i>n</i>	Mean				
1	15	873	15	1520	−647	96.0		
2	20	1255	20	2160	−905	106.8		
3	20	1620	20	2410	−790	171.5		
4	20	1215	20	1990	−775	67.7		
5	20	1100	20	2010	−910	87.9		
6	23	1317	22	2155	−837	105.2		
7	18	1317	20	2310	−993	120.6		
8	10	1110	12	1900	−790	125.9		
9	17	1553	18	3056	−1503	207.7		
Total ^c	163	1194	167	2034	−840	34.9	−909 to −772 ($p < 0.001$)	$p = 0.02$

Note. FSH: follicle stimulating hormone.

^a Standard error of estimate.

^b CI: confidence interval.

^c Mean adjusted for center.

conventional IVF and ICSI, respectively. For both fertilization procedures, the embryo development rates in the 100- and 200-IU groups were comparable (IVF: 62 and 60%; ICSI: 56 and 52%, respectively). For both IVF and ICSI the number of transferable embryos was significantly higher in the high-dose group as compared with the low-dose group (IVF: 5.2 vs. 3.4, $p < 0.001$; ICSI: 6.1 vs. 3.5, $p < 0.001$). In the 100-IU group, a mean number of 2.5 embryos were transferred compared with 2.8 embryos in the

200-IU group (not significant). The mean number of embryos frozen was 1.0 in the 100-IU group and 3.4 in the 200-IU group. Per age group the mean number of oocytes retrieved in the 100- and 200-IU group is given in Table V. Similar differences per age category are shown in the number of oocytes retrieved as shown in the overall analysis for all dose groups, except for the women aged 37–39 years, where the mean number of oocytes retrieved was 6.6 in both groups.

Table IV. Results (Means Adjusted for Center) on Main Secondary Parameters

Parameter	100 IU (<i>n</i> = 163)	200 IU (<i>n</i> = 167)	95% CI of treatment difference	<i>p</i> -value
Follicles ≥ 13 mm ^a , <i>n</i>	7.9	10.5	—	NA
Follicles ≥ 15 mm ^a , <i>n</i>	5.9	7.8	−2.6 to −1.1	$p < 0.001$
Follicles ≥ 17 mm ^a , <i>n</i>	4.5	5.5	—	NA
Follicles ≥ 19 mm ^a , <i>n</i>	2.0	2.2	—	NA
Serum estradiol ^a , pmol/L	4568	6649	−2711 to −1451	$p < 0.001$
Serum LH ^a , U/L	2.4	2.4	−0.3 to −0.3	NS
Serum FSH ^a , U/L	6.8	11.7	−5.5 to −4.3	$p < 0.001$
Serum progesterone ^a , nmol/L	1.5	2.1	−0.8 to −0.3	$p < 0.001$
Treatment days, <i>n</i>	12.8	11.0	—	NA
Mature oocytes, <i>n</i>	6.0	11.0	—	NA
Transferable embryos after IVF, <i>n</i>	3.4	5.2	−2.9 to −0.8	$p < 0.001$
Transferable embryos after ICSI, <i>n</i>	3.5	6.1	−3.8 to −1.5	$p < 0.001$
Embryo development rate, %	60	56	—	NS
Embryos transferred, <i>n</i>	2.5	2.8	—	NS
Embryos frozen, <i>n</i>	1.0	3.4	—	NA
Clinical PR per started cycle, %	20	18	—	NS
Clinical PR per ET, %	26	21	—	NS
Miscarriage rate, %	1.8	2.4	—	NS
Implantation rate, %	12.1	10.1	—	NA
Ongoing PR per started cycle, %	16.6	15.0	−6.1 to 9.5	NS
Ongoing pregnancy rate per ET, %	22.9	17.0	−3.5 to 15.3	NS

Note. NA: not applicable/not available; NS: not statistically significant ($p < 0.05$); CI: confidence interval; FSH: follicle stimulating hormone; LH: luteinizing hormone; IVF: in-vitro fertilization; ICSI: intracytoplasmic sperm injection; PR: pregnancy rate; ET: embryo transfer.

^a At the day of human chorionic gonadotropin injection.

Table V. The Mean Number of Oocytes Retrieved Per Age Category Per Cycle Started

Age category (years)	Mean number of oocytes retrieved per age category ^a	
	100 IU	200 IU
18–25	5.3 (2.3)	19.6 (9.5)
26–29	7.1 (6.1)	15.2 (8.5)
30–33	5.1 (4.5)	12.5 (9.7)
34–36	4.4 (3.3)	10.6 (8.3)
37–39	6.6 (7.9)	6.6 (5.6)

^a Values in parentheses are standard deviations.

The clinical and ongoing pregnancy rates were not statistically significantly different in the 100- and 200-IU group. The clinical pregnancy rates in the 100- and 200-IU group were per started cycle 20 versus 18% and per embryo transfer 26 versus 21%, respectively. The ongoing pregnancy rates in the 100- and 200-IU group were per started cycle 16.6 versus 15.0% and per embryo transfer 22.0 versus 17.0%, respectively. Out of 52 ongoing pregnancies in total 18 were multiple pregnancies resulting in a multiple pregnancy rate, as of 33% (9/27) in the 100-IU group and 36% (9/25) in the 200-IU group.

Cycle Cancellations

Of the 163 subjects that started in the 100-IU group 39 (24%) and, of the 167 subjects that started in the 200-IU group 22 subjects (13%) had no embryo transfer. Reasons for cancellation differed between both treatment groups. In the 100-IU group, insufficient ovarian response ($n = 31$), no/too few/bad quality oocytes recovered ($n = 2$), no fertilization ($n = 3$), and other ($n = 3$) were reported. In the 200-IU group, the reasons for cancellation were insufficient ovarian response ($n = 10$), no/too few/bad quality oocytes recovered ($n = 2$), risk for hyperstimulation ($n = 2$), no fertilization ($n = 6$), and other ($n = 2$).

Safety

Four subjects (2.5%) in the 100-IU group reported one or more serious adverse events and six subjects (3.6%) did so in the 200-IU group. In the 100-IU group reasons for serious adverse events were 4 subjects with OHSS (2.5%). In the 200-IU group reasons for serious adverse events were three subjects with OHSS (1.8%): one subject with abdominal pain, one subject with an ectopic pregnancy, and one subject with frequent micturition and renal pain following catheterization. All events were of mild to moderate intensity.

DISCUSSION

The results of this study in Asian women showed that a dose–response relationship exists between gonadotropin dose and the number of oocytes retrieved. In the high-dose group nearly twice as much oocytes were retrieved as compared with the low-dose group. However, with the 100-IU regimen, a significantly lower total rFSH dose (>800 IU) was needed to reach preovulatory conditions. Ongoing pregnancy rates directly following fresh embryo transfer were not influenced by the rFSH doses employed. Similar findings were reported in previous published multicenter double-blind studies comparing daily doses of 100 and 200 IU in Australia, Canada, Europe, and Israel (3,4).

The rFSH fixed dose protocol in this study clearly deviates from the clinical practice of adapting the dose according to the individual ovarian response. It is interesting to note that some studies in which the gonadotropin dose was increased, in case of poor ovarian response, either within a cycle or in a subsequent cycle, no better outcome was observed (8,9). Since recruitment of the cohort of follicles takes place in the late luteal phase of the preceding cycle one might question the benefit of augmenting the gonadotropin dose at a later stage in the follicular phase. Obviously, a direct comparison of a fixed dose regimen versus a step-up regimen will be able to give the ultimate answer to this question. In addition, the real challenge might be to select the optimal gonadotropin dosing regimen on the basis of individual prognostic markers. This would allow us to find rational FSH starting dose criteria to optimize follicular response in terms of the number of oocytes retrieved and to minimize the risk of OHSS, without the risk of unnecessary cycle cancellations and with hopefully a better cost-effectiveness.

In terms of pregnancy outcome directly following fresh transfer there is no advantage of the 200-IU group over the 100-IU group in this study. From a cost-effectiveness point of view in terms of total rFSH dose needed, therefore, a lower dosing regimen seems to be valuable. However, with almost twice as many oocytes available in the 200-IU group and with more embryos available for the cryoprogram (3.4 vs. 1.0) the real benefit in terms of cumulative pregnancy outcome might be with the high-dose regimen. This indeed has been previously confirmed in an analysis of the impact of the cryoprogram comparing a large database of a study between rFSH and uFSH (10). In case a cryoprogram is successfully employed, more embryos available for embryo cryopreservation can

ultimately lead to a significantly higher cumulative pregnancy rate (11).

Whether the use of either a long follicular or a long luteal GnRH agonist downregulation protocol might have an impact on outcome with respect to the two treatment groups has not been subject to analysis in this study. In total 43 women did not reach the state of oocyte retrieval. The most important reason for this was cycle cancellation due to low ovarian response. This was observed more often in the 100-IU group as compared with the 200-IU group (19 vs. 6%). The significantly higher serum FSH levels and serum estradiol levels in the 200-IU group as compared to the 100-IU group are merely a reflection of the higher daily dose of FSH administered and consequently the higher number of follicles that developed in that group. The significantly higher serum progesterone levels in the 200-IU group as compared with the 100-IU group could be explained by the higher serum FSH levels leading to a greater FSH-induced LH receptivity in granulosa cells (12).

The relationship between the rFSH dose administered and the number of oocytes retrieved as shown in this study was not confirmed in another study comparing a dosing regimen of 150- and 250-IU in women between 30 and 39 years of age (13). Interestingly, in this study an increase of oocytes due to a higher starting dose could only be proven in the younger cohort of women between 30 and 33 years of age. In this study, an additional subset analysis in relation to age also showed a difference in the number of oocytes retrieved in the various age categories, except for the cohort of women between 37 and 39 years of age. More prospective, randomized studies are needed to give a final answer to the question whether high gonadotropin doses pose any benefits to patients.

In conclusion, this study has shown that in Asian women a rFSH 200-IU fixed dose regimen as compared with a 100-IU fixed dose regimen is more effective in terms of the number of oocytes retrieved and the lower cancellation rate but is less efficient, as indicated by a higher total rFSH dose needed. There is no difference between the two dosing regimens in terms of ongoing pregnancy rate directly following fresh embryo transfer; however, less spare embryos were available for freezing in the low-dose group.

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