

# A double-blind clinical trial comparing a fixed daily dose of 150 and 250 IU of recombinant follicle-stimulating hormone in women undergoing in vitro fertilization

*The Latin-American Puregon IVF Study Group*

**Objective:** To determine the efficacy and efficiency of two fixed doses of recombinant follicle-stimulating hormone (FSH) in controlled ovarian hyperstimulation.

**Design:** Randomized, double-blind clinical trial.

**Setting:** Fifteen IVF clinics in Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela.

**Patient(s):** Women between 30 and 39 years of age undergoing IVF or intracytoplasmic sperm injection (ICSI).

**Intervention(s):** Daily doses of either 150 IU or 250 IU of recombinant FSH (Puregon) until at least two follicles  $\geq 20$  mm were seen on ultrasound.

**Main Outcome Measure(s):** Number of cumulus–oocyte complexes retrieved and total dose of recombinant FSH used.

**Result(s):** Two hundred one women received 150 IU and 203 used 250 IU. In the low-dose group 8.9 oocytes were retrieved compared to 10.2 in the high-dose group (not significant). The 150 IU-treated women received a total of 1,589 IU and the total dose used in 250 IU treated women was 2,492 IU. Implantation rates were 10.0% in the 150 IU group and 10.9% in the 250 IU group. The vital pregnancy rates per started cycle in the low-dose and high-dose groups were 17.1% and 16.7%, respectively. Two women, both in the 250 IU group, were hospitalized because of the ovarian hyperstimulation syndrome (OHSS).

**Conclusion(s):** An increase from 150 IU to 250 IU daily dose of recombinant FSH in women between 30 and 39 years of age has only limited value in augmenting ovarian response. (Fertil Steril® 2001;76:950–6. ©2001 by American Society for Reproductive Medicine.)

**Key Words:** IVF, ICSI, FSH, Puregon, Follistim, dose, randomized clinical trial

At present, the use of fertility drugs to augment ovarian response before IVF has become routine. Lopata et al. (1) first described in 1978 the use of clomiphene for that purpose. The availability of multiple oocytes for IVF will decrease the chance for losing a cycle caused by fertilization failure and it creates the opportunity of transferring more than one embryo and also the replacement of one selected embryo. In addition, the freezing of a surplus of embryos enables the transfer of frozen-thawed embryos in future cycles, thereby increasing cumulative conception rates.

Usually, controlled ovarian hyperstimulation (COH) is performed using gonadotropins. Increasingly, the medical community is shifting from urinary gonadotropins to recombinant FSH preparations. These preparations are more

bioactive than the traditional urinary gonadotropins (2, 3). In addition, a recent Cochrane meta-analysis showed that their use is associated with a 3.7% absolute increase in clinical pregnancy rate as compared to urinary FSH (4). The most appropriate dose of gonadotropins in general and recombinant FSH in particular to achieve an adequate ovarian response has hardly been studied in randomized controlled trials.

In many clinics, the gonadotropin starting dose is increased with rising age. Recently, it was shown in a relatively small study (5) that an increase in recombinant FSH daily dose from 150 to 250 IU did not result in a higher number of retrievable oocytes in older women (37–39 years). The objective of the current larger study was to assess the impact of two

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dosing regimens in pituitary down-regulated women between 30 and 39 years of age undergoing COH before IVF or intracytoplasmic sperm injection (ICSI) on the number of oocytes retrieved and total dose used.

## MATERIALS AND METHODS

### Study Design

This was a prospective, randomized, double-blind, multicenter study comparing a fixed dose of 150 or 250 IU of recombinant FSH (follitropin beta, Puregon/Follistim, NV Organon, Oss, The Netherlands). The study was performed between June 1998 and September 1999, in 15 specialized infertility centers in Argentina (n = 5), Brazil (n = 3), Chile (n = 2), Colombia (n = 2), Mexico (n = 1), and Venezuela (n = 2). The aim was to include 450 patients with 225 patients in each treatment group (see sample size considerations). The study was approved by the Institutional Review Boards of the individual study centers. Each subject had given written informed consent before participating in the study. The study was conducted in compliance with the Declaration of Helsinki and according to the European Community note on Good Clinical Practice for trials on medicinal products in the European Community (6).

### Selection of Patients

Inclusion criteria were as follows: at least 30 and at most 39 years of age at the time of screening; cause of infertility potentially solvable by IVF or ICSI; normal regular cycles with a mean length of between 24 and 35 days; good physical and mental health; and a body mass index (BMI) between 18 and 29 kg/m<sup>2</sup>.

Exclusion criteria were as follows: infertility caused by endocrine abnormalities such as hyperprolactinemia, polycystic ovary syndrome (PCOS), and absence of ovarian function; one ovary or a history of ovarian resection; severe endometriosis (grade III and IV); previous COH cycles in which less than three oocytes were retrieved; previous hospitalization due to the ovarian hyperstimulation syndrome (OHSS); chronic cardiovascular, hepatic, renal, or pulmonary disease; a history of (within 12 months) or current abuse of alcohol or drugs; administration of nonregistered investigational drugs within 3 months before screening.

When all inclusion criteria and none of the exclusion criteria were met, the subject was considered to be eligible.

### Study Drugs and Study Procedures

Pretreatment with leuprolide for pituitary down-regulation was started in the midluteal phase. Recombinant FSH (follitropin beta, Puregon/Follistim, batch nos. CP 097122, 096149, 097123, 096027) was supplied as lyophilized spheres in ampules containing 50, 100, or 150 IU FSH in vivo bioactivity. For subcutaneous injection, two ampules were reconstituted with 1 mL of solvent. hCG (Pregnyl, NV Organon) in doses of 5,000 IU per ampule was supplied to

trigger ovulation. For IM injection of hCG, two ampules were reconstituted with 1 mL of solvent.

During the admission visit, demographic and other subject variables were obtained. In addition, the general medical and gynecological history was obtained, a general medical and gynecological examination was performed, and endocrinologic, biochemical, and hematologic analyses of blood were performed. All general medical, biochemical, and hematologic measurements were performed according to routine procedures of the individual study centers.

Eligible subjects were randomized by receiving a subject number from a randomization list corresponding with patient boxes in which the medication was kept. The 50-, 100-, and 150-IU ampules were indistinguishable. The randomization was done in blocks of four and was computer-generated using random numbers. The randomization was stratified for age to achieve equal number of subjects in each treatment group for the age groups 30–36 and 37–39 years.

When E<sub>2</sub> serum levels were <200 pmol/L, treatment with recombinant FSH was started and continued until at least two follicles ≥20 mm had developed. Dose adaptations were not allowed. The maximum treatment period was 3 weeks. hCG (10,000 IU) was given to trigger ovulation. After oocyte pick-up and IVF or ICSI, a maximum of four embryos was replaced. Luteal phase support was given as P in a route of administration and dosage regimen as routinely done in each center.

Serum concentrations of E<sub>2</sub>, P, FSH, and LH were measured at baseline (moment of down-regulation) and on the day of hCG injection using local assays. Cycle monitoring included frequent vaginal ultrasound investigations and E<sub>2</sub> measurements.

### Study End Points

The primary end points were the number of cumulus-oocyte complexes and the total dose of recombinant FSH used.

Secondary end points included treatment length, the number of follicles ≥14 mm, ≥16 mm, ≥18 mm, ≥20 mm at the day of hCG administration, levels of FSH, LH, P, and E<sub>2</sub> at the day of hCG administration, number of mature oocytes, the number of transferable embryos, embryo development rate, clinical pregnancy rate, implantation rate, and vital pregnancy rate.

Classification of oocytes as either mature or immature, and embryos as type 1, 2, 3, or 4 was done according to previously published criteria (7). In oocyte classification no distinction was made between women who underwent IVF or ICSI and the maturity was based on the appearance of the cumulus cells, the corona radiata, and the nuclear status. Type 1, 2, and 3 embryos were considered to be transferable. The embryo development rate was defined as the number of transferable embryos divided by the total number of oocytes

incubated with semen (in conventional IVF) or injected with a spermatozoon (in ICSI).

The implantation rate was defined as the number of gestational sacs seen on transvaginal ultrasound examination divided by the total number of embryos replaced. Vital pregnancies were those pregnancies where a fetal heart beat was observed under ultrasound investigation.

No strict definition of the OHSS was given. In the analysis of the occurrence of this syndrome, its incidence and severity was based on the fact that the investigator reported it as such.

## Statistical Analysis

For the continuous variables to investigate the treatment effect related to the age of the subjects, the treatment groups were compared by means of an analysis of covariance (ANCOVA). Starting from the full ANCOVA model with age as covariable and treatment and center as fixed factors and all interactions, the most appropriate models for the primary parameters were derived. This was an ANCOVA with treatment and center as fixed factors and age as covariate and no interactions. The derived model assumes, for example, that there are common slopes for treatment by age (no statistically significant interaction treatment by age;  $P > .10$ ) and that each center has comparable age differences (no statistically significant interaction center by age;  $P > .10$ ). This model was also used for all other parameters. For the analysis of the serum hormone concentrations, the log transformation was applied.

For dichotomous variables, the treatment groups were compared by means of logistic regression with age as covariable and treatment and center as fixed factors. The results were presented for the age classes 30–33, 34–36, and 37–39 years.

The statistical analysis was performed for all subjects who received at least one injection of recombinant FSH.

## Sample Size Considerations

With 225 subjects included in each treatment group and under assumption of common slopes for treatment by age and assuming a standard deviation of 6.4 oocytes for the number of oocytes retrieved and a standard deviation of 2.5 treatment days, a difference of approximately 1.7 oocytes and 0.6 treatment day could be detected between the two treatment groups with a power of 80% using a two-sided  $t$ -test with a significance level of 5%.

## RESULTS

### Study Population

A total of 405 women were randomized in 15 centers. All except one were subsequently treated with recombinant FSH. Of these women, 120 were aged 30–33 years, 118 were 34–36 years, and 166 were between 37 and 39 years of age. Two hundred one subjects started treatment with 150 IU

**TABLE 1**

Demographics and infertility characteristics.

Characteristic	150 IU (n = 201)	250 IU (n = 203)
Mean age (years, SD)	35.1 (3.1)	35.3 (2.9)
Mean weight (kg, SD)	60.4 (8.2)	60.7 (8.5)
Mean height (cm, SD)	162.5 (6.0)	162.1 (6.4)
Mean body mass index (kg/m <sup>2</sup> , SD)	22.9 (2.7)	23.1 (2.7)
Mean cycle length (days, SD)	28.6 (1.5)	28.5 (1.4)
No. (%) of women with cause of infertility		
Tubal	46 (23%)	51 (25%)
Male infertility	91 (45%)	86 (42%)
Endometriosis	6 (3%)	11 (5%)
Other or unknown	25 (12%)	22 (11%)
Mixture of causes	33 (16%)	33 (16%)
Mean duration of infertility (years)	5.4 (3.3)	5.2 (3.5)
No. (%) of women with primary infertility	107 (53%)	124 (61%)
No. (%) of women with secondary infertility	94 (47%)	79 (39%)

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of recombinant FSH and 203 with 250 IU. The numbers of patients treated per center ranged between 7 and 49. The 150-IU daily dose treatment was given to 66 women between 30 and 33 years (mean 31.4 years, SD 1.4), to 52 women between 34 and 36 years (mean 35.1 years, SD 0.9), and 83 women between 37 and 39 years (mean 38.1 years, SD 0.9). In the 250-IU group, 54 women were between 30 and 33 years (mean 31.3, SD 1.3), 66 were between 34 and 36 years (mean 35.0, SD 0.8), and 83 were between 37 and 39 years (mean 38.0, SD 0.8).

Both groups had comparable demographic and infertility characteristics (Table 1). The main causes of infertility were tubal infertility (n = 46 [23%] vs. n = 51 [25%] in the low- and high-dose group, respectively) and male infertility (n = 91 [45%] vs. n = 86 [42%]). The mean duration of infertility was 5.4 years for the 150-IU group and 5.2 years for the 250-IU group. All women were down-regulated at the start of recombinant FSH treatment. Mean E<sub>2</sub> levels before COH were 86 and 96 pmol/L in the 150-IU and 250-IU groups, respectively. The corresponding LH levels were 3.0 and 2.5 IU/L.

### Primary End Points

Results on the primary end points are given in Table 2. The mean number of cumulus–oocyte complexes retrieved was 10.2 in the high-dose group compared to 8.9 in the low-dose group ( $P = .07$ ). Nearly 1,000 IU more were used in the women treated with 250 IU daily compared to the 150-IU group to reach the criterion to administer hCG (2,492 IU vs. 1,589 IU,  $P < .001$ ).

The mean number of oocytes retrieved in the various centers ranged from 4.3 to 12.4 in the 150-IU group, and from 6.4 to 13.9 in the 250-IU group. A test for treatment-center interaction was significant ( $P < .01$ ). Total doses of

**TABLE 2**

Statistical analysis of the number of oocytes retrieved and total dose used.

	150 IU (mean) <sup>a</sup>	250 IU (mean) <sup>a</sup>	150 minus 250 IU treatment group		
			Estimate of difference	SE <sup>b</sup>	95% confidence interval ( <i>P</i> value)
Number of oocytes retrieved	8.9	10.2	-1.3	0.7	-2.8 to 0.1 ( <i>P</i> =.07)
Total dose used (IU)	1589	2492	-904	39.3	-981 to -827 ( <i>P</i> <.001)

<sup>a</sup> Adjusted mean for center and age.

<sup>b</sup> Standard error of estimate of difference.

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recombinant FSH used ranged from 1,160 IU to 1,890 IU in the low-dose treated women, and from 1,850 IU to 3,063 IU in the high-dose group. A statistically significant treatment center effect was observed for this variable (*P*<.001).

The overall number of oocytes retrieved decreased from 12.2 to 9.6 and 7.9 in the different age categories 30–33, 34–36, and 37–39 years, respectively (unadjusted means, *P*<.001). Figure 1 shows the number of oocytes in the different treatment groups per age class. In the 30–33-year age class receiving the 250-IU dose, a surplus of 1.6 oocytes (13.1 vs. 11.5) was found, compared to 0.6 oocytes (9.2 vs. 9.8) in the 34–36-year category, and 2.0 oocytes (8.9 vs. 6.9) in the women between 37 and 39 years of age.

There was also a significant relation between the age classes and the amount of gonadotropins consumed (*P*<.01). Figure 1 shows an increase in the total dose used from 1,521

IU to 1,558 IU and 1,695 IU with increasing age group using a fixed daily dose of 150 IU. In the 250-IU group, the total doses used were 2,398 IU, 2,546 IU, 2,560 IU for the 30–33, 34–36, and 37–39 years of age categories, respectively.

### Secondary End Points

Results on the secondary variables are given in Table 3. The treatment length was slightly but significantly longer in the 150-IU treatment group (10.6 days) as compared to the 250-IU group (10.0 days, *P*<.01). No differences between the treatment groups were observed in the number of follicles ≥14 mm, ≥16 mm, ≥18 mm, and ≥20 mm at the day of hCG administration. However, there was a statistically significant relation between increasing age and the decreasing number of follicles of these sizes (*P*<.001).

Serum FSH levels at the day of hCG administration (or 1–3 days earlier) were 14.1 IU/L in the 250-IU group and 10.4 in the 150-IU group (*P*<.001). Progesterone levels in the corresponding period were 1.2 and 0.9 nmol/L in the high- and low-dose groups, respectively (*P*<.001). No significant differences were noted in the E<sub>2</sub> and LH concentrations. The serum E<sub>2</sub> level was higher with younger age, leading to a significant difference between the age classes (*P*<.001). For serum FSH, LH, and P, no significant relation with age was noted.

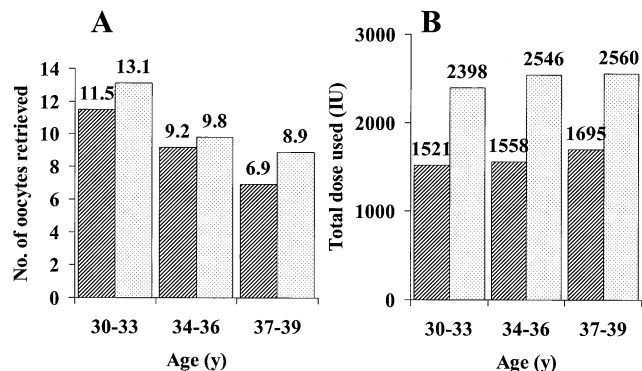
In total, 222 women (60%) underwent ICSI and 145 (40%) received conventional IVF. Per group, 107 (59%) and 75 (41%) received ICSI and IVF, respectively, in the 150-IU treated women, whereas 115 (62%) had ICSI and 70 (38%) IVF in the 250-IU group.

After conventional IVF, the number of transferable embryos in the 150-IU group was 4.1 compared to 4.3 in the 250-IU group. With ICSI, these numbers were 3.6 and 3.6, respectively. With both fertilization procedures, these figures were not significant different.

The embryo development rate, defined as the number of transferable embryos divided by the number of oocytes incubated or injected, was not significantly different between

**FIGURE 1**

Number of oocytes retrieved (A) and total dose (IU) used (B) in different age categories of women receiving a fixed daily dose of 150 or 250 IU of recombinant FSH. Hatched bars, 150 IU; stippled bars, 250 IU.



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TABLE 3

Results on secondary parameters.

Parameter	Mean <sup>d</sup>		150 IU minus 250 IU	P value
	150 IU	250 IU	95% CI of treatment difference	
Treatment length (days)	10.6	10.0	0.26 to 1.04	<.01
Follicles ≥14 mm (no.)	9.9	10.7	-2.0 to 0.4	NS
Follicles ≥16 mm (no.)	8.2	8.7	-1.5 to 0.5	NS
Follicles ≥18 mm (no.)	5.7	5.9	-1.0 to 0.6	NS
Follicles ≥20 mm (no.)	3.2	3.2	-0.5 to 0.5	NS
E <sub>2</sub> (pmol/l) at day hCG <sup>a</sup>	7410	7670	0.8 to 1.1 <sup>b</sup>	NS
LH (IU/l) at day hCG <sup>a</sup>	1.9	1.7	1.0 to 1.4 <sup>b</sup>	NS
FSH (IU/l) at day hCG <sup>a</sup>	10.4	14.1	0.7 to 0.8 <sup>b</sup>	<.001
P (nmol/l) at day hCG <sup>a</sup>	0.9	1.2	0.6 to 0.9 <sup>b</sup>	<.001
Mature oocytes (no.)	7.2	7.9	-1.9 to 0.4	NS
Transferable embryos (no.) in IVF	4.1	4.3	-1.1 to 0.8	NS
Transferable embryos (no.) in ICSI	3.6	3.6	-0.7 to 0.7	NS
Embryo development rate (%) in IVF	55.2	55.4	-9.6 to 9.1	NS
Embryo development rate (%) in ICSI	55.5	52.2	-3.6 to 10.2	NS
Embryos transferred (no.)	3.3	3.4	-0.4 to 0.1	NS
Clinical PR per started cycle (%)	23.3	24.0	-8.9 to 7.6	NS
Clinical PR per ET (%)	27.8	28.9	-10.6 to 8.4	NS
Vital PR per started cycle (%)	17.1	16.7	-6.8 to 7.7	NS
Vital PR per ET (%)	20.2	19.7	-7.9 to 9.0	NS
Implantation rate (%) <sup>c</sup>	10.0	10.9	-5.7 to 3.8	NS

<sup>a</sup> On day of hCG or 1 to 3 days earlier.<sup>b</sup> 95% confidence interval of estimated ratio of 150 IU to 250 IU.<sup>c</sup> Subjects with ET and without an ectopic pregnancy.<sup>d</sup> Adjusted mean for center and age.Abbreviations: CI = confidence interval; E<sub>2</sub> = estradiol; ET = embryo transfer; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; LH = luteinizing hormone; NS = not significant; P = progesterone; PR = pregnancy rate.*The Latin American Puregon IVF Study Group. Two doses of rFSH in IVF. Fertil Steril 2001.*

the low- and high-dose groups in the IVF population (55.2% and 55.4%, respectively) and in the ICSI groups (55.5% vs. 52.2%).

The mean number of embryos transferred was 3.3 in the 150-IU group and 3.4 in the 250-IU group (not significant). The number of embryos frozen was 0.9 in both groups.

Implantation rates were 10.0% in the 150-IU group and 10.9% in the 250-IU group. Vital pregnancy rates per started cycle were 17.1% in the low-dose group vs. 16.7% in the high-dose group (not significant). Vital pregnancy rates per started cycle in the 150-IU group for the ages 30–33, 34–36, and 37–39 years were 26.8%, 12.0%, 13.5%, respectively. For the 250-IU treated women, these percentages were 18.7%, 19.9%, and 12.6%. Of all vital pregnancies, 47% in the low-dose group and 29% in the high-dose group were multiple pregnancies. Seventeen twins, five triplets, and four quadruplets were reported.

For the secondary variables, significant treatment center effects were observed for all variables except for the number of embryos transferred and the vital pregnancy rate.

## Cycle Cancellations

Of 201 women who started on the low-dose group, 183 had an oocyte retrieval (91%) and 172 had embryo transfer (86%). In the high-dose group, 185 of 203 women (91%) who started recombinant FSH treatment had a retrieval and 171 (84%) had an embryo transfer.

Reasons for cancellation in the low-dose group were insufficient ovarian response (n = 14), risk for hyperstimulation (n = 1), no fertilization (n = 4), or other (n = 10); in the high-dose group, these reasons were insufficient ovarian response (n = 14), risk for hyperstimulation (n = 1), no fertilization (n = 7), or other (n = 10).

## Safety

Three women were hospitalized during the treatment period. One in the 150-IU group (extrauterine pregnancy) and two in the 250-IU group (OHSS). Of these two women, one was reported as moderate and one as severe OHSS. The OHSS was reported in five women (moderate: n = 4, severe: n = 1) in the 150-IU group (2.5%) and in eight women

(mild: n = 2, moderate: n = 5, severe: n = 1) receiving 250 IU of recombinant FSH (3.9%).

## DISCUSSION

To the best of our knowledge, this is the largest double-blind trial ever done in the field of COH (404 women). Although there was a tendency for more oocytes retrieved in the 250-IU group (10.2 vs. 8.9), the difference was not statistically significant. The difference of 1.3 oocytes in favor of the high-dose group was achieved using an extra 903 IU of recombinant FSH. The slight advantage in number of eggs did not reflect in the number of transferable embryos. Both after ICSI and conventional IVF those numbers were similar between the groups.

It is thought that the number of follicles to ovulate is determined by the length of time that the level of FSH remains above a certain critical threshold (8). Both the degree by which the threshold is surpassed and the time period during which such elevation exists (FSH window) are important parameters that determine follicular growth. A recent study comparing a single-shot of 375 IU of urinary FSH in the early follicular phase with a 5-day administration of 75 IU of urinary FSH in the mid/late follicular phase suggested that more follicular development occurred using moderate but continued elevation of FSH levels (9). This is in accordance with the current study where a nearly 75% higher FSH level at the day of hCG administration in the 250-IU group as compared to the 150-IU group led to the development of only one extra follicle  $\geq 14$  mm.

Not surprisingly, there was a significant decline in the number of oocytes retrieved with increasing age and also the total dose of recombinant FSH used was greater. However, in contrast to a previous double-blind study with the same design (5), the difference in number of collected eggs between the high- and low-dose groups did not become smaller with increasing age (Fig. 1). This suggests that it might still be worthwhile considering increasing the gonadotropin dose in older women. In the 37–39-year age group (n = 166), two additional oocytes could be retrieved in the 250-IU treated women. However, in the 34–36-year age group, that difference was only 0.6 oocyte. More research as to the individual patient characteristics is needed to explain this phenomenon.

The average BMI was approximately 23 kg/m<sup>2</sup> in this trial. Requirements for gonadotropins are dependent on body weight (10). Therefore, it might be possible that these findings are less applicable in women with higher BMI.

The small, albeit not statistically significant, difference in number of oocytes retrieved did not lead to a higher number of transferable embryos in the 250-IU group. This raises the question whether oocyte quality is jeopardized with increasing gonadotropin dosages. In trials comparing 100 and 200 IU of recombinant FSH (11, 12), the surplus in oocytes in the 200-IU group did lead to more embryos available for transfer

and freezing. However, the fact that this was not found in the current trial and another study comparing 150 and 250 IU of recombinant FSH (5), seems to suggest that there is a maximum number of oocytes that can be driven to maturity by means of recombinant FSH stimulation.

Serum P levels at the day of hCG were slightly, but significantly, increased in the high-dose group. This is in line with other studies comparing the effects of two fixed recombinant FSH doses (5, 11, 12). It seems likely that these increased levels are related to a greater FSH exposure, leading to an increased FSH-induced LH receptivity in granulosa cells (13).

This study was not set up to investigate differences in pregnancy rates. However, data from the current trial and other similar studies comparing different doses of recombinant FSH (100 vs. 200 IU [(11, 12)] and 150 vs. 200 IU [(14)]) strongly suggest that pregnancy rates are not influenced by gonadotropin doses. Apparently, endometrial receptivity and embryo quality are not fundamentally affected by daily recombinant FSH doses between 100 and 250 IU.

As seen frequently with multicenter trials in assisted reproduction, a large treatment center effect was noticed. Only the vital pregnancy rate and the number of embryos transferred in both groups were not influenced by the treatment center. Therefore, there was a high variability between centers for most of the outcome parameters. Although this can be seen as a disadvantage, the apparent advantage of multicenter studies is that more patients can be included and that it better reflects a real-life situation in which variability plays an important role.

In conclusion, this study has shown that an increase in the daily recombinant FSH dose from 150 to 250 IU in women between 30 and 39 years of age has only limited benefit. The total dose needed to reach the criterion for hCG administration increases with more than 900 IU, whereas only a trend toward more retrievable oocytes was seen. Therefore, the clinical usefulness of these higher doses can be questioned.

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