Recombinant follicle stimulating hormone in in-vitro fertilization treatment—clinical experience with follitropin alpha and follitropin beta

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The objective of this prospective study was to compare the outcome of ovarian hyperstimulation for in-vitro fertilization (IVF) using two different preparations of recombinant follicle stimulating hormone (FSH). The study was based on 296 consecutive IVF cycles in 1997, 199 performed using follitropin alpha (Gonal-F) and 97 performed using follitropin beta (Puregon). Outcome was compared regarding pregnancy rate, oestradiol and progesterone response, endometrial thickness, follicle number, number of retrieved oocytes, fertilized oocytes, sperm count and sperm motility. There was no significant difference in outcome of stimulation. Clinical pregnancy rate was similar, 29.1% for Gonal-F and 28.1% for Puregon. There was no difference in endometrial response, oestradiol response, number of smaller (12–15 mm) or larger (>15 mm) follicles, number of oocytes retrieved, fertilized, divided and replaced, in sperm counts or in sperm progressive motility. There was a lower follicle number in the Puregon group, but not statistically significant. The serum progesterone concentrations on the day of oocyte retrieval, however, were significantly lower in the Puregon group. In conclusion, it was not possible to find significant differences in the IVF programme with regard to stimulation outcome between Gonal-F and Puregon. The results of this study indicate that Gonal-F and Puregon may be equally suitable for use in ovarian stimulation for IVF.

Key words: FSH/IVF/oestradiol/ovary/progesterone

Introduction

Controlled ovarian hyperstimulation for in-vitro fertilization (IVF) using preparations containing follicle stimulating hormone (FSH) has been routinely performed since the 1980s. The early preparations used were urinary human menopausal gonadotrophins (HMGs) containing FSH and luteinizing hormone (LH) in a 1:1 ratio (Muasher et al., 1985; Navot and Rosenwaks, 1988; Palermo et al., 1988; Edelstein et al., 1990; Torok et al., 1991). In the 1990s, highly purified urinary FSH preparations were introduced because of a desire to provide drugs for s.c. injections and with a lower risk of allergic reactions (Howles et al., 1994). Expectations of future insufficient supplies of urine as a raw material to meet the demands of the increased use of FSH also made it necessary to find other sources than urine. Intensive research resulted in recombinant FSH, and in 1992, the first babies were born following treatment with FSH produced in that way (Devroey et al., 1992; Germond et al., 1992).

Since the autumn of 1996, two recombinant FSH preparations (Gonal-F and Puregon) have successively been introduced in IVF markets starting in Europe, and we now have experience of the two preparations available in Sweden for nearly 1 year. Both preparations had undergone extensive clinical trials in collaboration with several European centres (Loumaye et al., 1993; Devroey et al., 1994), and at the time of the introduction of the products in Sweden, it was emphasized that the two preparations were similar but not identical.

Data exist to suggest that recombinant FSH is more potent than the highly purified urinary FSH preparations (Out et al., 1996, 1997). Partially based on these studies, Puregon was believed to be somewhat more potent than Gonal-F; therefore, the drug was made available in ampoules of 50, 100 and 150 IU rather than the ‘standard’ size of 75 and 150 IU. Furthermore, recommended dosages were slightly lower than for Gonal-F.

Both preparations have been used at our clinic since the beginning of 1997. It was postulated that there might be a difference between the two preparations with regard to stimulation outcome, and therefore the present analysis of stimulation outcome in 296 consecutive cycles in 1997 was performed.

Materials and methods

Study population

The study population consisted of 218 patients treated at our clinic in 1997, and encompasses a total of 296 cycles. Gonal-F was given to 145 patients in 199 cycles, and Puregon was given to 73 patients in 97 cycles. Puregon was made available later than Gonal-F in Sweden, which is why a larger number of patients were given Gonal-F. As soon as both preparations were available, patients were assigned either Gonal-F or Puregon based on the odd or even last digit in their date of birth (year, month, day). Characteristics of the patients in the study are given in Table I.

Ovarian stimulation protocol

All patients followed our standard long gonadotrophin-releasing hormone agonist (GnRHa)-HMG protocol for stimulation as described earlier (Csemiczky et al., 1995; Fried et al., 1996). GnRHa (Suprefact; Svenska Hoechst AB, Stockholm, Sweden) was administered as a nasal spray 6×200 μg/day starting on day 21 of the menstrual cycle, and was reduced to half the dose when FSH injections were commenced. After down-regulation was verified by vaginal ultrasound scanning, 75–300 IU/day of recombinant FSH (Gonal-F; Serono

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Nordic AB, Sollentuna, Sweden; Puregon; Organon Sweden AB, Göteborg, Sweden) was administered s.c.

Starting dose was adjusted according to the same rules in both groups. The initial dose of FSH was generally 150 IU up to age 35 years, and 225 IU above this age, unless response to previous FSH stimulation at IVF indicated otherwise. In four cases in each group with the diagnosis of polycystic ovaries and a known tendency for strong response to FSH stimulation, the starting dose was 75–100 IU. In 13 Gonal-F cycles and five Puregon cycles, previously known low responders were given 300 IU FSH. In 12 Gonal-F and 10 Puregon cycles, the dose was raised by 50–75 IU after 7–8 days of stimulation due to poor ovarian response.

Follicular development and endometrial growth were monitored by vaginal ultrasonography using a Siemens Sonoline Si/200 in combination with blood samples for 17β-oestradiol assays. When an adequate stimulation was achieved, i.e. a controlled rise in serum oestradiol and a leading follicle diameter of at least 17 mm, 10 000 IU human chorionic gonadotrophin (HCG; Profasi; Serono Nordic AB, Stockholm, Sweden) was administered s.c. Approximately 35 h later ovum recovery was performed by transvaginal ultrasound-guided follicle aspiration. IVF, embryo transfer and pregnancy follow-up was performed as described elsewhere (Csemiczky et al., 1995). Luteal phase support was given using 400 mg micronized progesterone as vaginal pessaries three times daily until a pregnancy test was performed and if found positive, continued 8 weeks after embryo transfer. Pregnancy was defined as a serum HCG concentration >10 IU/l 2 weeks after embryo transfer and subsequently rising. Clinical pregnancy was defined as presence of an intrauterine fetus with regular heartbeats. Criteria for cycle cancellation were (i) no rise in oestradiol even after an increase in dose, (ii) only three or fewer follicles approaching 17 mm diameter, (iii) high risk for developing ovarian hyperstimulation syndrome – sharp rise in oestradiol and >25 follicles.

**Hormone assays**

Serum 17β-oestradiol and progesterone were assayed by the Central Laboratory for Clinical Chemistry, Karolinska Sjukhuset by radio-immunoassay, using reagents from the Farmos Group (Oulu, Finland).

**Statistical analysis**

Prior to statistical analysis, data were tested for Gaussian distribution using a normality test (the Kolmogorov–Smirnov test). Some data were found not to be normally distributed. Therefore, non-parametric statistics were used for all the data. Comparisons between mean values were made using the Mann–Whitney rank sum test. Although the standard errors were therefore not used for statistical comparisons, they have been appended to the mean values in the tables. Correlation analysis was performed using Spearman correlation. Tests were performed with the statistical package Graphpad Prism and Statmate (Graphpad Software Inc, San Diego, CA, USA). A P-value < 0.05 was considered significant.

**Results**

The characteristics of the study population are presented in Table I. There were no significant differences between the Gonal-F and Puregon groups with regard to age, reasons for infertility, duration of stimulation or presence of male factor. Regarding male factor, most of the male partners had sperm counts >5×10⁶/ml after swim-up preparation. However, 29 males (15.8%) in the Gonal-F group and 17 (19.5%) in the Puregon group had sperm counts <1×10⁶/ml. In 22 and 12 of these cases respectively, intracytoplasmic sperm injection (ICSI) was performed. There was no difference in the use of ICSI between the two groups. For the remaining patients, regular IVF was used. Cryopreservation was performed in eight cycles (seven Gonal-F, one Puregon) with a mean of 4.4 (three to six) preimplantation embryos. In five Gonal-F freeze cycles embryo transfer was performed, resulting in one twin pregnancy, whereas the embryo transfer in the Puregon freeze cycle was unsuccessful.

The outcome of stimulation of the two groups is shown in Table II. The pregnancy rate (calculated on the number of cycles where embryo transfer was performed) was not
Spermatozoa with good motility (%) 94.8
Oocytes retrieved (n/H11006) 11006
Endometrial thickness before oocyte 10.9
quality in 271 consecutive cycles where HCG was given and where oocyte correlated with oestradiol levels from 2 days prior to oocyte retrieval and on the day of embryo transfer. day of embryo transfer. before oocyte retrieval until 2 days before retrieval, in relation to total dose between the administered preparations used for stimulation.

The duration of stimulation was correlated to total dose within both the Gonal-F and the Puregon group, increasing with higher doses (Figure 2b). At a total dose of \( \leq 1500 \) IU, oocyte retrieval was performed at 13.4 ± 0.5 days in the Gonal-F group as compared to 14.6 ± 0.3 in the Puregon group. At a total dose of >3000 IU, the duration of the stimulation increased to 17.3 ± 0.5 and 16.5 ± 0.4 days respectively.

The serum concentrations of oestradiol at oocyte retrieval were also correlated to the total dose in both the Gonal-F and the Puregon group, and decreased with higher doses (Figure 2c). At a total dose of \( \leq 1500 \) IU, oestradiol was 3808 ± 283 nmol/l (n = 164) versus 30.3 ± 1.8 nmol/l (n = 76) (P = 0.005). In the patients who became pregnant, the corresponding values were 35.4 ± 2.8 nmol/l (n = 52, Gonal-F) versus 26.7 ± 3.3 nmol/l (n = 24, Puregon) (P = 0.03), and in the non-pregnant patients the values were 38.7 ± 1.8 nmol/l (n = 112, Gonal-F) versus 32.0 ± 2.1 nmol/l (n = 47, Puregon) (P = 0.04). No differences in progesterone concentrations were seen between the two groups or between pregnant and non-pregnant patients on the day of embryo transfer.

A correlation analysis regarding progesterone concentrations at oocyte retrieval revealed that in both the Gonal-F and the Puregon group, progesterone concentrations were strongly correlated with oestradiol levels from 2 days prior to oocyte retrieval, on the day of oocyte retrieval and on the day of embryo transfer (P < 0.0001). In addition, progesterone concentrations were also correlated with the number of small follicles (12–15 mm) (P = 0.03), the total number of oocytes retrieved (P = 0.005) and the number of cleaved oocytes (P < 0.0001).

A detailed analysis was performed regarding the total dose of FSH given in the two groups, in relation to pregnancy rate, duration of stimulation, oestradiol and progesterone at oocyte retrieval, number of smaller and larger follicles and number of oocytes retrieved and fertilized (Figure 2a–h). Patients given either Gonal-F or Puregon were assigned to five arbitrarily designed groups on the basis of the total dose of FSH given; \( \leq 1500, 1501–2000, 2001–2500, 2501–3000 \) and >3000 IU. No significant differences were found in pregnancy rate (Figure 2a) or in any of the other examined parameters (Figure 2b–h) in relation to total dose between the administered preparations used for stimulation.

The ovarian response in terms of oestradiol production/secretion is shown in Figure 1. Oestradiol levels in the early follicular phase were slightly higher in Gonal-F than in the Puregon cases, however, the difference was not significant up to 3 days before oocyte retrieval at oocyte retrieval or at embryo transfer. Oestradiol concentrations were compared in patients becoming pregnant and those remaining non-pregnant. Neither in the Gonal-F nor in the Puregon-treated group were the oestradiol levels at oocyte retrieval or at embryo transfer significantly different in this respect.

The progesterone levels in serum at oocyte retrieval, i.e. the day after HCG, were significantly higher in the Gonal-F group compared to the Puregon group, 37.7 ± 1.5 nmol/l (n = 164) versus 30.3 ± 1.8 nmol/l (n = 76) (P = 0.005). In the patients who became pregnant, the corresponding values were 35.4 ± 2.8 nmol/l (n = 52, Gonal-F) versus 26.7 ± 3.3 nmol/l (n = 24, Puregon) (P = 0.03), and in the non-pregnant patients the values were 38.7 ± 1.8 nmol/l (n = 112, Gonal-F) versus 32.0 ± 2.1 nmol/l (n = 47, Puregon) (P = 0.04). No differences in progesterone concentrations were seen between the two groups or between pregnant and non-pregnant patients on the day of embryo transfer.

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### Table V. Stimulation response, number of replaced embryos and sperm quality in 271 consecutive cycles where HCG was given and where oocyte retrieval was performed, using two different preparations of recombinant FSH. Values given as means ± SEM

<table>
<thead>
<tr>
<th></th>
<th>Gonal-F (n = 184)</th>
<th>Puregon (n = 87)</th>
</tr>
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<tbody>
<tr>
<td>Endometrial thickness before oocyte retrieval (mm)</td>
<td>10.9 ± 0.2</td>
<td>11.2 ± 0.3</td>
</tr>
<tr>
<td>Follicles 12–15 mm (n)</td>
<td>7.3 ± 0.5</td>
<td>6.5 ± 0.6</td>
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<tr>
<td>Follicles &gt;15 mm (n)</td>
<td>7.8 ± 0.5</td>
<td>6.2 ± 0.5</td>
</tr>
<tr>
<td>Oocytes retrieved (n)</td>
<td>7.9 ± 0.3</td>
<td>7.4 ± 0.4</td>
</tr>
<tr>
<td>Oocytes fertilized (n)</td>
<td>4.8 ± 0.2</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td>Oocytes cleaved (n)</td>
<td>4.7 ± 0.2</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>Sperm count (10^6/ml)</td>
<td>6.1 ± 0.3</td>
<td>5.2 ± 0.4</td>
</tr>
<tr>
<td>Spermatozoa with good motility (%)</td>
<td>94.8 ± 0.9</td>
<td>94.7 ± 1.3</td>
</tr>
<tr>
<td>Pre-embryos replaced (n) (170/80)</td>
<td>1.8 ± 0.04</td>
<td>1.8 ± 0.06</td>
</tr>
</tbody>
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Figure 1. Serum oestradiol concentrations (mean ± SEM) during cycles stimulated with either Gonal-F (open bars) or Puregon (hatched bars). Concentrations were measured daily from 9 days before oocyte retrieval until 2 days before retrieval, on the day of oocyte retrieval and on the day of embryo transfer.

**Follitropin alpha compared to follitropin beta in IVF**

significantly different between the two groups, resulting in clinical pregnancy rates of 29.1 and 28.9% for Gonal-F and Puregon respectively, whereas the ongoing pregnancy rates were 20.6% for both groups. The biochemical pregnancy rates were 34.1 and 35.0% per embryo transfer for Gonal-F and Puregon respectively.

There was no difference between the two groups in the ovarian and endometrial response to the FSH stimulation (Table V). The endometrial thickness before oocyte retrieval, as well as the numbers of smaller (12–15 mm) and larger (>15 mm) follicles, were similar. Neither were there any significant differences with regard to the number of oocytes retrieved, fertilized, cleaved and replaced, nor in sperm counts/ sperm progressive motility. There was a higher number of larger follicles in the Gonal-F group, but the difference was not statistically significant (P = 0.06).
Figure 2. Total dose of follicle stimulating hormone (FSH) given in cycles stimulated with either Gonal-F (open bars) or Puregon (hatched bars) (mean ± SEM) in relation to (a) pregnancy rate, (b) length of stimulation, (c) oestradiol at oocyte retrieval, (d) progesterone concentrations at oocyte retrieval, (e) number of smaller (12–15 mm) follicles, (f) number of large (>15 mm) follicles, (g) number of retrieved oocytes and (h) number of fertilized oocytes. Patients given either Gonal-F or Puregon were assigned to five arbitrarily designed groups (A–E) on the basis of the total dose of IU of FSH given; A, <1500; B, 1501–2000; C, 2001–2500; D, 2501–3000; and E, >3000 IU. The number of patients in each group was for Gonal-F/Puregon: A: 21/15, B: 73/18, C: 42/37, D: 24/9, E: 24/8.

pmol/l in the Gonal-F group as compared to 3459 ± 509 pmol/l in the Puregon group. The corresponding concentrations for a total dose of >3000 IU were 1928 ± 212 and 1508 ± 301 pmol/l. The serum concentrations of progesterone at oocyte retrieval were higher in the Gonal-F group at total doses up to 2500 IU (Figure 2d), but not above.
The numbers of smaller follicles (12–15 mm) were related to the total dose in both groups, decreasing with higher doses (Figure 2e). At ≤1500 IU, there were 10.2 ± 1.4 follicles in the Gonal-F group as compared to 7.3 ± 1.4 in the Puregon group. At >3000 IU, the corresponding numbers were 3.8 ± 0.8 and 2.3 ± 1.0 respectively. The numbers of larger follicles (>15 mm) did not vary significantly with total dose (Figure 2f).

The numbers of retrieved and fertilized oocytes were also correlated to the total dose in both groups, and decreased with a higher dose (Figure 2g, h). At ≤1500 IU, there were 9.3 ± 1.1 and 5.4 ± 0.8 oocytes respectively, in the Gonal-F group as compared to 7.2 ± 0.7 and 4.1 ± 0.7 oocytes in the Puregon group. At >3000 IU, the corresponding numbers were 5.4 ± 0.6 and 3.9 ± 0.6 respectively in the Gonal-F group as compared to 5.8 ± 1.1 and 2.8 ± 0.8 in the Puregon group.

Discussion
The present study clearly indicates that both of the recombinant FSH preparations currently on the market are equally well suitable for use in ovarian stimulation. Both can be self-administered s.c., which is a great clinical advantage. The results of this study reveal no significant clinical difference between Gonal-F and Puregon regarding number of follicles stimulated, number of oocytes retrieved and fertilized or in pregnancy rate. A recent comparison between Gonal-F and Puregon on a small number of patients, 22 in each group (Brinsden et al., 1998), is in agreement with the results presented here. The current study was designed as a prospective randomized study in 1997, but due to the later introduction of Puregon, there was a higher number of Gonal-F cycles. Even though this is a drawback, the two groups were well matched with regard to age, body mass index and indication for treatment (see Table I).

The only statistical difference found was that progesterone on the day of oocyte retrieval was higher in the Gonal-F group. A slightly higher number of follicles and higher levels of oestradiol in the Gonal-F group were also observed, although these were not statistically significant on the day of oocyte retrieval. The higher progesterone concentrations observed in the Gonal-F group may be related to this observation. The correlation of progesterone concentrations on the day of oocyte retrieval to the oestradiol concentrations, to the number of smaller follicles and to the number of oocytes retrieved strongly supports this suggestion. The recruitment of a higher number of follicles using Gonal-F would explain both higher oestradiol and progesterone concentrations. This is also supported by findings in a recent study comparing the efficacy of 100 IU versus 200 IU Puregon, where it was found that the 200 IU group had significantly higher progesterone concentrations on the day of HCG; this group also had more follicles and more oocytes retrieved (Out et al., 1999). In the current study, the Gonal-F group received a slightly higher total dose of FSH than the Puregon group, 2182 ± 61 as compared with 2105 ± 74, a difference of 77 IU. This difference may be related to the higher numbers of follicles in the Gonal-F group, but as mentioned above, neither the difference in total dose, nor the difference in follicle numbers was statistically significant.

The higher concentrations of progesterone found in the Gonal-F group did not appear to have any clinically relevant effects as compared to Puregon, i.e. the pregnancy rates were the same, as well as the proportion of biochemical pregnancies and miscarriages. Elevated progesterone concentrations in the follicular phase have been suggested to have a predictive value for the outcome of pregnancies achieved by IVF by some authors (Burns et al., 1994), but this has been questioned by others (Huang, 1996). In the present study, a difference was only seen on the day of oocyte retrieval, and as discussed above, may be related to the number of developing follicles.

On the day of embryo transfer there was no significant difference between the Gonal-F group and the Puregon group, indicating that there is no difference between the two in the luteal phase.

The small difference observed between Gonal-F and Puregon may be related to differences in molecular composition of the two preparations. It has been shown that the clinical efficacy of FSH principally may be related to the proportion and amount of acidic isoforms and to the degree of molecular complexity (Chappel, 1995). In a recent biochemical comparison between Gonal-F and Puregon, it was shown that Gonal-F is slightly more acidic than Puregon, whereas both Gonal-F and Puregon were far more similar to human urinary menopausal gonadotrophins (Fertinorm/Metrodin) than to highly purified urinary FSH (Fertinorm HP/Metrodin HP). Both recombinant FSH preparations, in addition, were shown to be more similar to human mid-cycle endogenous FSH than the urinary preparations (Robertson, 1998; see also Recombinant Human FSH Product Development Group, 1998). Earlier studies on human menopausal gonadotrophin preparations from these two suppliers have also indicated differences in molecular composition using isoelectric focusing (Harlin et al., 1986).

The analysis regarding stimulation outcome in relation to the total dose given revealed no difference in potency between Gonal-F and Puregon. The two preparations required a similar stimulation length for optimal effect, 15.2 days for Gonal-F and 16 days for Puregon (given as days from start of FSH injections until oocyte retrieval, in terms of days of FSH-injections this translates to 12.2 days for Gonal-F and 13 days for Puregon). It has been claimed that recombinant FSH is more effective than highly purified urinary FSH (Bergh et al., 1997; Out, 1996; Recombinant Human FSH Product Development Group, 1998). Recombinant FSH in this respect may be more similar to the original HMG preparations. It should however be noted that duration of stimulation and total dose required may be dependent on the type of down-regulation used, why direct comparisons between studies with different protocols are difficult to evaluate. Even when a common protocol was used, variation between clinics was identified as an important factor potentially contributing to observed differences in the five-centre prospective, randomized, double-blind clinical trial of two fixed doses of Puregon (Out et al., 1999). In a previous study, HMG (Pergonal) was compared with highly purified FSH (Fertinorm-HP/Metrodin) using the same type of down-regulation used in the present study, and
it was observed that stimulation length as defined above was 13.9 days for Pergonal and 14.3 days for Fertinorm-HP (Fried et al., 1996).

In conclusion, this study shows that the two available recombinant FSH preparations for ovarian stimulation in IVF are equally well suited, and both fulfill the essential requirements for acceptable pregnancy rates.

Acknowledgements

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