Human Reproduction Vol.21, No.11 pp. 2817–2822, 2006 doi:10.1093/humrep/del265
Advance Access publication July 27, 2006.

The use of a decremental dose regimen in patients treated with a chronic low-dose step-up protocol for WHO Group II anovulation: a prospective randomized multicentre study

J.N.Hugues[1,3], I.Cédrin-Durnerin[1], C.M.Howles[2], On Behalf of the Recombinant FSH OI Study Group

[1]Reproductive Medicine Unit, Jean Verdier Hospital, University Paris XIII, Paris, France and [2]Serono International, S.A. Chemin des mines 15 bis, Geneva, Switzerland

[3]To whom correspondence should be addressed at: Reproductive Medicine Unit, Jean Verdier Hospital, University Paris XIII, Avenue du 14 Juillet, Bondy, Paris, France. E-mail: jean-noel.hugues@jvr.ap-hop-paris.fr

M.Amram, Marseille; A.Angelini, Perugia; A.Balen, Leeds; D.Barbereau, Bron; M.Birkhauser, Bern; A.Boujenah, Paris; V.De Leo, Siena; G.De Placido, Napoli; S.Dessole, Sassari; S.Favrin, Toulouse; E.Ferrazi, Milano; C.Gay, Strasbourg; M.Germond, Lausanne; B.Hedon, Montpellier; C.Hocke, Bordeaux; C.Jolly, Caen; E.Lamarca-Roth, Mulhouse; A.Lanzone, Roma; F.Marchand, Nantes; G.Marcolin, Lille; G.Mascaretti, Coppito; L.Moreau, Strasbourg; M.Massobrio, Torino; C.Nappi, Napoli; G.Pardi, Milano; G.Pennehouat, Chartres; E.Porcu, Bologna; M.Seibert, Mulhouse; L.Selvaggi, Bari; D.Thiers, Aix-en-Provence; P.Venturini, Genova.

BACKGROUND: In women with chronic anovulation, the choice of the FSH starting dose and the modality of subsequent dose adjustments are critical in controlling the risk of overstimulation. The aim of this prospective randomized study was to assess the efficacy and safety of a decremental FSH dose regimen applied once the leading follicle was 10–13 mm in diameter in women treated for WHO Group II anovulation according to a chronic low-dose (CLD; 75 IU FSH for 14 days with 37.5 IU increment) step-up protocol. METHODS: Two hundred and nine subfertile women were treated with recombinant human FSH (r-hFSH) (Gonal-f) for ovulation induction according to a CLD step-up regimen. When the leading follicle reached a diameter of 10–13 mm, 158 participants were randomized by means of a computer-generated list to receive either the same FSH dose required to achieve the threshold for follicular development (CLD regimen) or half of this FSH dose [sequential (SQ) regimen]. HCG was administered only if not more than three follicles ≥16 mm in diameter were present and/or serum estradiol (E_2) values were <1200 pg/ml. The primary outcome measure was the number of follicles ≥16 mm in size at the time of hCG administration. RESULTS: Clinical characteristics and ovarian parameters at the time of randomization were similar in the two groups. Both CLD and SQ protocols achieved similar follicular growth as regards the total number of follicles and medium-sized or mature follicles (≥16 mm: 1.5 ± 0.9 versus 1.4 ± 0.7, respectively). Furthermore, serum E_2 levels were equivalent in the two groups at the time of hCG administration (441 ± 360 versus 425 ± 480 pg/ml for CLD and SQ protocols, respectively). The rate of mono-follicular development was identical as well as the percentage of patients who ovulated and achieved pregnancy. CONCLUSIONS: The results show that the CLD step-up regimen for FSH administration is efficacious and safe for promoting mono-follicular ovulation in women with WHO Group II anovulation. This study confirms that maintaining the same FSH starting dose for 14 days before increasing the dose in step-up regimen is critical to adequately control the risk of over-response. Strict application of CLD regimen should be recommended in women with WHO Group II anovulation.

Key words: chronic low-dose step-up protocol/decremental dose protocol/ovulation induction/r-hFSH/WHO Group II anovulation

Introduction

WHO Group II anovulation is a common cause of subfertility in women (Franks, 1995). First-line therapy is usually clomiphene citrate. However, ~20% of women are clomiphene citrate resistant and therefore require gonadotrophin administration to achieve follicle development. During ovulation induction in these women, the two major risks are the occurrence of ovarian hyperstimulation syndrome (OHSS) and the development of multiple pregnancies. This latter risk is specifically high in women whose chronic anovulation is the only cause of subfertility.

Therefore, in the past 15 years, two different protocols have been designed to reduce the adverse effects of ovarian stimulation: the so-called step-up (Kamrava *et al*., 1982; Buvat *et al*., 1989; Sagle *et al*., 1991; Shoham *et al*., 1991; White *et al*., 1996) and

step-down protocols (Mizunuma *et al*., 1991; Fauser and Van Heusden, 1997). Some studies comparing efficacy and safety of these two regimens for FSH administration were performed with a limited number of selected subjects and reported conflicting results (Mizunuma *et al*., 1991; Van Santbrink and Fauser, 1997; Andoh *et al*., 1998; Balasch *et al*., 2001). More recently, a prospective multicentre study performed on many participants with polycystic ovary syndrome (PCOS) has shown that a step-up protocol is safer for routine clinical practice than the step-down regimen (Christin-Maitre *et al*., 2003).

An alternative protocol combining the step-up and step-down approaches was proposed by Hugues *et al*. (1996). It consists of sequential (SQ) administration of FSH with an initial low-dose (LD) step-up regimen to achieve the threshold for follicular development, followed by a decremental dose regimen once the leading follicle reached 14 mm in diameter. This so-called SQ regimen proved to be effective in reducing the number of medium-sized follicles in PCOS women. This issue is critical because it has been established that the number of medium-sized follicles is positively correlated with the risk of multiple pregnancy (Homburg and Howles, 1999).

Another major issue of the 'step' protocols is the duration of the initial dose administration as well as the regimen for FSH dose adjustments. Regarding the step-up protocols, some studies have shown that a chronic administration of LDs of FSH for 14 days, the so-called chronic LD (CLD) regimen, is safer than a protocol with FSH dose adjustment every 7 days, the so-called LD regimen (Hedon *et al*., 1998; Homburg and Howles, 1999). Compiled data from clinical studies on the results of a LD step-up FSH protocol in clomiphene citrate-resistant women recorded a fecundity rate/cycle of 20%, uni-ovulation rate of 70%, severe OHSS 0.14% and multiple pregnancy rate of 5.7%. A strict adherence to a 14-day starting period using a standard 75 IU FSH dose seems to be critical for reducing the risk of over-response (more than three follicles ≥16 mm). This protocol was not applied in our previous study assessing the use of an SQ regimen (Hugues *et al*., 1996) in women with anovulation related to PCOS. In the former study, FSH was administered according to a 7-day LD regimen (75 IU/day) (with a subsequent incremental FSH dose of 37.5 IU). Therefore, it remains uncertain whether a decremental dose regimen for FSH administration is only useful in women treated in a 7-day dosing regimen or whether it could also be recommended in women treated according to a strict CLD step-up regimen with FSH dose adjustment after 14 days.

Therefore, a prospective randomized study was set up in women with WHO Group II anovulation to assess whether a decremental dose regimen for FSH administration might be helpful in reducing further any over-response in women treated according to a CLD protocol.

Patients and methods

Patients

Two hundred and thirteen women with subfertility due to WHO Group II anovulation were asked to participate in this study. All women were seeking pregnancy.

The diagnosis of normogonadotrophic anovulation was made according to WHO classification (Rowe *et al*., 1993). Study inclusion criteria were (i) oligomenorrhoea (bleeding interval between 35 days and 6 months) or regular cycles with anovulation attested by serum progesterone values <10 nmol/l in luteal phase, (ii) serum FSH levels within normal limits (<10 IU/l), (iii) normal prolactin and thyroid-stimulating hormone levels, (iv) age 19–38 years and BMI (weight divided by height squared) ≤30 and (v) previous unsuccessful treatment with clomiphene citrate (100 mg/day for 5 days)—anovulation during at least three consecutive cycles or failure to conceive in six ovulatory clomiphene citrate cycles. None of them had experienced previous stimulation with FSH preparations.

A normal hysterosalpingogram or laparoscopy had to be carried out in the past 3 years before study enrolment. With regard to a possible male factor, the sperm count was considered abnormal if sperm concentration was $<25 \times 10^6$/ml, progressive motility measured at 1 h <40% and/or teratospermia >40%. Only women whose partner had normal sperm characteristics were enrolled in the study.

Other exclusion criteria were the presence of systemic or metabolic diseases, ovarian organic cyst or any addiction to drugs or alcohol.

Methods

Study design

The design was a prospective, randomized, multicentre study. Each principal investigator per centre received numbered sealed envelopes to be used in numerical order. The randomization list was randomly generated by computer. Randomization was stratified by blocks of six and was blind to the physician who performed ultrasound. Women agreeing to participate in the study were treated for only one cycle.

Recombinant human FSH (r-hFSH) (Gonal-f®, Serono International SA, Switzerland, 75 IU/vial) was administered subcutaneously starting on day 2–3 of a spontaneous cycle or after a withdrawal bleed induced by a short course of progestin. Serial vaginal ultrasound scanning and serum estradiol (E_2) measurements were performed every 2–3 days after the initial 7 days of FSH stimulation. The daily starting dose of FSH (75 IU) was maintained for up to 14 days according to the CLD regimen. If no dominant follicle (>9 mm maximum diameter) was present at day 14 of stimulation, the FSH dose was increased by 37.5 IU according to the step-up regimen. Any further increments were by 37.5 IU, at weekly intervals up to a maximum of 187.5 IU.

When the leading follicle reached a diameter of 10–13 mm, participants were randomized to receive either the same dose of FSH up to the time of hCG administration (CLD step-up protocol) or half of the current FSH dose required to reach this criteria (SQ protocol). Women were excluded from randomization if a leading follicle was >13 mm in diameter or if more than four follicles between 10 and 13 mm in diameter were observed on ultrasound.

In both protocols, a single dose of hCG (5000 IU) (Profasi, Serono International SA) was administered subcutaneously when one leading follicle reached a diameter of ≥16 mm. HCG administration was withheld if more than three follicles ≥16 mm in diameter were present and if serum E_2 level was ≥1200 pg/ml. In this study, luteal phase supplementation was not applied. Ovulation was assessed by measurement of serum progesterone levels 7–10 days after hCG administration.

The study was approved by the local ethic committees. Participants signed an informed consent form.

Outcome parameters

The primary end-point was the number of follicles ≥16 mm at the time of hCG administration. The secondary end-points were the proportion of cycles with mono-follicular development, the rate of multifollicular development, the duration of FSH stimulation, the total FSH consumption and the percentage of cycles with successful ovulation.

Sample size calculation

The main objective was to show the equivalence between both protocols using as primary efficacy end-point the number of mature follicles. In a previous study using recombinant FSH stimulation according to a CLD regimen in a similar population, the mean number of mature follicles on hCG day was 1.5 ± 0.8. Both protocols were to be declared clinically equivalent if the difference in the mean number of mature follicles on hCG day was shown to be within [–0.3; +0.3]. Equivalence was tested using a two-sided 90% confidence interval (CI) for the difference in the mean number of mature follicles between the two groups. To demonstrate this equivalence with a power of 95% and a type I error of 5%, 112 patients were required in each group.

Statistical analysis

Data were analysed using SAS software. For continuous variables, a two-way analysis of variance (ANOVA) with centre and treatment as factors was performed. For the categorical variables, χ^2 tests or Fisher's test were used. Results are expressed as mean ± SD.

Results

Twenty-four centres from four different countries were selected for this clinical trial performed from the end of 1999 to the beginning of 2002. As shown in Figure 1, 4 of 213 patients initially included in the clinical trial did not start the study for personal reasons. Therefore, 209 actually received r-hFSH. As they did not meet the criteria as regards the ovarian response to FSH, 51 women were not randomized. Twenty-six (51%) displayed an advanced follicular growth (foll ≥14 mm), another 15 (29%) presented with a low follicular growth or in one patient (2%) an excessive ovarian response to FSH. In nine (18%) women, randomization was not performed for personal reasons. Therefore, 158 participants were randomized to one of the two protocols (intention to treat population *n* = 158, CLD protocol *n* = 80; SQ protocol *n* = 78). In 44 women, deviations from the protocol regimens were observed with a similar proportion in each group: inadequate FSH starting doses (7), non-compliance as regards criteria for randomization (10), dose adjustment (12) or hCG administration (8). Therefore, the final analysis was performed in 114 women (per protocol population, CLD protocol *n* = 59; SQ protocol *n* = 55).

As summarized in Table I, the clinical characteristics of participants enrolled in this study were similar in both groups. Moreover, the ovarian parameters at the time of randomization assessed in women subsequently treated with CLD or SQ protocols were comparable as regards the duration of stimulation, the dose of r-hFSH and the number of medium-sized (10–13 mm)

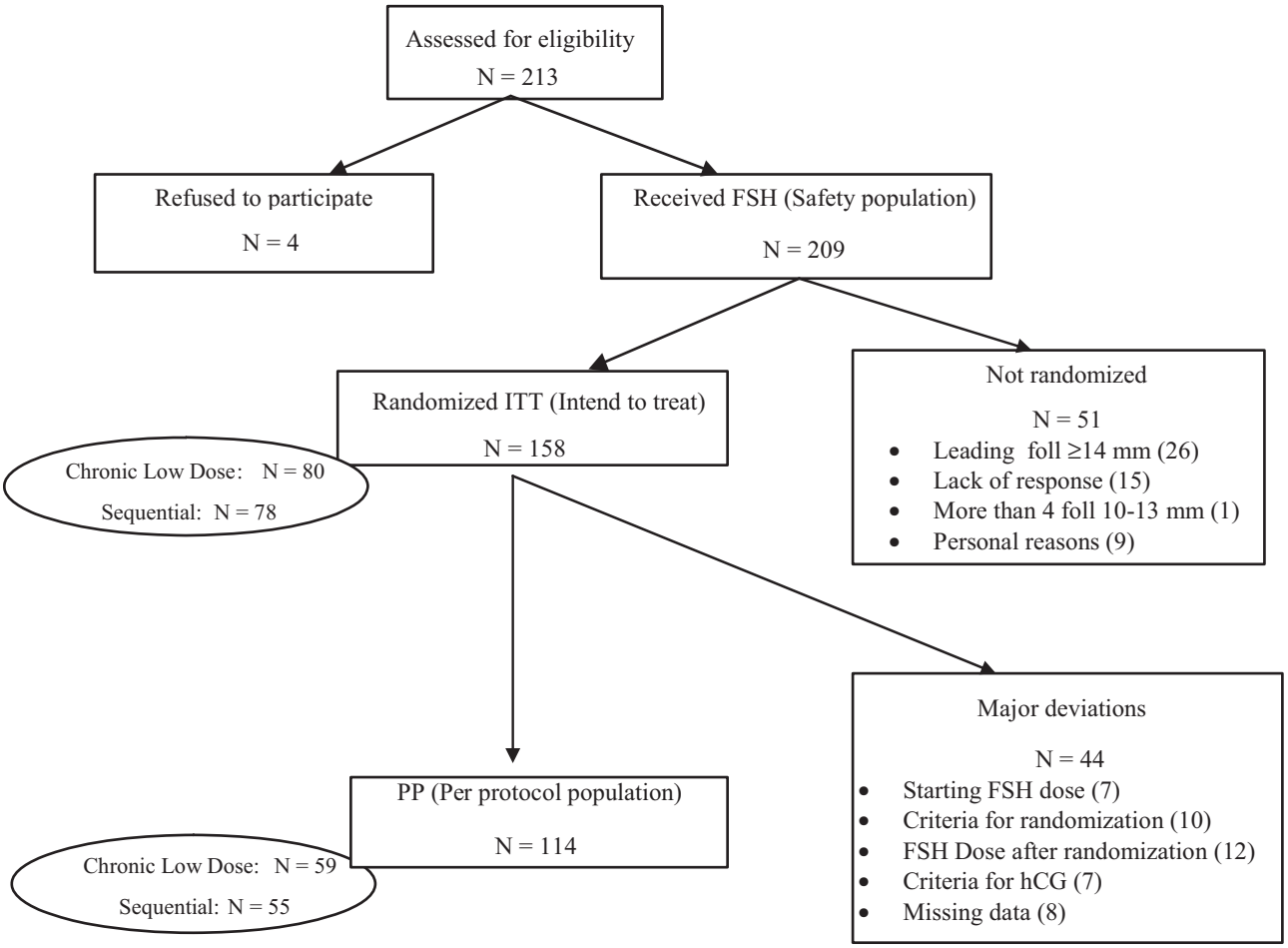

Figure 1. CONSORT statement flow diagram.

Table I. Clinical characteristics of enrolled women and stimulation parameters at the time of randomization

	CLD protocol (n = 80)	SQ protocol (n = 78)	P
Clinical characteristics			
Age (years)	29.4 ± 4.1	29.5 ± 3.5	NS
Weight (kg)	61 ± 9.3	61.8 ± 10.9	NS
Height (cm)	163.1 ± 5.5	163.4 ± 5.8	NS
BMI (kg/m^2)	23 ± 3.5	23.1 ± 3.6	NS
Duration of infertility (years)	3.23 ± 2.3	3.4 ± 2.7	NS
Primary infertility (%)	71	71	NS
Stimulation parameters at day of randomization			
Duration of treatment (days)	9.5 ± 6.5	10.7 ± 7.3	NS
75 IU threshold dose (%)	85	79	NS
Total dose of r-hFSH (IU)	780 ± 657	894 ± 755	NS
Number of follicles between 10 and 13 mm	2.3 ± 2.4	1.8 ± 1.1	NS

CLD, chronic low dose; NS, not significant; r-hFSH, recombinant human FSH; SQ, sequential.
Results are expressed as mean ± SD.

follicles. Furthermore, the percentage of women who had actually achieved the threshold for follicular growth with the daily FSH dose of 75 IU was equivalent in both groups, and only a small proportion of women (<10%) required adjustment of the initial FSH starting dose.

Table II displays the results and the outcomes of cycles in participants randomized to receive either the CLD or the SQ administration of FSH. It shows that women randomized in the SQ protocol achieved criteria for hCG administration after a non-significant longer duration of FSH administration. At the time of hCG administration, the numbers of large- or medium-sized follicles as well as the total number of follicles ≥10 mm were similar in both treatment groups. Moreover, the percentage of women who develop one, two or three large follicles ≥16 mm in diameter was not significantly different between groups. Finally, serum E_2 levels on the day of hCG administration were comparable in both groups. hCG was administered in 100% of women treated with CLD and SQ regimens. The ovulation rate was not significantly different between regimens as attested by a similar proportion of women with adequate serum progesterone values in the mid-luteal phase. At the end of treatment, the rates of clinical pregnancy and multiple pregnancy were not significantly different as well as the incidence of mild or moderate OHSS or miscarriage. Neither ectopic pregnancy nor severe OHSS was observed during the study.

Discussion

Induction of ovulation in women with WHO Group II anovulation has been associated with a high incidence of OHSS and multiple pregnancies (Sagle *et al*., 1991; Homburg *et al*., 1995). Therefore, administration of LDs of FSH in a stepwise fashion (step-up, step-down protocol or a combination of step-up and step-down) has been suggested and proved to be effective to significantly reduce those risks (Homburg and Howles, 1999). Therefore, the 'step' protocols are currently used to induce follicle development in clomiphene citrate-resistant women with WHO Group II anovulation. Although only a few studies have compared the efficacy and safety of step-up and step-down protocols within the same study (Mizunuma *et al*., 1991; Van Santbrink and Fauser, 1997; Andoh *et al*., 1998; Balasch *et al*., 2001), a large multicentric randomized study has recently shown that the CLD regimen of recombinant FSH administration is as effective as , but safer than, the step-down regimen (Christin-Maitre *et al*., 2003). The rate of mono-follicular development was significantly higher, and the rate of multifollicular development was significantly lower with the

Table II. Clinical results (mean ± SD) of chronic low dose (CLD) and sequential (SQ) administration of recombinant human FSH (r-hFSH)

ITT	CLD protocol (n = 80)	SQ protocol (n = 78)	P
Parameters between randomization and hCG			
Duration of treatment (days)	4.6 ± 3.5	5.6 ± 4.4	0.14
Amount of r-hFSH (IU)	394 ± 355	307 ± 303	0.1
Parameters at the time of hCG administration			
Duration of treatment (days)	14.1 ± 7.4	16.3 ± 8.5	0.09
Total amount of r-hFSH (IU)	1174 ± 818	1197 ± 934	0.87
Number of follicles ≥10 mm at hCG	2.9 ± 2.3	2.7 ± 2.4	0.94
Number of follicles between 10 and 13 mm at hCG	1.0 ± 1.5	0.9 ± 1.9	0.96
Number of follicles between 14 and 15 mm at hCG	0.4 ± 0.7	0.5 ± 0.8	0.59
Number of follicles ≥16 mm at hCG	1.5 ± 0.9	1.4 ± 0.7	0.85
Rate of mono-follicular development (%)[a]	54 (42–65)	56 (45–68)	0.7
Rate of bi-follicular development (%)[a]	25 (16–36)	23 (14–34)	0.75
Rate of tri-follicular development (%)[a]	5 (1–12)	4 (1–11)	0.95
Estradiol plasma value at hCG (pg/ml)	441 ± 360	425 ± 480	0.82
Endometrium thickness (mm)	9.6 ± 1.9	9.5 ± 2.1	0.86
hCG administration (%)	100	100	NS
Patients with ovulation (%) (P4 > 10 ng/ml)[a]	54 (42–66)	45 (34–57)	0.25
Progesterone values in luteal phase (ng/ml)	21.8 ± 24	23.7 ± 24	0.74
Clinical pregnancy/cycle (%)[a]	17 (21) (13–32)	9 (12) (5–21)	0.12
Multiple pregnancy/clinical pregnancy (%)	2 (12)	1 (11)	NS
Mild and moderate OHSS (%)	2 (3)	3 (4)	NS
Miscarriages (%)	3 (4)	2 (3)	NS

ITT, intent to treat; NS, not significant; OHSS, ovarian hyperstimulation syndrome.
[a]For binary parameters, the 95% confidence interval was also presented.

step-up protocol as compared with the step-down regimen. Another reason for this finding is that in routine clinical practice, the step-down protocol is more difficult to manage.

Several factors are known to be critical to promote a limited number of growing follicles in stimulation protocols, including the daily FSH starting dose and the regimen of FSH dose adjustment.

Determining the most appropriate starting dose is crucial to reduce the risk of overstimulation. These data show that, in non-obese women with WHO Group II anovulation, a starting daily dose of 75 IU is adequate to ensure selection of a limited number of follicles. Indeed, dose adjustment to achieve initiation of follicular growth was unnecessary in the vast majority (>90%) of participants. As previously reported by Imani *et al.* (2002), several parameters such as BMI, cycle history, ovarian response to clomiphene citrate and basal serum FSH values are significantly correlated with the individual FSH response. Therefore, a strict adjustment of the FSH starting dose based on initial screening characteristics is required to improve the safety but also the convenience of LD regimens. As recently observed by Christin-Maitre *et al*. (2003), using a lower daily starting dose of r-hFSH (50 IU), a dose adjustment was required in ~50% of women, and as a consequence, the duration of stimulation was significantly extended. Therefore, the choice of an optimal FSH starting dose is essential to improve the acceptance of the CLD step-up protocols.

Another major issue of the step protocols is the FSH dose adjustment, which must take into account both the duration of the initial FSH dose and the dose increment or decrement. Regarding the step-up protocols, several studies have previously shown that a chronic administration of low FSH doses for 14 days according to the so-called CLD is safer than a regimen with FSH dose adjustment after 7 days (Hedon *et al*., 1998; Homburg and Howles, 1999). Our data confirm that a strict adherence to a 14-day starting period using a persistent dose is effective, resulting in a low risk of overstimulation. In our series, ~90% of women did not require a dose adjustment, and most of them recruited a low number of follicles. It is still unclear why extending the period of constant FSH administration for up to 14 days may be effective whilst no follicular growth occurs after the seventh day of stimulation. Some reasons have been proposed, such as the fluctuating levels of endogenous FSH production (Brown, 1978), the long half-life of the FSH preparations (Le Cotonnec *et al*., 1994) and the up-regulation of FSH receptors by FSH itself (Lapolt *et al*., 1992).

As regards the dose adjustment, the CLD step-up protocol recommends the use of small incremental FSH doses if follicular selection is not observed after the initial 14-day administration. Conversely, a decremental dose regimen is required if the number of developing follicles is suboptimal (Hugues *et al*., 1996). Our data show that if the number of medium-sized (10–13 mm) follicles emerging from the cohort is ≤3, reducing the FSH dose by half is not necessary because there is no actual risk of overstimulation (more than three follicles ≥16 mm). These results contrast with our previous report (Hugues *et al*., 1996), where a decremental regimen proved to be effective in reducing the number of intermediate follicles at the time of hCG administration. However, in this earlier study, only women with PCOS were enrolled, and more importantly, the FSH dose adjustment was performed on day 7 of the stimulation. In that situation, a decremental dose regimen is recommended because FSH dose reduction leads to a decrease in the circulating FSH level and the number of medium-sized follicles (Schoot *et al*., 1992; Hugues *et al*., 1996). Similarly, this concept of dose reduction may also account for the results observed in Balasch's study, where a coasting period was performed from day 3 to day 5 of the stimulation (Balasch *et al*., 2001). Owing to the long half-life of FSH preparations, it seems prudent to follow a CLD protocol with small incremental doses, particularly in PCOS women who are highly sensitive to FSH. Therefore, in these women, a careful assessment of early follicular development is helpful to timely adjust the FSH dose.

In conclusion, our data provide new evidence that a strict application of a 14-day starting dose regimen seems to be critical for lowering the risk of overstimulation. During this interval, most women (>90%) will respond to a dose of 75 IU FSH. Even if this regimen taxes the patience of physicians, it seems the most appropriate to adequately control the number of developing follicles and therefore to reduce the risk of multiple pregnancy in women with WHO Group II anovulation. When this regimen is applied, reducing the FSH supply in the late part of FSH stimulation does not offer any clinical advantage.

Acknowledgements

We thank Dr Françoise Truong, Quyen Nguyen and the clinical research associates from Serono SA who supported this study.

References

Andoh K, Mizunuma H, Liu X, Kamijo T, Yamada K and Ibuki Y (1998) A comparative study of fixed-dose, step-down, and low-dose step-up regimens of human menopausal gonadotropin for patients with polycystic ovary syndrome. Fertil Steril 70,840–846.

Balasch J, Fabregues F, Creus M, Puerto B, Penarrubia J and Vanrell JA (2001) Follicular development and hormone concentrations following recombinant FSH administration for anovulation associated with polycystic ovarian syndrome: prospective, randomized comparison between low-dose step-up and modified step-down regimens. Hum Reprod 16,652–656.

Brown JB (1978) Pituitary control of ovarian function – concepts derived from gonadotrophin therapy. Aust N Z J Obstet Gynaecol 18,47–54.

Buvat J, Buvat HM, Marcolin G, Dehaene JL, Verbecq P and Renouard O (1989) Purified follicle-stimulating hormone in polycystic ovary syndrome: slow administration is safer and more effective. Fertil Steril 52,553–559.

Christin-Maitre S, Hugues JN, On Behalf of the Recombinant FSH Study Group (2003) A comparative randomized multicenter study comparing the step-up versus step-down protocol in polycystic ovary syndrome. Hum Reprod 18,1626–1631.

Fauser B and Van Heusden AM (1997) Manipulation of human ovarian function: physiological concepts and clinical consequences. Endocr Rev 18,71–105.

Franks S (1995) Polycystic ovary syndrome. N Engl J Med 333,853–861.

Hedon B, Hugues JN, Emperaire JC, Chabaud JJ, Barbereau D, Boujenah A, Howles CM and Truong F (1998) A comparative prospective study of a chronic low dose versus a conventional ovulation stimulation regimen using recombinant human follicle stimulating hormone in anovulatory infertile women. Hum Reprod 13,2688–2692.

Homburg R and Howles CM (1999) Low-dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, results, reflections and refinements. Hum Reprod Update 5,493–499.

Homburg R, Levy T and Ben-Rafael Z (1995) A comparative prospective study of conventional regimen with chronic low-dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome. Fertil Steril 63,729–733.

Hugues J, Cedrin-Durnerin I, Avril C, Bulwa S, Herve F and Uzan M (1996) Sequential step-up and step-down dose regimen: an alternative method for ovulation induction with follicle-stimulating hormone in polycystic ovarian syndrome. Hum Reprod 11,2581–2584.

Imani B, Eijkemans M, Faessen GH, Bouchard P, Giudice LC and Fauser BC (2002) Prediction of the individual follicle-stimulating hormone threshold for gonadotropin induction of ovulation in normogonadotropic anovulatory infertility: an approach to increase safety and efficiency. Fertil Steril 77,83–90.

Kamrava M, Seibel MM, Berger MJ, Thompson I and Taymor ML (1982) Reversal of persistent anovulation in polycystic ovarian disease by administration of chronic low-dose follicle-stimulating hormone. Fertil Steril 37,520–523.

LaPolt PS, Tilly JL, Aihara T, Nishimori K and Hsueh AJ (1992) Gonadotropin-induced up- and down-regulation of ovarian follicle-stimulating hormone (FSH) receptor gene expression in immature rats: effects of pregnant mare's serum gonadotropin, human chorionic gonadotropin and recombinant FSH. Endocrinology 130,1289–1295.

Le Cotonnec JY, Porchet HC, Beltrami V, Khan A, Toon S and Rowland M (1994) Clinical pharmacology of recombinant human follicle-stimulating hormone (FSH). I. Comparative pharmacokinetics with urinary human FSH. Fertil Steril 61,669–678.

Mizunuma H, Takagi T, Yamada K, Andoh K, Ibuki Y and Igarashi M (1991) Ovulation induction by step-down administration of purified urinary follicle-stimulation hormone in patients with polycystic ovarian syndrome. Fertil Steril 55,1195–1196.

Rowe PJ, Comhaire FH, Hargreave TB and Mellows HJ (1993) *WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple*. Cambridge University Press, Cambridge, pp. 54–55.

Sagle M, Hamilton-Fairley D, Kiddy DS and Franks S (1991) A comparative, randomized study of low-dose human menopausal gonadotropin and follicle-stimulating hormone in women with polycystic ovarian syndrome. Fertil Steril 55,56–60.

Schoot D, Pache TD, Hop WC, de Jong FH and Fauser BCJM (1992) Growth patterns of ovarian follicles during induction of ovulation with decreasing doses of human menopausal gonadotropin following presumed selection in polycystic ovary syndrome. Fertil Steril 57,1117–1120.

Shoham Z, Patel A and Jacobs HS (1991) Polycystic ovary syndrome: safety and effectiveness of a step-wise and low-dose administration of purified FSH. Fertil Steril 55,1051–1056.

Van Santbrink E and Fauser BCJM (1997) Urinary follicle-stimulating hormone for normogonadotropic clomiphene-resistant anovulatory infertility: prospective, randomized comparison between low dose step-up and step-down dose regimens. J Clin Endocrinol Metab 82,3597–3602.

White D, Polson DW, Kiddy D, Sagle P, Watson H, Gilling-Smith C, Hamilton-Fairley D and Franks S (1996) Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. J Clin Endocrinol Metab 81,3821–3824.

Submitted on March 2, 2006; resubmitted on May 24, 2006; accepted on June 5, 2006