Clinical Endocrinology (2007) **67**, 563–569 doi: 10.1111/j.1365-2265.2007.02925.x

ORIGINAL ARTICLE

Recombinant human luteinizing hormone, lutropin alfa, for the induction of follicular development and pregnancy in profoundly gonadotrophin-deficient women

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Summary

Objective To provide evidence of efficacy and safety for use of lutropin alfa in inducing follicular development and pregnancy in hypogonadotrophic hypogonadal women with profound gonadotrophin deficiency.

Design An open-label, noncomparative extension of a randomized, double-blind, placebo-controlled study

Patients A total of 31 hypogonadotrophic hypogonadal women with profound gonadotrophin deficiency in 23 medical centres in four countries were studied.

Interventions Lutropin alfa 75 IU and follitropin alfa (75–225 IU), individually based on each patient's response as is consistent with usual medical practice.

Measurements Follicular development as defined by (i) at least one follicle ≥ 17 mm; (ii) preovulatory serum oestradiol level ≥ 109 pg/ml on the day of hCG administration; and (iii) midluteal phase P_4 level ≥ 7·9 ng/ml. Pregnancy and over-response leading to cycle cancellation were considered treatment successes. Pregnancy rates were assessed.

Results In a total of 54 cycles, 27 of 31 (87·1%) profoundly gonadotrophin-deficient patients achieved follicular development within three cycles. Twenty of 27 patients (74·1%) who achieved follicular development and received hCG became pregnant; 16 (59·3%) continued to clinical pregnancy. One patient was hospitalized for severe ovarian hyperstimulation syndrome. Lutropin alfa was well tolerated.

Conclusions Coadministration of lutropin alfa 75 IU and follitropin alfa is safe and effective in inducing follicular development and pregnancy in hypogonadotrophic hypogonadal women with profound gonadotrophin deficiency in a setting consistent with established medical practice.

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(Received 31 March 2006; returned for revision 5 May 2007; finally revised 7 February 2007; accepted 7 February 2007)

Introduction

Hypogonadotrophic hypogonadism (HH) is a rare endocrine deficiency, with an estimated prevalence of 1 in 50 000 women,[1] characterized by absent or attenuated hypothalamic–pituitary drive on gonadal function that can range from mild to severe in nature.[2] Deficiency of pituitary gonadotrophins in women results in anovulation, amenorrhoea and oestrogen deficiency. The origin of the disorder may rest in either the pituitary gland, disrupting secretion of LH and FSH, or more commonly in the hypothalamus, interrupting the release of GnRH.[2]

Replacement of both FSH and LH in women with HH[3–6] has been shown to be essential in achieving successful stimulation of follicular development, ovulation and fertility.[3–9] Clinical evidence confirms that full follicular development, ovulation, and endometrial growth sufficient for implantation and early pregnancy are unlikely to occur in the absence of LH.[3,4,7] HH patients with the most severe deficiency have been recognized as those patients who would most likely benefit from LH supplementation.[10,11] Shoham *et al.*[12] identified that women with a basal serum LH of less than 1·2 IU/l showed a clear differentiation in response to combination treatment with LH and FSH compared with FSH alone.

Clinical trials assessing lutropin alfa treatment have shown that, in women with the most profound degrees of gonadotrophin deficiency, follicular development is directly correlated with the dose of lutropin alfa administered.[9] In women with less profound deficiency, including some subjects with primary amenorrhoea, some patients respond to FSH alone. A serum LH level of 1·2 IU/l appears to identify the threshold for LH dependence, which is consistent with the threshold of 1·2 IU/l determined by Shoham *et al.*[12,13] When LH supplementation is required, 75 IU appears to be the optimal dose for coadministration with follitropin alfa, promoting optimal follicular development in the majority of patients.[9]

A prospective, randomized, placebo-controlled, double-blind, multicentre study was conducted to confirm whether LH is needed to support FSH-induced follicular development in women with profound gonadotrophin deficiency (study 21008, Serono Inc., Rockland, MA). The data from this trial confirmed the findings of the dose-finding study on the efficacy, safety and suitability of lutropin alfa coadministered with follitropin alfa for induction of follicular development in infertile women with profound LH and FSH deficiency.[9] Furthermore, these data were consistent with the literature reporting the effects of LH in this population of HH women.[4,5,7]

During the clinical investigations that evaluated lutropin alfa, approximately 170 women with gonadotrophin deficiency were enrolled, treated and studied, which provides a sizable body of clinical information in patients with this rare condition. These studies utilized a fixed dose of lutropin alfa and follitropin alfa in order to focus on the LH effect and to avoid a variable follitropin alfa dose as a potential confounding variable. Because these studies were based on a single cycle of treatment, and because fixed dosing of follitropin alfa was required, an open-label extension of the randomized study was undertaken in order to evaluate the outcome of usual FSH dose titration and individualization, and of multiple sequential cycles of treatment as would both occur in usual established clinical practice. This study provided a continuing opportunity to achieve pregnancy for women who had participated in the earlier single-cycle, randomized, double-blind, placebo-controlled study but who had not achieved pregnancy during that study. The extended study was designed to provide additional safety and efficacy information on lutropin alfa coadministered with flexible dosing of follitropin alfa for induction of follicular development in the more usual clinical context of dose individualization and sequential treatment cycles.

Materials and methods

Study design

The study was designed as an open-label, multicentre, international, noncomparative, extension of a randomized, double-blind, placebo-controlled study (study 21008) and was carried out in 23 medical centres in four countries, 18 in the USA, three in Australia, one in Canada, and one in Israel. The study consisted of three cycles of treatment, with patients receiving a fixed dose of lutropin alfa 75 IU and an individualized dose of follitropin alfa (75–150 IU to start with and up to 225 IU) based on each patient's previous response.

The primary end-point of the study was achievement of follicular development as defined by a composite end-point that included the following three criteria to reflect follicle growth, endocrine response and successful luteinization: (i) at least one follicle with a mean diameter ≥ 17 mm; (ii) preovulatory serum oestradiol (E_2) level ≥ 109 pg/ml (400 pmol/l) on the day of hCG; and (iii) midluteal phase progesterone (P_4) level ≥ 7·9 ng/ml (25 nmol/l).[14–23] Patients who did not receive hCG because of over-response or who became pregnant were considered to have achieved follicular development. Over-response was conservatively defined as an ultrasound scan showing more than three follicles with a diameter ≥ 15 mm indicating a risk of multiple ovulation and multiple pregnancy, and a serum E_2 concentration exceeding 1100 pg/ml indicating a threshold for risk of ovarian hyperstimulation syndrome (OHSS).[24]

Additional efficacy end-points included total and clinical pregnancy rates. The total pregnancy rate included all patients having a positive beta-hCG test (> 10 mIU/ml) on or after day 15 following hCG administration. Clinical pregnancy was defined by the presence of a foetal sac on pelvic endovaginal ultrasound performed approximately 35 days after hCG administration. Follicle size and number, serum E_2 level, endometrial growth, all on the day of hCG administration, and evidence of ovulation as indicated by serum progesterone in the luteal phase of the treatment cycle were also assessed.

Safety was assessed by monitoring adverse events and signs of OHSS, and by laboratory evaluations (haematology, clinical chemistry, and urinalysis). Laboratory evaluations were performed before the start of lutropin alfa/follitropin alfa treatment and 2–4 weeks after hCG injection (or within 2 weeks of the last dose of lutropin alfa/follitropin alfa if hCG was not administered).

Patient population

Patients who completed treatment in accordance with the previous randomized clinical protocol (study 21008), who had not achieved a clinical pregnancy and who did not have a serious drug-related adverse event, drug hypersensitivity reaction or serious OHSS complications of treatment were eligible for this study.

Study entry criteria specified that patients should be premenopausal women with HH, aged 18–39 years who desired pregnancy, with a profound endocrine secretory defect. Eligible patients met the following criteria during screening for the previous study from which these patients were drawn: screening serum values of FSH < 5·0 IU/l, LH < 1·2 IU/l, and E_2 < 60 pg/ml, and a baseline endovaginal pelvic ultrasound scan showing (i) no clinically significant uterine abnormality; (ii) no ovarian tumour or cyst; and (iii) ≤ 13 follicles with mean diameter ≤ 10 mm in the largest section through each ovary. Endocrine assays have been described previously. Eligible patients had a body mass index (BMI) between 18·4 and 31·4 kg/m^2. No patients had a previous history of severe OHSS, and all had a negative response to a progestin challenge test.

The study was approved by an appropriately constituted ethics committee at each study centre and all patients provided written informed consent before receiving study treatment.

Study procedures

Patients entered into this study within 6 weeks of the poststudy visit for study 21008. Following the consent procedure, each patient underwent a prestudy evaluation to ensure that she met the study's eligibility criteria. Patients began treatment within 2 weeks after all eligibility criteria had been satisfied.

Patients received a fixed dose of lutropin alfa 75 IU (Luveris®, Laboratoires Serono, Aubonne, Switzerland) and an individualized dose of follitropin alfa (Gonal-F®, Laboratories Serono, Aubonne, Switzerland) at the recommended starting dose of 75–150 IU. Both follitropin alfa and lutropin alfa were administered once daily as a 0·5-ml subcutaneous injection, and could be combined and coadministered as a single 0·5-ml injection. If a patient's response

was suboptimal based on follicular development and serum E_2 levels after 7 days of treatment, the dose of follitropin alfa was increased to up to a maximum of 225 IU, or decreased at any time as required. The total length of treatment with gonadotrophins was not to exceed 21 days unless serum E_2 levels and/or follicular growth, as demonstrated by ultrasound, indicated imminent follicular maturation.

When follicular response was adequate (i.e. at least one follicle ≥ 17 mm and no over-response to treatment), ovulation was triggered by a single intramuscular injection of 10 000 units (10 000 IU at non-US sites) of hCG (Profasi®, Serono International, S.A.). Intrauterine insemination was permitted.

Following completion of a treatment cycle, patients could undergo an additional cycle of treatment, up to a total of three cycles, provided they did not achieve pregnancy, and did not experience a medication-related serious adverse event, drug hypersensitivity reaction or serious OHSS. A negative pregnancy test was required before each cycle of treatment.

Statistical methods

As this was an open-label study with no comparison, descriptive statistics are only provided for all efficacy and safety end-points. Ninety-five per cent confidence intervals (CI) for the proportions of patients within each cycle based on the F-distribution method, and for the means based on normal distribution, were used.

Follicular development, the primary efficacy end-point, was analysed using the intent-to-treat (ITT) population, which included patients who received at least one injection of study treatment. For the primary analysis, patients who did not receive hCG because of over-response to treatment or who became pregnant were considered treatment successes (i.e. as achieving follicular development). A post hoc analysis of the primary efficacy end-point, using over-response leading to cycle cancellation as a failed response, was also conducted. Pregnancy rate was summarized using descriptive statistics for both the ITT population and for patients who received hCG population. Follicle size and number, serum E_2 level, and endometrial growth, all on the day of hCG, and midluteal phase serum P_4 were summarized using descriptive statistics for the patients who received hCG.

Additional analyses of the primary efficacy end-point and pregnancy rate of patients entering this extension study (study 21415) from the placebo arm of the previous placebo-controlled study (study 21008) were performed. McNemar's test was used to assess the impact of first lutropin alfa exposure on this subgroup of patients, referred to as LH-naive patients.

Results

Disposition of patients

Thirty-one of the 39 patients from a previous randomized, placebo-controlled study (study 21008) were enrolled in this study. Of these 31 patients, 11 had been in the placebo/150 IU follitropin alfa treatment group and 20 had been in the 75 IU lutropin alfa/150 IU follitropin alfa treatment group in study 21008. All 31 patients received at least one dose of lutropin alfa and follitropin alfa during cycle 1 of the current study and formed the basis of the ITT population; 15 patients received at least one dose during cycle 2, and eight patients received at least one dose during cycle 3. During the course of the treatment cycles, seven patients withdrew for various reasons. Of the 24 patients (77·4%) who completed the study, 16 patients achieved clinical pregnancy and eight patients completed three treatment cycles without achieving clinical pregnancy.

Patient demographics

The median patient age was 30 years, with a range of 21–40 years. The median BMI was 23·8 kg/m^2 and ranged from 18·4 to 35·9 kg/m^2. The majority (80·6%) of the patients were Caucasian, 12·9% were Hispanic, 3·2% were African American and 3·2% were reported as 'other'.

Of the 31 patients, 16 (51·6%) reported primary amenorrhoea and 15 (48·4%) reported secondary amenorrhoea. The median age of menarche for the 15 patients with secondary amenorrhoea was 13 years (range 11–18 years). Overall, 80·6% of patients reported primary infertility and 19·4% reported secondary infertility. The median duration of infertility was 24 months (range 4–180 months). Most patients (90·3%) reported no family history of HH.

The median serum LH at screening of the 31 patients was 0·3 IU/l (range 0·2–1·1 IU/l). The median screening serum FSH was 1·1 IU/l (range 0·5–3·7 IU/l), and median serum E_2 was 10·0 pg/ml (range 10·0–28·0 pg/ml).

Follicular development

Twenty-one of the 31 patients (67·7%) achieved follicular development in cycle 1 (Table 1). When over-response leading to cycle cancellation was considered a treatment failure, 16 of these 31 patients (51·6%) achieved follicular development in cycle 1. In the following cycles 2 and 3, there were no cycles cancelled due to over-response. Therefore, the overall cumulative rate of follicular development (87·1%) was the same in both analyses, whether over-response is counted as a positive outcome or as a negative one.

Pregnancy rates and outcomes

The cumulative pregnancy rates are summarized in Table 1. Twenty of the 27 patients (74·1%) who achieved follicular development and received hCG became pregnant within three cycles of treatment, and 16 (59·3%) continued to clinical pregnancy. The pregnancy rate per patient for all patients who received at least one dose of treatment (ITT population, $n = 31$) was 64·5% and 51·6% for the clinical pregnancy rate. The cycle pregnancy rate for the ITT population was 37·0% (20 pregnancies/54 cycles) and 29·6% (16 clinical pregnancies/54 cycles) for the clinical pregnancy rate.

Of the 16 clinical pregnancies, 14 (87·5%) resulted in live births (Table 2). One of these 14 patients miscarried one foetus as well as having a live birth and two elected to have a selective reduction performed. Data were not available for two patients who were lost to follow-up. Eight (57·1%) of the 14 patients gave birth to singletons, five (35·7%) to twins, and one (7·1%) to triplets.

Across all infants for whom birth weight information was available, the median birth weight was 2500 g, ranging from 909 to 3700 g and

Table 1. Cumulative follicular development rates and pregnancy rates in patients treated with concomitant follitropin alfa and 75 IU lutropin alfa

	Cycle 1	Cycle 2	Cycle 3
Cumulative follicular development rate	21/31 (67·7%)	26/31 (83·9%)	27/31 (87·1%)
95% CI	51·3%–84·2%	70·9%–96·8%	75·3%–98·9%
Cumulative follicular development rate, patients who received hCG	16/23 (69·6%)	24/27 (88·9%)	25/27 (92·6%)
95% CI	50·8%–88·4%	77·0%–100%	82·7%–100%
Cumulative pregnancy rate	11/31 (35·5%)	20/31 (64·5%)	20/31 (64·5%)
95% CI	18·6%–52·3%	47·7%–81·4%	47·7%–81·4%
Cumulative pregnancy rate, patients who received hCG	11/23 (47·8%)	20/27 (74·1%)	20/27 (74·1%)
95% CI	27·4%–68·2%	57·5%–90·6%	57·5%–90·6%
Cumulative clinical pregnancy rate	11/31 (35·5%)	16/31 (51·6%)	16/31 (51·6%)
95% CI	18·6%–52·3%	34·0%–69·2%	34·0%–69·2%
Cumulative clinical pregnancy rate, patients who received hCG	11/23 (47·8%)	16/27 (59·3%)	16/27 (59·3%)
95% CI	27·4%–68·2%	40·7%–77·8%	40·7%–77·8%

Table 2. Pregnancy outcomes in patients treated with concomitant follitropin alfa and 75 IU lutropin alfa

Outcome	No. of patients
Patients seeking pregnancy	31
Cycles of treatment in patients seeking pregnancy	54
Clinical pregnancies	16
Live births	14
Singleton	8*
Twins	5
Triplets	1
Ectopic pregnancy	0
Miscarriage	1*
Lost to follow-up	2
Other	2†

*One patient had both a miscarriage and a live birth.
†Two patients had a selective reduction. One patient had three foetal sacs reduced to one, and another patient had four foetal sacs reduced to two.

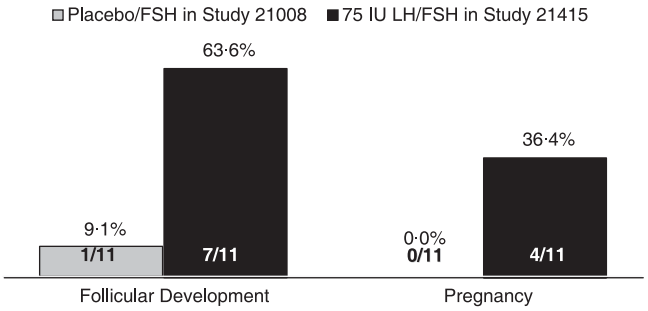

Fig. 1 Follicular development and pregnancy in 11 LH-naive patients.

the mean was (2286·3 g, 95% CI 1839·2–2733·4 g). The median birth weight for singletons ($n = 8$) was 3062 g (range 2813–3700 g; mean 3206·3 g; 95% CI 2942·1–3470·4 g), for twins ($n = 8$) was 1483·5 g (range 909–2750 g; mean 1688·6 g; 95% CI 1149·0–2228·2 g), and for triplets ($n = 3$) was 1469 g (range 1290–1522 g; mean 1427 g; 95% CI was not applicable owing to insufficient data). Infant birth weights were not reported for three patients, one for whom one foetal sac was visualized, and two for whom two foetal sacs were visualized. No congenital abnormalities or neonatal deaths were reported.

LH-naive patients

The 31 patients entering this extension study had been treated in a previous, double-blind, randomized trial with either 75 IU lutropin alfa and follitropin alfa ($n = 20$), or placebo and follitropin alfa ($n = 11$). The 11 LH-naive patients provide additional data on first exposure to lutropin alfa in cycle 1 of the extension study. Seven of these 11 patients (63·6%) achieved follicular development when treated with 75 IU lutropin alfa in cycle 1 (Fig. 1), while only one patient (9·1%) achieved follicular development during placebo treatment in study 21008 ($P = 0·07$; McNemar's test). Four of the seven patients (57·1%) who achieved follicular development also achieved clinical pregnancy in this cycle.

Follicle size and number, serum E_2 levels, endometrial growth and midluteal phase serum P_4

The findings for the secondary end-points of follicle size and number, serum E_2 levels, endometrial growth, and midluteal serum P_4 levels are shown in Table 3 by treatment cycle. The median number of follicles ≥ 17 mm on the day of hCG administration (DhCG) was 2 (range 1–5 follicles) for the 44 treatment cycles where patients received hCG and had an ultrasound performed. All patients had an endometrial thickness ≥ 6·0 mm for the 44 treatment cycles. Furthermore, median serum E_2 over 39 cycles was 448 pg/ml (range 39·0–2386 pg/ml) on DhCG and median midluteal serum P_4 over 38 cycles was 63·8 ng/ml (range 1·1–359·6 ng/ml) at 6–7 days post hCG administration.

Safety

Safety analyses included data from all 31 patients treated in cycle 1, 15 patients in cycle 2, and eight patients in cycle 3. Across all treatment cycles, the median exposure to lutropin alfa was 1125·0 IU per

Table 3. Number of follicles, serum E_2 levels and endometrial thickness in patients treated with concomitant follitropin alfa and 75 IU lutropin alfa

Variable		Cycle 1	Cycle 2	Cycle 3
Serum E2 levels on DhCG (pg/ml)	No. of patients	20	13	6
	Mean (95% CI)	563·2 (399·3–727·1)	717·1 (295·0–1139·2)	296·2 (NA)
	Median (range)	491 (39·0–1471)	432 (70·0–2386)	335·5 (118·0–492·0)
No. of follicles ≥ 17 mm on DhCG	No. of patients	22	14	8
	Mean (95% CI)	2·3 (1·8–2·8)	1·6 (1·0–2·1)	1·6 (1·0–2·2)
	Median (range)	2·0 (1·0–5·0)	1·0 (1·0–4·0)	1·5 (1·0–3·0)
No. of follicles > 10 mm on DhCG or last assessment	No. of patients	30	14	8
	Mean (95% CI)	8·4 (6·6–10·2)	6·2 (4·1–8·3)	6·9 (3·1–10·6)
	Median (range)	9·0 (0–18·0)	6·0 (1·0–12·0)	6·5 (1·0–13·0)
Endometrial thickness on DhCG (mm)	No. of patients	22	14	8
	Mean (95% CI)	9·6 (9·0–10·2)	9·3 (8·3–10·3)	9·7 (8·8–10·7)
	Median (range)	9·4 (7·0–12·0)	9 (6·0–13·2)	10 (8·0–11·0)
Midluteal phase serum P4 (ng/ml)*	No. of patients	19	12	7
	Mean (95% CI)	94·0 (55·0–133·1)	45·0 (24·2–65·8)	28·6 (NA)
	Median (range)	90·9 (1·1–359·6)	45·6 (4·0–86·8)	27·0 (6·3–56·3)

*Midluteal phase serum P4 levels were assessed at 6–7 days post-hCG administration. DhCG, day of hcG administration. NA, not applicable because of insufficient data.

cycle (range 675·0–3450·0 IU) and 1800·0 IU per patient (range 675·0–9525·0 IU). The median exposure to follitropin alfa was 2212·5 IU per cycle (range 1165·5–7125·0 IU) and 3900·0 IU per patient (range 1500·0–13 050·0 IU). For both lutropin alfa and follitropin alfa treatments, the median treatment duration across all treatment cycles was 15 days, ranging from 9 to 28 days.

A total of 65 adverse events were recorded in 15 (48·4%) patients. The most frequently reported adverse events (occurring in two or more patients) were flatulence, constipation, abdominal pain, nausea, breast pain, and headache. All other reported adverse events occurred in one patient each. The majority of adverse events were judged by the investigator to be mild or moderate in severity. Three (4·6%) events in two (6·5%) patients were judged to be severe: abdominal pain and injection-site inflammation in one patient; and severe OHSS in the second patient, which was also considered as a serious adverse event. The patient with severe OHSS was subsequently noted to be pregnant. The OHSS resolved and the pregnancy resulted in a live birth. No patients withdrew prematurely from the study as a result of an adverse event.

There were no clinically significant abnormalities for any of the blood chemistry, haematology, or urinalysis parameters assessed. There were also no clinically significant changes in vital signs during the study.

Discussion

The data from this open-label extension study demonstrate the cumulative clinical benefit of lutropin alfa for stimulation of follicular development in women with profound gonadotrophin deficiency, the majority of whom have primary amenorrhoea. Continued treatment with lutropin alfa 75 IU and an individualized dose of follitropin alfa resulted in an increasing cumulative rate of follicular development with an associated decrease in over-response when compared with a fixed-dose regimen. Over-response leading to cycle cancellation itself had no impact on the patient's ability to continue treatment and conceive in subsequent cycles. Among patients achieving follicular development, there was a high probability of achieving pregnancy (74·1%) within three cycles of treatment. Thus, when lutropin alfa 75 IU is administered with follitropin alfa in the usual clinical setting, as represented by this open-label extension study, a high patient response rate, a low cycle cancellation rate, and a satisfactory pregnancy rate are observed in this difficult-to-treat population.

In this study, the patient response rate to combined lutropin alfa and follitropin alfa during cycle 1 was similar to that of two previous lutropin alfa clinical studies.[9] Further confirmation of this patient response rate was observed when the data were analysed for the 11 LH-naive patients in this study (i.e. placebo patients from the previous randomized study who were enrolled in this extension study). One of 11 patients (9·1%) had achieved follicular development when treated with placebo in the previous randomized trial. However, seven of the 11 LH-naive patients (63·6%) achieved follicular development when treated with 75 IU lutropin alfa in cycle 1 of the extension study, and four achieved clinical pregnancy in that first exposure cycle. Although this result for follicular development fails to reach statistical significance ($P = 0·07$), this is largely a consequence of the small patient numbers and the effect is still clinically meaningful. Thus, across studies, patients treated with 75 IU lutropin alfa showed a remarkable consistency of response, ranging from 63·6 to 67·7%. Overall, these studies showed a four- to sevenfold difference in follicular development rates between treatment with follitropin alfa alone and treatment with 75 IU lutropin alfa coadministered with follitropin alfa. The data from the LH-naive patients also demonstrate the clinical benefit of combined therapy when compared with individual patients' experiences when treated with FSH alone and are consistent with the literature reporting the requirement for LH support of FSH in this population for this indication.[4,5,7,9]

As expected, the cumulative patient response rate over three treatment cycles was higher than that of the two previous lutropin alfa clinical studies conducted in this population with a fixed-dose regimen, which were designed for only one 75 IU lutropin alfa treatment cycle and no adjustment of follitropin alfa dose (study 21008).[9] The median dose of follitropin alfa per patient was higher in this study than in the previous randomized, placebo-controlled study (study 21008). However, no cycles were cancelled as a result of over-response in cycles 2 and 3 of this extension study. Thus, when adjustment of follitropin alfa dose accommodated for individual patient response, the potential for over-response leading to cycle cancellation was reduced. Among the 11 patients whose cycles were cancelled because of over-response in either the randomized, double-blind phase of treatment or this extension study, four progressed to pregnancy in a subsequent cycle. Furthermore, following three cycles of treatment, the results and conclusions from this extension study are unchanged, whether follicular development is analysed with over-response as an efficacy success or as an efficacy failure, demonstrating the robustness of the data.

The achievement of follicular development was associated with a high probability of achieving clinical pregnancy, as evidenced by a clinical pregnancy rate of 59·3% for patients who achieved follicular development and received hCG. The cycle clinical pregnancy rate of 29·6% demonstrated in this study offers a reasonable expectation of success for this population.[25] Overall, 45% of patients had at least one live birth, which is a reasonable outcome when compared with the literature.[26] The number of multiple births observed (43%) was similar to reports available for the HH population.[16,27,28] However, another study investigating the use of LH supplementation in women with HH reported a rate of only 26%, which is close to the rate of 25% typically seen for ovarian stimulation cycles in assisted reproductive techniques. This may be because of the high amounts of exogenous FSH and LH required by the profoundly LH-deficient women participating in our study. No congenital abnormalities or neonatal deaths were reported. The observed pregnancy outcome rates were consistent with the literature reports in this population[16,27] and in previous studies evaluating LH supplementation in patients with HH.

Women with profound LH deficiency lack the ability to produce adequate E_2 to ensure a mature follicle competent for ovulation and to support pregnancy. This study demonstrated an approximate 40-fold increase in median serum E_2 levels across all treatment cycles when compared with screening levels, which is similar to the increase observed in the previous randomized, placebo-controlled study. A twofold increase in median midluteal serum P_4 was observed in this study as compared with the previous study. Endometrial thickness for individual patients on the day of hCG administration ranged from 6 to 13·2 mm, demonstrating that the thickness of the endometrium was above the minimal threshold for implantation and pregnancy following concomitant treatment with lutropin alfa and follitropin alfa.[29,30]

The main limitations of this study were that it was nonblinded and there was no control group for comparison. However, unlike previous studies in patients with HH, it provides valuable insight into the use of LH as part of a more flexible dosing regimen, reflecting more closely the likely situation in routine clinical practice. Further studies are required to confirm our observations, and these would ideally combine individualized dosing regimens with a blinded, randomized, placebo-controlled study design.

In summary, this study provides further evidence that coadministration of lutropin alfa 75 IU and follitropin alfa is safe and effective in inducing follicular development in HH women with profound gonadotrophin deficiency. In addition, in contrast to the more rigid constraints of a blinded, placebo-controlled trial, an individualized, flexible-dosing regimen consistent with established medical practice minimizes cycle wastage for failed stimulation or over-response and achieves a very satisfactory pregnancy rate.

Acknowledgments

The following individuals were clinical investigators in the Study 21415 Investigator Group: Australia: Mark Bowman, MD, Sydney; Graeme Hughes, MD, Randwick; Howard Smith, MD, Westmead; Canada: Femi A. Olatunbosun, MD, Saskatoon; Israel: Zeev Shoham, MD, Tel Aviv; USA: Samuel J. Chantilis, MD, Dallas, TX; Christos Coutifaris, MD, Philadelphia, PA; Heber Dunaway, MD, Metairie, LA; Randall C. Dunn, MD, Houston, TX; Carlene Elsner, MD, Atlanta, GA; Seth L. Feigenbaum, MD, MPH, San Francisco, CA; Inderbir Gill, MD, Saginaw, MI; Jacqueline Gutmann, MD, Philadelphia, PA; Gill Haas, MD, Oklahoma City, OK; Magdalen E. Hull, MD, Mineola, NY; Paul Kaplan, MD, Eugene, OR; Robert A. Kaufmann, MD, Mt. Pleasant, SC; Drew Moffitt, MD, Phoenix, AZ; Gregory Neal, MD, San Antonio, TX; Carlos Soto-Albors, MD, Roseville, CA; Laurel Stadtmauer, MD, PhD, Cary, NC; Thomas Vaughn, MD, Austin, TX; Timothy Yeko, MD, Tampa, FL.

This study was financially supported by Serono Inc., Rockland, MA, USA.

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