SHORT COMMUNICATION

LUEBECK, GERMANY

FSH Time-Concentration Profiles Before and After Administration of 0.25 mg Cetrorelix in the GnRH-Antagonist Multiple-Dose Protocol for Ovarian Hyperstimulation

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Submitted March 30, 2004; accepted May 4, 2004

Purpose: To determine FSH concentration behavior before and after cetrorelix 0.25 mg administration in the GnRH-antagonist multiple-dose protocol on day 6 of ovarian stimulation with 150–300 IU daily recombinant FSH.

Methods: Blood samples for FSH measurements were drawn from seven women every 15 min from 8 h prior to the first cetrorelix administration in the GnRH-antagonist multiple-dose protocol until 15–32 h thereafter.

Results: No significant change of FSH concentration was observed.

Conclusions: This observation indicates that no rationale exists of increasing the daily FSH dosage concomitantly to the GnRH-antagonist administration to compensate for a drop of endogenous FSH.

KEY WORDS: Cetrorelix; GnRH-antagonist; GnRH-antagonist multiple-dose protocol; recombinant FSH.

INTRODUCTION

GnRH-antagonists, such as cetrorelix and ganirelix, immediately and rapidly inhibit gonadotropin release by the anterior pituitary gland by competitive blockage of the GnRH receptor, preventing and interrupt-

ing LH surges in controlled ovarian hyperstimulation [COH] for infertility treatment.

Besides an immediate drop in serum LH, a concomitant drop in endogenous serum FSH occurs after antagonist administration (1). It was speculated that this drop, although comparatively lesser in extent, might impair follicular development and lead some developing follicles to atresia during COH, and might be partially responsible for the lower numbers of cumulus-oocyte-complexes retrieved in antagonist as compared to agonist cycles in phase III clinical licensing studies (2).

Consequently, it was suggested to compensate for such a drop in endogenous FSH by increasing the daily FSH dosage to improve the stimulation outcome in terms of follicular growth dynamics and number of retrieved oocytes (3).

The purpose of the current clinical trial was to study FSH time-concentration profiles in women undergoing ovarian hyperstimulation with recombinant FSH [recFSH] to assess if any significant changes of FSH concentration occur subsequently to the first administration of 0.25 mg cetrorelix.

MATERIALS AND METHODS

Seven normoovulatory, normogonadotropic women undergoing IVF or ICSI treatment for tubal or male factor infertility were included in the study. Inclusion criteria were age < 39a, regular menstrual cycle, natural luteal phase before treatment, no polycystic ovaries, and two ovaries. Ovarian stimulation started on day 2 of the natural cycle with daily 150–300 IU recFSH [Gonal F®] at 8.00 A.M. The FSH dosage was chosen depending on the body weight of the patient and previous response to ovarian stimulation and was fixed for the first 6 days. After this period, the recFSH could be adjusted. Cetrorelix [Cetrotide®] 0.25 mg was given daily at 8.00 A.M. from day 6 of the stimulation onward until the day of hCG administration.

Blood samples were retrieved every 15 min using an automatic blood pump system [Conflo®, Carmeda, Sweden] from 8 h prior to the first antagonist administration on stimulation day 6 until 15–32 h thereafter. Serum FSH levels were assayed with the electrochemiluminescence immunoassay “ECLIA” [Roche Diagnostics, Inc., Germany] on the Roche Elecsys 2010 automated immunoassay analyser. Intra-assay and inter-assay coefficients of variation were <2% and <6%, respectively.

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Fig. 1. Mean value from four FSH measurements taken within 60 min represent one icon. The seven icons represents the seven study patients (* = four missing values).

Statistical Analysis

Data were explored by one-way repeated measures ANOVA using NCSS 2001 [Number Cruncher Statistical Systems, Kaysville, Utah] software and are presented as mean $\pm$ standard deviation.

RESULTS

The age of the women was 30 [± 3] years, the BMI 27.04 [± 7.3]. All women had blood samples retrieved starting at 8 h prior to the first cetrorelix administration. In three women, blood sampling was continued after cetrorelix injection for another 24 h.

The other four women had samples drawn for another 7, 9, 9, and 13 h, respectively. Mean values of the FSH concentration from four serum samples per hour taken at 15 min intervals are depicted in Fig. 1 for the seven women. The serum time-concentration profile from an individual patient is depicted in Fig. 2. No significant change of FSH concentration was observed after cetrorelix 0.25 mg administration. None of the patients showed a drop of FSH.

DISCUSSION

In contrast to the “long” GnRH-agonist protocol, ovarian stimulation in the GnRH-antagonist protocol

Fig. 2. Plot of FSH levels measured every 15 min for 32 h in an individual patient.

starts at a time (usually cycle day 2 or 3) when follicular recruitment by a late luteal endogenous rise of FSH has started. The summation of exogenous and endogenous FSH in early follicular phase is reflected in a shorter duration of stimulation and reduced gonadotropin consumption for COH in the GnRH-antagonist protocol as compared to the "long" luteal agonist protocol (2).

In the natural cycle, the majority of feedback regulation of gonadotropin secretion is mediated by the actions of gonadal steroids at the hypothalamic and pituitary level. Both estradiol and inhibin are long-known potent suppressors of FSH secretion, leading to a progressive decline of FSH secretion during the mid to late follicular phase. In contrast, corresponding circulating LH levels exhibit a progressive increasing trend, ultimately leading to ovulation (4).

In the nonstimulated natural cycle, a single dosing of 0.25 mg cetrorelix leads a decrease of serum FSH by 23% within 6 hours (1). In two previous phase II studies on the GnRH-antagonists cetrorelix and ganirelix, no decrease of serum FSH after antagonist administration under HMG and recFSH stimulation was observed; in contrast to the present work, however, measurement of FSH was performed only twice a day (5,6). At a higher single-dose of cetrorelix, a slight decrease in FSH has been noted (7), yet, this finding was not affirmed in a lower single-dose COH protocol (8).

Our finding supports the notion that on stimulation day six in COH the vast majority of circulating FSH derives from exogenous administration and that the inhibition of endogenous FSH secretion by a dosage of 0.25 mg cetrorelix is negligible or nonexistent, taking into account the supraphysiological estradiol levels usually achieved by COH. In the current study, estradiol levels were 632 [± 422.8] at the time of first antagonist administration; however, other negative feedback mechanisms than estradiol-mediated mechanisms operant through inhibin or follistatin might play a role.

The question arises, whether the present data from only seven women can be generalized. The antagonistic action of cetrorelix at the GnRH receptor is dependent on the equilibrium between endogenous GnRH and applied antagonist. Modification of the dosage of GnRH-antagonists administered to the patient modifies this equilibrium and therefore, the antagonistic effect of the drug is dose-dependent (9). Thus, it was speculated that a dosing of 0.25 mg antagonist might lead to an oversuppression of the pituitary in very lean patients. This may be of importance, since the patients in the current work are on average adipose.

However, a recent retrospective work found no association between body weight and clinical outcome of antagonist cycles (10). Still, it cannot be ruled out, that in cycles with low ovarian response in terms of low estradiol levels, a subtle drop of FSH might occur with the onset of the antagonist administration which might impair follicular development in a certain subset of patients.

Following repeated administration, recombinant FSH accumulates threefold in the circulation achieving a steady state within 3–4 days. In the present trial, serum FSH levels ranged from 6 to 14.2 mIU/mL on stimulation day 6, leading to 14.5 [± 4.3] cumulus-oocyte-complexes retrieved by transvaginal puncture after 12.4 [± 1.6] days of stimulation. If increasing the gonadotropin dose with the onset of the antagonist yields more favorable clinical results in terms of better reproductive outcome should best be tested by a randomized controlled trial comparing the two treatment modalities, with and without dosage increment. The current work does, however, not favor a dose increment with the rationale of compensating for a deficit of endogenous FSH.

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