Intercycle variability of the ovarian response in patients undergoing repeated stimulation with corifollitropin alfa in a gonadotropin-releasing hormone antagonist protocol

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Objective: To determine whether individual subject variation in ovarian response between repeated cycles with the same ovarian stimulation protocol can be predicted.
Design: Retrospective data analysis.
Setting: Multicenter, open-label, uncontrolled clinical trial.
Patient(s): Women aged 18–39 from a phase 3, open-label, uncontrolled trial with complete data across all cycles (n = 176).
Intervention(s): Up to three cycles of a single injection of 150 μg corifollitropin alfa for 7 days, then daily recombinant FSH/hMG until three follicles reached ≥17 mm. Gonadotropin-releasing hormone antagonist from stimulation day 5 until day of hCG administration.
Main Outcome Measure(s): Numbers of follicles ≥11 mm on day of hCG in cycles 1–3, transition in ovarian response type between cycles from low (0–<6), normal (6–<18), and high (≥18), and serum FSH concentrations and antral follicle count (AFC) at each cycle start.
Result(s): The mean (SD) numbers of follicles ≥11 mm on day of hCG were 13.4 (6.2), 13.3 (5.4), and 13.8 (6.4) in cycles 1, 2 and 3, respectively. Between cycles 1 and 2, 11.9% switched from normal to low or high response, and 12.5% switched from low or high to normal response; 75.6% remained in the same category. Between cycles 2 and 3, 15.9% switched from normal to low or high response, and 10.2% switched from low or high to normal response; 73.9% remained in the same category. These shifts are symmetrical in nature, in that the percentage of subjects who shift from normal to low or high response is comparable to the percentage of subjects who shift from low or high to normal response. Baseline FSH and AFC did not significantly predict transition in ovarian response.

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Conclusion(s): The variability in ovarian responses between repeated cycles using the same protocol was not explained by baseline FSH and AFC.
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Key Words: Corifollitropin alfa, GnRH antagonist, repeated ovarian stimulation, ovarian response, controlled ovarian stimulation

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A large number of studies have attempted to predict ovarian response to ovarian stimulation for IVF, and by altering the stimulation regimen, to ultimately impact on ovarian response and IVF treatment outcome (1–6). To put such studies in perspective, it is mandatory to know the naturally occurring variability in ovarian response between subsequent treatment cycles within one subject. For such assessment, repetitive cycles should be performed, ideally within a short time frame, and stimulation (e.g., FSH dose, GnRH analogue protocol, and decisions on patient management) should be kept constant.

In the Trust trial, a large population of women received ovarian stimulation uniformly with 150 μg corifollitropin alfa (a long-acting recombinant FSH [rFSH]) in a GnRH antagonist protocol for up to three cycles (7). Serum FSH concentrations and antral follicle count (AFC) on day 1 of ovarian stimulation have been identified as predictors of low or high ovarian response in GnRH antagonist cycles (8).

The objectives of the present analysis were to determine the variation between treatment cycles in terms of numbers of growing follicles, to calculate the relative frequency of a switch between cycles from a normal ovarian response to a high or low ovarian response and vice versa, and to investigate whether the changes in ovarian response per cycle can be explained by changes in such predictors as, for example, AFC and serum hormones at the start of each cycle of stimulation.

MATERIALS AND METHODS

Study Design and Population

Trust was a multicenter, open-label, uncontrolled clinical trial, the details of which have been reported previously (7). The study was conducted in accordance with principles of good clinical practice and was approved by the appropriate institutional review boards and regulatory agencies. Written, informed consent was provided by all subjects. Women aged 18–39 years with a body weight of >60 kg and a regular menstrual cycle underwent up to three ovarian stimulation cycles. No women were taking birth control pills before beginning stimulation. Patients who conceived in a cycle were not allowed another cycle. Demographic and fertility characteristics of patients in the Trust trial have been reported previously (7, 9).

In each cycle, subjects received a single injection of 150 μg corifollitropin alfa (Elonva, Merck & Co., Inc.) for the first 7 days of stimulation, followed by a daily dose of ≤225 IU FSH (either rFSH or hMG) starting on day 8 until the criterion for oocyte maturation with hCG was reached (three follicles ≥17 mm). A GnRH antagonist (0.25 mg ganirelix or cetrorelix acetate) was administered once daily, starting on stimulation day 5 up to and including the day of hCG administration. Either urinary hCG (10,000 IU or 5,000 IU in case of a high ovarian response) or recombinant hCG (250 μg) was administered for final oocyte maturation.

In case of too high of an ovarian response, the dose of FSH could be reduced, or withheld for a maximum of 3 days up to and including the day of hCG administration. For normal responders, the recommended daily dose of FSH was 150 IU. If the ovarian response was too high in the opinion of the investigator, the cycle could be canceled at any time. If there was a risk of ovarian hyperstimulation syndrome (>30 follicles ≥11 mm on transvaginal ultrasound), hCG was withheld and the treatment cycle was canceled. The maximum total duration of stimulation was 19 days. The mean number of days (95% confidence interval [CI]) between cycles were 144.3 (131.1–157.5) and 171.3 (155.4–187.2), for cycle 1 to cycle 2 and cycle 2 to cycle 3, respectively.

Statistical Analysis

Women who received hCG and who had non-missing values across all three cycles for the number of follicles ≥11 mm on the day of hCG were included in the analysis (n = 176).

The numbers of follicles ≥11 mm on the day of hCG for each cycle were extracted from a longitudinal data analysis on patients repeated across cycles and correcting for region. Given that each patient was measured across three cycles, an unstructured variance–covariance matrix was specified to allow for a separate estimate of variability between and within cycles, accounting for the between-cycle correlation from repeated measurements across patients. Additionally, patients were assigned into subgroups if they received the same dose of rFSH stimulation between two consecutive cycles (cycles 1 and 2; and cycles 2 and 3). No correction for multiplicity was made in this exploratory analysis.

The number of follicles ≥11 mm on the day of hCG and the number of oocytes retrieved were also categorized as low responders (0–<6), normal responders (6–<18), and high responders (≥18) (8) and summarized (frequencies and percentages) by cycle. Switches from one category to another from cycle 1 to cycle 2 and between cycle 2 and cycle 3 were also summarized. The significance of the directionality of switches was evaluated using Bowker's Test of Symmetry (i.e., test the null hypothesis that $n_{ij} = n_{ji}$, where the number of patients are