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.
Clinical Trial Registration Number: NCT00696878 Protocol P05714. (Fertil Steril® 2015;104: 884–90. ©2015 by American Society for Reproductive Medicine.)
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

TABLE 1

Demographic and stimulation characteristics: three cycle completers.

Baseline	Cycle 1 (n = 176)	Cycle 2 (n = 176)	Cycle 3 (n = 176)
Age (y)	33.3 (3.5)		
Body mass index (kg/m^2)	24.3 (2.3)		
Race			
Asian	2.3		
Black	0.6		
Caucasian	96.0		
Other	1.1		
Primary infertility	55.7		
Duration of infertility (y)	3.6 (2.7)		
Cause of infertility[a]			
Male factor	58.0		
Tubal factor	28.4		
Endometriosis	13.6		
Cervical mucus problems	0.6		
Unexplained infertility	15.9		
Other	1.7		
Start cycle			
Duration of stimulation (d)	10.2 (1.3)	10.3 (1.7)	10.4 (1.8)
Total dose of FSH from day 8 onward (IU)	455.3 (277.5)	478.7 (316.6)	504.8 (362.8)
AFC[b]	10.8 (4.4)	11.0 (4.7)	11.1 (4.7)
Serum E_2 concentration (pmol/L)[c]	125.1 (83.0)	117.8 (41.1)	117.1 (40.8)
Serum FSH concentration (IU/L)[c]	7.2 (1.9)	7.0 (2.0)	7.5 (5.4)
Serum LH concentration (IU/L)[c]	5.0 (1.8)	5.0 (1.6)	5.0 (1.9)
Day of hCG			
Serum E_2 concentration (pmol/L)[d]	5,442.4 (3,354.7)	5,210.2 (2,822.7)	5,743.1 (3,754.9)
Serum FSH concentration (IU/L)[d]	13.7 (3.2)	13.6 (3.7)	13.6 (3.5)
Serum LH concentration (IU/L)[d]	1.6 (1.8)	1.6 (1.4)	1.8 (2.7)

Note: Data are presented as mean (SD) or percentage.
[a] A patient could have multiple causes of infertility.
[b] Ten, eight, and four missing values in cycles 1, 2, and 3, respectively.
[c] Five, ten, and eight missing values.
[d] Two, five, and five missing values.

Rombauts. Ovarian response intercycle variability. Fertil Steril 2015.

compared in cell numbers 12 vs. 21, 13 vs. 31, and 23 vs. 32 in a 3 × 3 table). In other words, if the shifts are of random nature and do not reflect a change in direction of the overall response category but rather a similar number of subjects shifting in either direction, *P* values will be reported as >.05. Bowker's test reduces to the more familiar McNemar's test for 2 × 2 tables.

Correlations with age, AFC, FSH, LH, and E_2 on stimulation day 1, as well as duration of stimulation and total dose of rFSH, were calculated by cycle, and a multiple regression coefficient was obtained from a linear regression model. A similar analysis was performed for changes in ovarian response (between cycles 1 and 2, between cycles 2 and 3, and between cycles 1 and 3, respectively) and changes in predictors of ovarian response.

RESULTS

Baseline Demographics and Stimulation Parameters

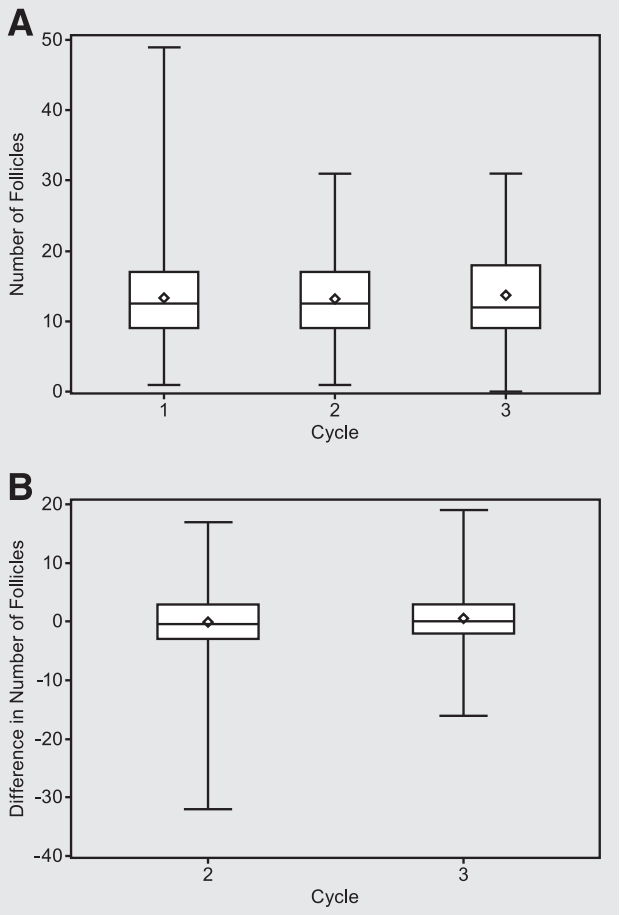
In total, 176 patients were treated and included in the analysis from 25 centers in Australia (25 patients in 4 centers), Europe (71 patients in 12 centers), and South America (80 patients in 9 centers). The median number of patients analyzed in each center was six patients in Australia, five in Europe, and nine in South America.

Total exposure to rFSH ranged from 0 to 2,250 IU across the 176 women completing the three cycles, with only 13 women reporting the same total dose across all three cycles. The number of women who received the same dose of rFSH stimulation in two consecutive cycles includes 44 (25.0%) from cycle 1 to cycle 2, and 37 (21.0%) from cycle 2 to cycle 3. Demographic and stimulation characteristics are given in Table 1.

Ovarian Response as Measured by the Number of Follicles ≥11 mm on the Day of hCG

Box plots of the number of follicles in cycles 1, 2, and 3 and the change in follicle number from cycle 1 to 2 and from cycle 2 to 3 are shown in Figure 1. The mean (SD) number of follicles ≥ 11 mm on the day of hCG was 13.4 (6.2), 13.3 (5.4), and 13.8 (6.4) in cycles 1, 2, and 3, respectively (Table 2). Patients receiving the same dose of rFSH stimulation in cycles 1 and 2 report slightly higher means of 14.4 (5.7) and 14.8 (5.1), respectively, but this trend was not replicated in cycles 2 and 3, in which means of 13.3 (5.6) and 12.8 (5.8) were equal to or less than the number of follicles reported across all subjects in the analysis. Therefore, on the basis of comparing the means and SD between the same-dose rFSH subgroups and the overall analysis population, there does not seem to be a significant difference in response attributable to maintaining the same dose of rFSH.

FIGURE 1



Box plots of (**A**) the number of and (**B**) the difference "delta" vs. the previous cycle in the number of follicles (≥11 mm) on the day of hCG per cycle. Displayed are maximum (endpoint of upper whisker), third quartile (upper edge of box), median (line inside box), mean (◇), first quartile (lower edge of box), and minimum (endpoint of lower whisker).

Rombauts. Ovarian response intercycle variability. Fertil Steril 2015.

Comparing the ovarian response between the first and second cycles in all women in the analysis, the number of follicles was similar, with a reduction of 0.1 (−0.7%), not statistically significant (P=.798). Comparing the ovarian response between the second and third cycles, the number of follicles was also similar, with an increase of 0.5 (3.9%), not statistically significant (P=.126). The number of follicles was also similar between the first and third cycles, with an increase of 0.4 (3.3%), also not statistically significant (P=.301). Standard deviations of the changes between cycles ranged from 4.7 to 5.7, indicating a measure of within-subject variability between cycles, with between-cycle correlations ranging from 0.59 to 0.70. Therefore, even though there is a measure of within-subject variability across cycles, mean responses seem to be relatively constant.

The mean number of oocytes retrieved and the ovarian response as measured by the number of oocytes retrieved are presented as Supplementary Data (Supplemental Table 1 and Supplemental Figures 1 and 2).

Intercycle Switching between the Three Ovarian Response Categories (according to the Number of Follicles ≥11 mm on the Day of hCG)

Intercycle variability can be described further by assigning the number of follicles to low, normal, and high response categories. If the percentage of women who switch from a normal to a low/high category is similar to the percentage of women who switch from a low/high to a normal category, the switch in response categories are more reflective of a symmetric distribution around a mean, which can be attributed to a random distribution of follicle numbers, rather than a directional shift indicating an overall change in response between cycles. The percentages of low (0–<6 follicles), normal (6–<18 follicles), and high (≥18 follicles) responders, respectively, were 5.7%, 72.7%, and 21.6% in cycle 1, 5.1%, 73.3%, and 21.6% in cycle 2, and 6.8%, 67.6%, and 25.6% in cycle 3 (Supplemental Table 2, available online). According to the number of follicles, the majority of patients (per cycle, 67.6%–73.3%) had a normal ovarian response throughout all three cycles. The distribution of low, normal and high response based on the number of oocytes retrieved is presented in the Supplementary Data (Supplemental Table 3).

None of the women switched from low to high ovarian response (or vice versa) either between consecutive cycles or between cycles 1 and 3. In the second cycle, 75.6% remained in the same response category as in the first cycle, 11.9% switched from normal to low/high response, and 12.5% switched from low/high to normal ovarian response (Table 3). The switches in response categories were not statistically significant in (P=.879), supporting a symmetric distribution of subjects from normal to low/high and low/high to normal response categories. In the third cycle, 73.9% remained in the same response category as in the second cycle, 15.9% switched from normal to low/high response, and 10.2% switched from low/high to normal ovarian response (Table 3), again supporting a symmetric distribution of switch in response categories (P=.140). Confirming the analysis of the number of follicles, even though there is variability in response, there does not seem to be a measurable pattern of a change in follicles across the cycles.

Intercycle switching between the three ovarian response categories based on the number of oocytes retrieved is presented as Supplemental Data (Supplemental Table 4).

Intercycle Switching from a Normal to a Low/High Ovarian Response and Vice Versa (according to the Number of Follicles ≥11 mm on the Day of hCG)

For women with a normal ovarian response in the first cycle (n = 128), the percentage (95% CI) of women switching to a low/high ovarian response in the second cycle was 16.4% (10.5%–24.0%) and the percentage (95% CI) of those with a low/high ovarian response in the first cycle (n = 48) switching to a normal response in the second cycle was 45.8% (31.4%–60.8%) (Table 4). The percentage (95% CI) of women with a normal ovarian response in the second cycle (n = 129) switching to a low/high ovarian response in

TABLE 2

Number of follicles ≥11 mm on the day of hCG.

A. Overall and by subgroup of same rFSH stimulation dose between cycles

	Cycle 1			Cycle 2			Cycle 3		
Patients	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Overall[a]	176	13.4	6.2	176	13.3	5.4	176	13.8	6.4
Same-stimulation subgroup									
Cycles 1 to 2[b]	44	14.4	5.7	44	14.8	5.1			
Cycles 2 to 3[c]				37	13.3	5.6	37	12.8	5.8

B. Overall differences between cycles

Cycles	LS mean change (SD)	Percent change	Difference *P* value
1 to 2	−0.1 (5.0)	−0.7	.798
2 to 3	0.5 (4.7)	3.9	.126
1 to 3	0.4 (5.7)	3.3	.301

Note: Analysis output extracted from repeated-measures analysis on patients across cycles and controlled for region. LS = least squares.
[a] $P \geq .126$ for the differences between cycles (between cycle $\rho_{12} = 0.64$, $\rho_{13} = 0.59$, $\rho_{23} = 0.70$).
[b] $P = .577$ for the difference between cycles 1 and 2 ($\rho = 0.69$ between cycles).
[c] $P = .634$ for the difference between cycles 2 and 3 ($\rho = 0.60$ between cycles).

Rombauts. Ovarian response intercycle variability. Fertil Steril 2015.

the third cycle was 21.7% (14.9%–29.8%), and the percentage (95% CI) of those with a low/high ovarian response in the second cycle (n = 47) switching to a normal response in the third cycle was 38.3% (24.5%–53.6%) (Table 4).

Correlation between Follicles ≥11 mm on the Day of hCG Administration and Number of Oocytes Retrieved

As expected, there was a correlation between the number follicles ≥ 11 mm on the day of hCG and the number of oocytes retrieved: correlation coefficients were 0.60, 0.65, and 0.67 in cycles 1, 2, and 3, respectively ($P < .0001$; Supplemental Table 5). The correlation between the number of oocytes retrieved and the number of follicles ≥ 11 mm on the day of hCG are provided as Supplemental Data (Supplemental Table 6).

TABLE 3

Variability in ovarian response between cycles according to the number of follicles (≥11 mm) on the day of hCG.

	Cycle number (compared with cycle in left-most column)			
Frequency	**Low**	**Normal**	**High**	**Total**
Cycle 1		Cycle 2		
Low	5	5	0	10
Normal	4	107	17	128
High	0	17	21	38
Total	9	129	38	176
Test of symmetry		$P = .991$		
Cycle 2		Cycle 3		
Low	3	6	0	9
Normal	9	101	19	129
High	0	12	26	38
Total	12	119	45	176
Test of symmetry		$P = .536$		
Cycle 1		Cycle 3		
Low	5	5	0	10
Normal	7	99	22	128
High	0	15	23	138
Total	12	119	45	176
Test of symmetry		$P = .647$		

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Correlation between Predictors of Ovarian Response and Number of Follicles ≥11 mm on the Day of hCG Administration per Cycle

The correlation between the number of follicles ≥ 11 mm on the day of hCG and predictors of ovarian response (age, AFC, and prestimulation E_2, FSH, and LH, as well as duration of stimulation and total dose of rFSH) are given in Supplemental Table 5. Correlations with AFC and FSH were moderate (correlation coefficient magnitudes were approximately 0.3–0.5). Multiple correlation coefficients (combining all seven predictors) were 0.58, 0.66, and 0.60 in cycles 1, 2, and 3, respectively ($P < .0001$).

The correlation between the number of oocytes retrieved and predictors of ovarian response are provided as Supplemental Data (Supplemental Table 6).

Can Baseline FSH and AFC Predict a Change in Ovarian Response per Cycle?

The correlation between changes in ovarian response (between cycles 1 and 2 and between cycles 2 and 3) and changes in predictors of ovarian response (Supplemental Table 7) were numerically small. Multiple correlation coefficients (combining all seven predictors as in Supplemental Table 7) were 0.42 and 0.40 between cycles 1 and 2 and between cycles 2 and 3, respectively ($P < .001$).

The correlation between cycle differences in the number of oocytes retrieved, the number of follicles ≥ 11 mm on the day of hCG and changes in predictors of ovarian response are provided as Supplemental Data (Supplemental Table 8).

TABLE 4

Summary of intercycle variability.

Variable	From first to second cycle (n = 176)	From second to third cycle (n = 176)	From first to third cycle (n = 176)
Patients with or without a switch in ovarian response, n (%)			
Normal to low/high response	21 (11.9)	28 (15.9)	29 (16.5)
Low/high to normal response	22 (12.5)	18 (10.2)	20 (11.4)
Low/high to low/high	26 (14.8)	29 (16.5)	28 (15.9)
Normal to normal response	107 (60.8)	101 (57.4)	99 (56.3)
Probability of a switch in ovarian response, %			
Switch from normal to low/high response (95% CI)[a]	21/128 (16.4) (10.5–24.0)	28/129 (21.7) (14.9–29.8)	29/128 (22.7) (15.7–30.9)
Switch from low/high to normal response (95% CI)[a]	22/48 (45.8) (31.4–60.8)	18/47 (38.3) (24.5–53.6)	20/48 (41.7) (27.6–56.8)
Test of symmetry (McNemar's test)	*P*=.879	*P*=.140	*P*=.199

Note: Data are presented as number (percentage) except where noted otherwise.
[a] 95% CI of percentage calculated using the Clopper-Pearson exact method.

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DISCUSSION

This is the first study, to our knowledge, to examine the intercycle variability of the ovarian response across three consecutive IVF cycles with the same protocol. Our study shows that although the percentage of low, normal, and high ovarian responders to ovarian stimulation overall is similar after up to three stimulation cycles, an individual's ovarian response with an identical treatment protocol can vary from one cycle to a subsequent cycle. Only approximately 75% of patients remained in the same response category (low, normal, or high) compared with the previous cycle. However, mean differences between subsequent cycles were small (on average, less than half a follicle and less than one oocyte). Although population statistics demonstrated only minimal changes from cycle to cycle, patients also need to be aware that individual responses can vary significantly in a subsequent cycle with the same protocol (Fig. 1B), though not in any particular direction toward an increase or decrease in follicles.

The data from the Trust trial analyzed in this study also successfully illustrate the regression to the mean effect in patients with an extreme response (i.e., low response or high response) (10). In the Trust study, 45.8% of low/high responders in cycle 1 went on to have a normal response in cycle 2 without changes in the stimulation protocol. Similarly, 38.3% of low/high responders in cycle 2 went onto have a normal response in cycle 3. This is of particular importance when interpreting poorly designed studies that compare "before" and "after" effects of interventions in selected populations with a previous poor ovarian response. Any claimed benefits of interventions in such study designs are likely the result of regression to the mean.

The data presented herein are useful for the design of future clinical trials, because this study provides accurate estimates both of the variance in ovarian response in women aged <40 years and of the natural variability in ovarian response between cycles with the same treatment protocol. Accurate sample size calculations depend not only on the predicted effect size but also on the variance of the underlying measure.

The number of follicles on the day of hCG administration correlated well with the number of oocytes retrieved. The reduction in range of follicles ≥11 mm on the day of hCG administration from cycle 1 to cycle 3 may be due to negative selection of patients for a subsequent cycle when an extreme response occurred in a previous cycle. Accordingly, the true intercycle variation in ovarian response might have been underestimated in this study because subjects with an extreme response in a first cycle could not contribute to the well-known regression to the mean effect if not put on the same protocol again for a subsequent cycle. Furthermore, intercycle drop-out occurred with pregnancy in the Trust trial.

The AFC and FSH levels on stimulation day 1 correlated positively and negatively, respectively, with the ovarian response in each cycle, but there was a weak correlation with LH and E_2 levels on stimulation day 1. The AFC and baseline FSH levels have previously been identified as predictive factors for ovarian response in ovarian stimulation protocols in a GnRH antagonist protocol (8).

The intercycle variability in ovarian response to controlled ovarian stimulation was, however, not strongly linked to individual patient demographics, infertility characteristics, or baseline predictors. This is of importance because it may be assumed that every cycle is individually different, especially in the size of the growing follicular cohort, which then might explain some of the intercycle variation in response. Changes between cycles in the predictor variable AFC, a proxy for the follicular cohort becoming FSH sensitive at the beginning of each cycle, did indeed show the best correlation with variation observed in the number of growing follicles. However, this correlation is quite small and therefore potentially of limited utility when it comes to predicting and individualizing treatment according to baseline variables.

The study has some weaknesses. In the Trust trial, no measurements of serum antimüllerian hormone were performed, and we were therefore unable to correlate this predictor to the actual ovarian response in a fixed stimulation protocol. The original study design of the Trust trial also dictated that patients dropped out after a successful cycle. There is, therefore, some selection bias in this retrospective

analysis of the Trust trial data. Additionally, no adjustment was made for the different type of gonadotropins used after day 7. However, a number of important factors strengthen the quality of this study. The large sample size allowed for an accurate estimation of population statistics for the ovarian response across three consecutive cycles. In addition, for each of the three IVF cycles, all women received the same protocol and, importantly, the stimulation dose was entirely fixed for the first week (150 μg corifollitropin alfa).

In conclusion, the average ovarian response may seem very similar across subsequent cycles, but the underlying individual ovarian response may vary between three subsequent controlled ovarian stimulation cycles. Awareness of an individual subject's intercycle variability is essential, because it may affect the accuracy of ovarian response prediction. Individual subject serum FSH concentrations and AFC at the beginning of each cycle did not strongly predict a switch in the ovarian response.

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SUPPLEMENTAL DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fertnstert.2015.06.027.

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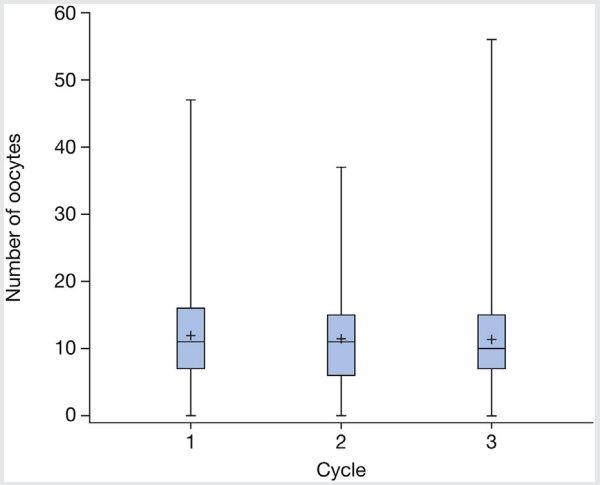
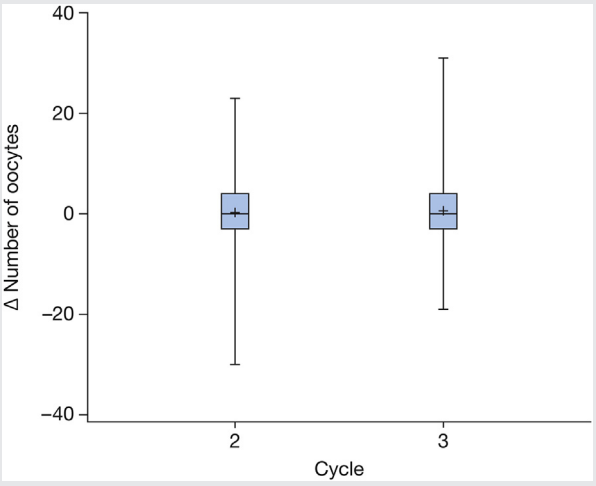
SUPPLEMENTAL FIGURE 1



Box plot of the number of oocytes per cycle. Displayed are maximum (endpoint of upper whisker), third quartile (upper edge of box), median (line inside box), mean (+), first quartile (lower edge of box), and minimum (endpoint of lower whisker).

Rombauts. Ovarian response intercycle variability. Fertil Steril 2015.

SUPPLEMENTAL FIGURE 2



Box plot of the difference "delta" of the number of oocytes vs. the previous cycle. Displayed are maximum (endpoint of upper whisker), third quartile (upper edge of box), median (line inside box), mean (+), first quartile (lower edge of box), and minimum (endpoint of lower whisker).

Rombauts. Ovarian response intercycle variability. Fertil Steril 2015.