Predictors of ovarian response in women treated with corifollitropin alfa for in vitro fertilization/ intracytoplasmic sperm injection

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Objective: To identify predictors of ovarian response in women undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol and determine specific thresholds for the prediction of low and excessive responders.
Design: Retrospective cohort study.
Setting: University-based tertiary care center.
Patient(s): Infertile women undergoing ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection.
Intervention(s): Controlled ovarian hyperstimulation with corifollitropin alfa in a GnRH antagonist protocol.
Main Outcome Measure(s): Relationship between ovarian reserve tests and ovarian response.
Result(s): Antimüllerian hormone (AMH) and antral follicle count (AFC) were the only independent predictors for low and excessive ovarian response. In prediction of excessive response, the area under the receiver operating characteristic curve [AUC (95% CI)] for AMH was 0.890 (0.832–0.947) and 0.897 (0.829–0.964) for AFC. The optimal thresholds for identifying excessive responders were 3.52 ng/mL for AMH (sensitivity 89.5, specificity 83.8) and 16 for AFC (sensitivity 80.0, specificity 84.5). AMH and AFC also predicted low ovarian response: AUCs AMH 0.836 (0.783–0.889) and AFC 0.830 (0.767–0.894). The optimal thresholds for predicting low response were 1.37 ng/mL for AMH (sensitivity 74.1, specificity 77.5) and 8 for AFC (sensitivity 72.2, specificity 84.6). For both excessive and low ovarian responses, a logistic regression model combining the biomarkers was associated with improved discrimination.
Conclusion(s): AMH and AFC are the best predictors for low and excessive response in women treated with corifollitropin alfa in an antagonist protocol. Using AMH and AFC to select suitable candidates for treatment with corifollitropin alfa may result in a safe and convenient stimulation. (Fertil Steril® 2013;100: 430–7. ©2013 by American Society for Reproductive Medicine.)
Key Words: Corifollitropin alfa, poor responders, OHSS, antimüllerian hormone, AMH, AFC

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Over the past decade, an increasing body of evidence has been published examining predictors of ovarian response in women undergoing ovarian stimulation for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI). Although several studies have examined different parameters for the prediction of ovarian response, antral follicle count (AFC) and antimüllerian hormone (AMH) appear to be the best predictors of low and excessive ovarian response (1, 2). In single-center studies AFC represents a marker with a high ability to predict low or excessive ovarian response, whereas AMH is increasingly being established as the serum biomarker of choice for predicting ovarian response to stimulation in IVF/ICSI cycles (3). Although the high predictive ability of AMH for the prediction of poor (4–6) or excessive ovarian response (1) was initially established in GnRH agonist down-regulated cycles, this has now been extended to GnRH antagonist cycles with equivalent predictive capacity (7).

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Recently, a novel recombinant gonadotropin with sustained follicle-stimulating activity, corifollitropin alfa, has been introduced in clinical practice with pregnancy rates equivalent to treatment with rFSH (8). The main difference of corifollitropin alpha compared with treatment with rFSH is its different pharmacokinetic profile, with a long half-life of up to 68 hours (9) during which it may induce and sustain multifollicular growth for an entire week (10). However, because of this difference, corifollitropin appears to result in higher follicular recruitment and higher number of oocytes retrieved compared with rFSH. Therefore, although AFC and AMH have been proven to be the best predictors for low and excessive responses in the antagonist setting after treatment with rFSH, extrapolation to patients treated with corifollitropin alfa may not be appropriate owing to its markedly different pharmacokinetics.

To date we are not aware of any attempt to evaluate predictors of ovarian response such as AMH or AFC in patients undergoing stimulation with corifollitropin alfa for IVF/ICSI. However, the clinical importance of these markers may be even more imperative in women treated with this long-acting FSH owing to the different pharmacodynamics of the drug. With careful case selection, no higher risk for ovarian hyperstimulation syndrome (OHSS) has been demonstrated with the use of corifollitropin alfa in infertile women (11). However, a recent systematic review, including the initial dose-finding studies of corifollitropin alfa, has suggested that corifollitropin results in a higher number of oocytes retrieved compared with rFSH, with some evidence of increased ovarian response due to cancelled cycles because of overstimulation for women treated with corifollitropin alfa (12).

Therefore, we considered it to be appropriate to examine the predictive ability of AMH and other ovarian reserve markers in patients treated with corifollitropin alfa in an antagonist protocol for IVF/ICSI, to define specific cutoffs for the prediction of excessive and low responses to stimulation.

METHODS

Institutional Review Board approval was obtained for the conduction of the study from the Ethical Committee of Universitair Ziekenhuis Brussel (decision number BUN 14320121503, April 10, 2012).

Eligibility Criteria

The eligible cohort were all consecutive patients between 18–44 years old with a body mass index (BMI) of 17–40 kg/m^2 who fulfilled the following criteria: 1) had $\geq$2 years of infertility; 2) underwent an IVF/ICSI attempt in 2010–2011; 3) had not been treated before with corifollitropin alfa; 4) were treated with a fixed GnRH antagonist protocol; and 5) had their AMH values tested in our lab with the Immunotech Beckman Coulter AMH ELISA kit during the preliminary fertility work-up at their first consultation. Corifollitropin alfa was given in accordance with the summary product characteristics provided by the manufacturer (13). In this regard, women with polycystic ovary syndrome (PCOS), a history of OHSS, or an earlier stimulation cycle that resulted in >30 follicles $\geq$11 mm measured by ultrasound examination were excluded from treatment, because treatment with corifollitropin alfa is contraindicated for those patients.

AMH Measurement

Serum AMH samples were obtained obtained at the first consultation, regardless of the day of the menstrual cycle. Blood was drawn in plain serum tubes, centrifugation was performed within 1 hour, and serum was separated and immediately stored at −80°C until analysis. All samples were measured with the Immunotech Beckman Coulter AMH ELISA kit. The AMH assay demonstrated stable intra- and interassay coefficients of variation <9.5% and a functional sensitivity of 0.35 ng/mL.

Treatment Plan

Patients received a single dose of 100 or 150 μg corifollitropin alfa administered on day 2 of the treatment cycle, depending on patient weight per the manufacturer's instructions (Elonva; Organon). Women with an earlier poor ovarian response to stimulation and expected poor responders were treated with a starting dose of 150 μg corifollitropin alfa, regardless of patient weight. Five days later, administration of a GnRH antagonist at a daily dosage of 0.25 mg was initiated until the day of oocyte retrieval. On day 8 (cycle day 9) of the stimulation, a daily dose of rFSH or hMG at dose of 100–300 IU, depending on patient age, BMI, and ovarian response in an earlier cycle, was administered until the day before oocyte retrieval.

To induce final oocyte maturation, 10,000 IU hCG was given as soon as two or three follicles >17 mm were present on ultrasound scan. Patients at risk of developing OHSS (>14 follicles of 11 mm on the day of ovulation triggering) were triggered with either 5,000 IU hCG or a bolus of GnRH agonist (0.2 mg Decapeptyl; Ipsen), based on the physician's discretion. Oocytes were retrieved after 36 hours, followed by IVF or ICSI.

In case of monofollicular development, rescue intrauterine insemination was performed, and in case of no follicular development, the treatment cycle was cancelled. In both cases, this cycle was included in our analysis and the number of cumulus-oocyte complexes was considered to be 0.

Definition of Low and Excessive Ovarian Responses

The cutoff value for defining a patient as a low responders was $\leq$3 oocytes retrieved, in accordance with the recently developed "Bologna criteria" for poor ovarian response (14). This strategy was adopted to provide data in a uniform way that may be helpful for comparisons and combined analyses in the future (15) and to avoid the wide diversity of the definitions for poor ovarian responders that have been described (16). Excessive responders were considered to be women with >20 oocytes retrieved at oocyte pick-up, to comply with earlier trials evaluating the predictive ability of AMH in infertile patients (17).

Statistical Analysis

Continuous variables are presented as mean and SD or as median and interquartile range when highly skewed. Kruskal-Wallis comparisons were performed for continuous variables, owing to the lack of normality in the distribution of the results, and chi-square tests for categoric variables.

Spearman rank correlation coefficients and corresponding *P* values were calculated for the candidate predictive variables and oocyte yield as outcome parameter. Univariate logistic regression analysis was performed to identify the best predictors for high (>20 oocytes) and low (≤3 oocytes) ovarian responses. Subsequently, significant parameters were entered in a logistic regression model, to identify independent significant factors for prediction of high ovarian response (>20 oocytes) and low (≤3 oocytes) ovarian responses. The significance level of the candidate predictive factors to enter the model was set to .05, and to stay in the model it was set to .10. Multicollinearity was assessed to evaluate the independence of the predictive parameters included in the model. After selection of the candidate predictive factors, the final model included those prognostic factors with statistical significance according to the Wald statistic test at a threshold of .05. The goodness of fit of the normal regression models was assessed by the Hosmer-Lemeshow goodness-of-fit test.

In addition, receiver operating characteristic (ROC) curves were calculated and the area under the ROC curves (AUCs) used to assess the discriminative power of independent predictors as well as of the logistic regression models. Finally, comparisons between AUC of the logistic regression models and the AUC of the individual predictors qualifying in the models were performed with a level of significance of $<.05$.

Correlation analysis, logistic regression analysis, and ROC analysis were performed in SPSS 20 SE statistical software, and comparisons between AUCs were performed in Stata 10 SE.

RESULTS

Patient Characteristics

The cohort characteristics are described in Figure 1. Overall, 210 patients were included in the analysis: 181 women were treated with 150 μg and 29 women with 100 μg corifollitropin alfa.

Patients' baseline characteristics, ovarian reserve markers, and stimulation characteristics are presented for the total population included in the study (Table 1). In addition, all variables are presented according to the level of ovarian response. As shown, patients' age and ovarian reserve markers (basal FSH, AMH, and AFC) significantly differed between low, normal, and excessive responders. In addition, statistical significant differences were observed between different categories for most of the stimulation characteristics (corifollitropin dose, additional dose of rFSH or hMG from day 8 of stimulation onward, and total days of stimulation).

Parameters Correlated with Oocyte Yield

Spearman correlation coefficients revealed a statistically significant correlation of age with the number of oocytes retrieved ($\rho = -0.552$; $P<.0001$). In addition, oocyte yield was significantly associated with basal FSH ($\rho = -0.497$; $P<.0001$), AMH ($\rho = 0.726$; $P<.0001$), and AFC ($\rho = 0.635$; $P<.0001$). Finally, oocyte yield was significantly associated with corifollitropin starting dose ($\rho = -0.338$; $P<.0001$), total days of stimulation ($\rho = -0.137$; $P=.047$), and the additional dose of rFSH or hMG administrated from day 8 of stimulation onward ($\rho = -0.266$; $P<.0001$).

Prediction of Oocyte Yield

ROC analysis showed that AMH had an excellent predictive ability for low and excessive ovarian responses ($P<.0001$): AUCs (95% CI) 0.836 (0.783–0.889) and 0.890 (0.832–0.947), respectively (Fig. 2). The optimal threshold for identifying potential low ovarian responders was 1.37 ng/mL, which equated to a sensitivity of 74.1 and specificity of 77.5. This equated to positive and negative likelihood ratios (LRs) of 3.29 and 0.33, respectively. At the other extreme of ovarian response, the optimal threshold for identifying patients with >20 oocytes retrieved was 3.52 ng/mL, with a sensitivity of 89.5, specificity of 83.8, +LR 5.51, and −LR 0.13.

AFC also demonstrated an excellent predictive ability for low and excessive ovarian responders ($P<.0001$). The AUCs (95% CI) were 0.830 (0.767–0.894) for low ovarian response and 0.897 (0.829–0.964) for excessive response (Fig. 2). A threshold AFC of eight had a sensitivity of 72.2, specificity of 84.6, +LR 4.41, and −LR 0.33 to predict low ovarian response, and a threshold AFC of 16 predicted excessive ovarian response with a sensitivity of 80, specificity of 84.5, +LR 5.17, and −LR 0.24.

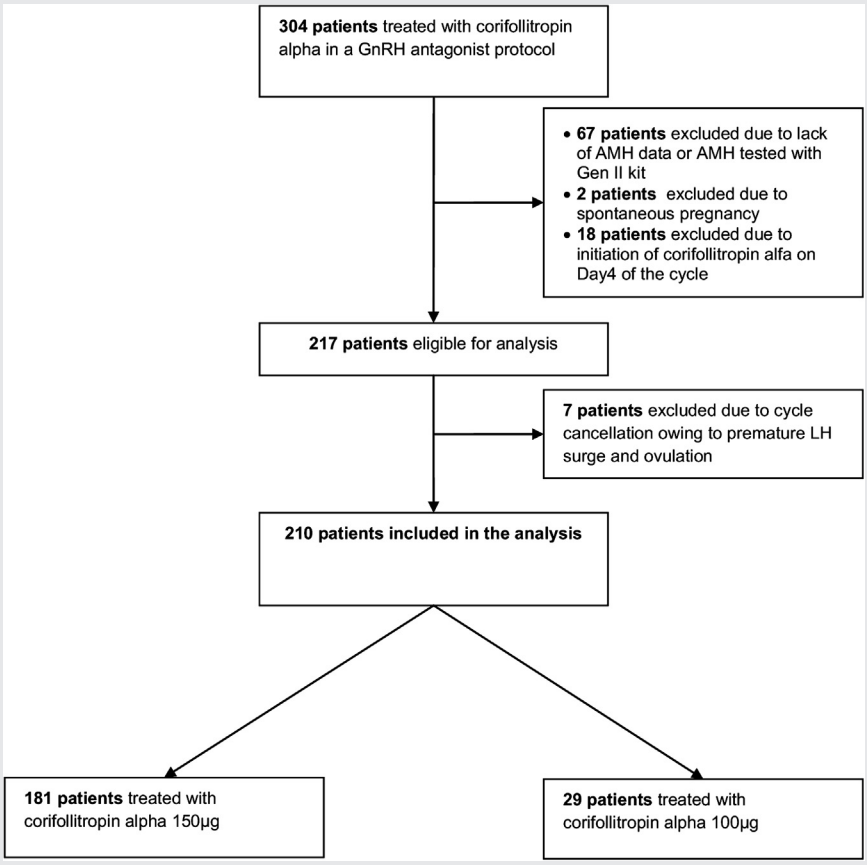
Basal FSH and age were also associated with low and excessive ovarian responses, but their results in ROC analyses were significantly lower than AMH and AFC (data not shown).

Predictive Model for Excessive and Low Ovarian Responses

Univariate logistic regression analysis was performed and significant parameters for predicting low and excessive ovarian responses identified. Age, ovarian reserve tests (AMH, AFC, basal FSH), and ovarian stimulation characteristics (dose of corifollitropin alfa and additional dose of rFSH or hMG from day 8 of stimulation onward) were significant predictors of both low and excessive ovarian responders in the univariate analysis. In multivariable logistic regression, no multicollinearity existed between the variables included in the model. However, only AMH and AFC qualified to stay in the model as independent predictors for the prediction of both low and excessive responses. In the prediction of low response, AMH and AFC were the only independent predictors ($P<.0001$), with an AUC (95% CI) for the model including these parameters of 0.877 (0.827–0.928). The odds ratios (95% CI) for predicting low response ($P=.001$) were 0.37 (0.21–0.67) for AMH and 0.84 (0.76–0.93) for AFC. The AUC of the model was significantly higher than the AUC of AFC alone ($P=.013$) but not of AMH alone ($P=.11$; Fig. 2). The logistic regression equation for low ovarian response according to the model was $z = 2.161 - (0.991 \times \text{AMH}) - (0.171 \times \text{AFC})$.

Similarly, AMH and AFC were the only two independent parameters that predicted excessive ovarian response. The

FIGURE 1



Flowchart of patient selection process. AMH = antimüllerian hormone.

Polyzos. AMH and AFC in corifollitropin alfa cycles. Fertil Steril 2013.

odds ratios (95% CI) for predicting excessive response (P=.002) were 1.78 (1.07–2.57) for AMH and 1.19 (1.07–1.32) for AFC. The AUC for the model including AMH and AFC revealed an excellent accuracy for the prediction of an oocyte yield >20 oocytes with an AUC (95% CI) of 0.939 (0.878–1.00; P<.0001; Fig. 2). The AUC of the model was significantly higher than the AUC of AMH alone (P=.001) but not of AFC alone (P=.12). The logistic regression equation for excessive ovarian response according to the model was $z = -6.782 + (0.577 \times \text{AMH}) + (0.172 \times \text{AFC})$.

DISCUSSION

This study is, to our knowledge, the first study to examine predictors of ovarian response in women treated with corifollitropin alfa. Our data suggest that AMH and AFC are independently associated with oocyte yield, that they are capable of predicting low and excessive responses, and that overall model performance can be enhanced by their combination. To facilitate clinical utility, we derived thresholds for prediction of response categories using AMH and AFC in isolation and a model combining them.

Analysis of agonist and antagonist cycles with recombinant and highly purified urinary gonadotropins has previously shown that AMH and AFC are associated with oocyte yield and capable of predicting ovarian response categories (3). In the present study we extend this to confirm that AMH and AFC are also capable of predicting ovarian response with similar efficacy in corifollitropin-treated patients. Both AMH and AFC were independently associated with oocyte response category and could be combined in a logistic regression model to further enhance prediction. This is in marked contrast to the recent multicenter study (MEGASET: Menopur in GnRH Antagonist Cycles with Single-Embryo Transfer) using antagonist-based stimulation, which did not observe an association of AFC with ovarian response but did for AMH (18). This may reflect in part the high level of interoperator variability in AFC across multiple centers participating in that trial compared with our single-center experience (19, 20). In support of this would be the multitude of single-center studies showing that AFC can predict ovarian response and the recent individual patient data meta-analysis of ovarian response combining these single-center studies which also demonstrated an association of AFC with response category (1, 2). That we demonstrate that AFC is associated with oocyte yield for corifollitropin alfa is reassuring and consistent with the original licensing studies. Given the fact that corifollitropin has only recently

TABLE 1

Patient characteristics, ovarian reserve markers, and stimulation characteristics according to the level of ovarian response.

	All patients	Low responders	Normal responders	High responders	*P* value
Patient characteristics, mean (SD)					
No. of patients	210	72	120	18	
Age (y)	34.4 (5.2)	37.5 (4.5)	33.3 (4.7)	29.7 (4.5)	<.0001
BMI	24.1 (4.8)	25.5 (5.8)	23.4 (4.2)	23.5 (3.1)	.112
Primary infertility cause, n (%)					.620
Male factor	68 (33)	20 (28)	42 (35)	6 (33)	
Idiopathic	114 (54)	40 (56)	65 (54)	9 (50)	
Tubal factor	13 (6)	5 (7)	6 (5)	2 (11)	
Ovulatory	2 (1)	2 (2)	0	0	
Endometriosis	8 (4)	4 (6)	4 (3)	0	
Genetic (preimplantation genetic diagnosis)	5 (2)	1 (1)	3 (3)	1 (6)	
Ovarian reserve markers					
AMH (ng/mL), median (IQR)	1.7 (0.9–3.3)	0.9 (0.6–1.3)	2.0 (1.2–3.6)	4.6 (3.8—5.8)	<.0001
Basal FSH (IU), mean (SD)	9.2 (4.2)	11.2 (4.6)	8.4 (3.6)	5.8 (3.6)	<.0001
AFC, median IQR	9 (4–14)	4 (2–7)	10 (6–15)	20 (16–28)	<.0001
Stimulation characteristics					
Corifollitropin alfa dose (IU)					<.0001
150 μg	181	72	97	12	
100 μg	29	0	23	6	
Cumulative dose of FSH or hMG from stimulation day 7 onward (IU), median (IQR)	425 (150–900)	600 (300–1,200)	400 (150–875)	200 (75–463)	.002
Duration of stimulation (d), mean (SD)	9.5 (1.9)	9.8 (2.6)	9.2 (1.8)	8.6 (1.3)	.196
Number of COCs, median (IQR)	6 (2–13)	1 (0–2)	8 (6–13)	25 (22–31)	<.0001

Note: AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; COC = cumulus-oocyte complex; IQR = interquartile range.

Polyzos. AMH and AFC in corifollitropin alfa cycles. Fertil Steril 2013.

been introduced in clinical practice, the present study provides important threshold levels for the successful prediction of the extremes of response to stimulation after treatment with this new long-acting FSH to guide physicians toward a safer stimulation.

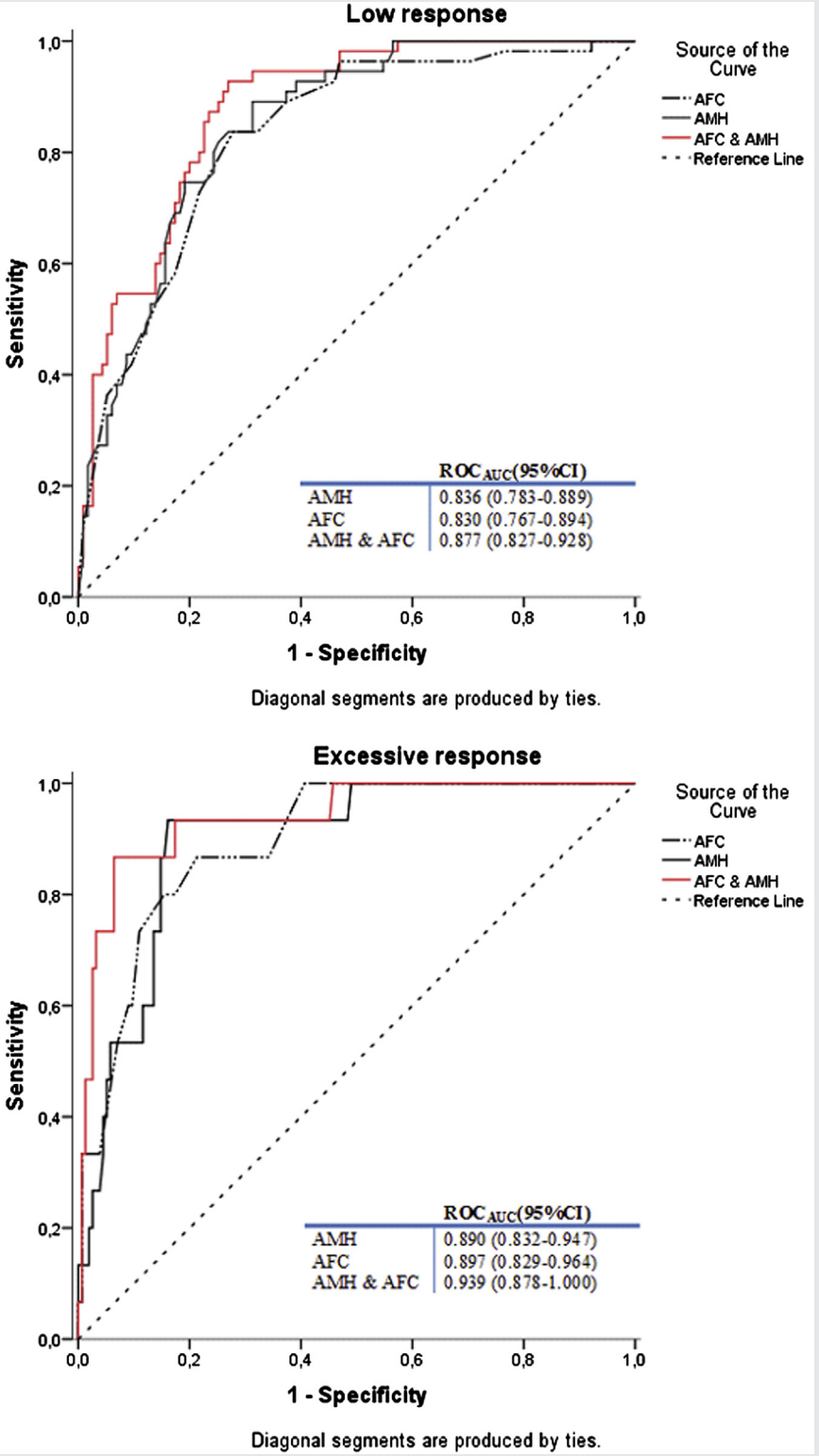
Based on our results, at threshold values of 3.52 ng/mL for AMH and 16 for AFC, both markers may successfully predict women who are likely to have >20 oocytes retrieved and are therefore at risk for developing OHSS if hCG is used to trigger oocyte maturation. These thresholds are very similar to those from earlier studies in GnRH agonist cycles with conventional gonadotropins (5, 21, 22); however, both sensitivity and specificity for the detection of excessive responders were higher in our dataset of patients receiving corifollitropin alfa. For the identification of women at risk of poor response, our optimal cutoff levels of AMH and AFC were 1.37 ng/mL and 8, respectively, also similar to earlier studies using shorter-acting gonadotropins (6, 23).

Although the choice of appropriate thresholds to select patients suitable for treatment would be ideal, our study does not support that being feasible at present. It is a fact that a false positive test may exclude patients that are likely to respond well to treatment, and exceptionally high prediction characteristics would be required to avoid inappropriate exclusion. Rather, the AMH and AFC cutoffs provided here for low response should be interpreted as being purely indicative of an expected low response in a forthcoming cycle with the use of corifollitropin alfa; they should not be used as a tool to exclude patients from future IVF/ICSI cycles. For excessive ovarian response, patients with an AMH value >3.52 ng/mL and an AFC value >16 should be considered to be at risk for developing OHSS following treatment with corifollitropin alfa. Fortunately, there is now a wide range of options for the prevention of OHSS, the most important of these being the use of an agonist trigger and segmentation of the IVF cycle (24). Additional strategies, including consideration of closer monitoring and use of alternative gonadotropins, may also be beneficial.

In addition, we need to emphasize that although specific thresholds for the prediction of the extremes of ovarian response are provided in the present study, these thresholds should be interpreted with caution in everyday clinical practice, because they reflect thresholds obtained from a single-center study. Therefore, although they may provide initial guidance for treatment, they should not be strictly followed for the inclusion or exclusion of patients suitable for treatment. Nonetheless, the present data clearly suggest that AMH and AFC can be used in everyday clinical practice for the prediction of low and excessive ovarian responses in patients treated with corifollitropin alfa.

A limitation of the present study is its retrospective design. Because of this study design, we have to acknowledge that several treatment parameters differed among treated patients. For example, gonadotropin (rFSH or hp-hMG) dose administered after day 8 of stimulation considerably varied in our population, based on patient age and response in earlier cycles with conventional gonadotropins. In addition, expected poor responders received a starting dose of 150 μg corifollitropin alfa, regardless of their weight. Thus, potential excessive responders may have received lower doses of gonadotropins and potential low responders may have received higher doses, resulting in misclassification of several of the cases. However, such a bias may have resulted in an

FIGURE 2



Receiver operator characteristic curves for low and excessive response. AFC = antral follicle count; AMH = antimüllerian hormone; CI = confidence interval; ROC_{AUC} = area under the receiver operating characteristic curve.

Polyzos. AMH and AFC in corifollitropin alfa cycles. Fertil Steril 2013.

underestimation, not an overestimation, of the accuracy of the markers, which further supports their very good predictive ability for low and excessive responses. Furthermore, given that in the logistic regression models constructed, none of the stimulation characteristics were independent predictors for either low or excessive response, it is rather unlikely that either the dose of corifollitropin alfa or the additional dose of FSH or hMG might have had any influence in the prediction of the extremes of stimulation.

Another limitation of the study is its small sample size. Especially if we compare our study with the large-scale studies published in the past examining the predictive ability of ovarian reserve markers in agonist-treated patients, we need to be cautious when interpreting the results. Therefore, data from ongoing large studies are essential to confirm our results regarding the predictive ability of AMH and AFC in women undergoing ovarian stimulation with corifollitropin alfa (25).

A major strength of our study is the fact that we examined the predictive ability of ovarian reserve markers in women treated with a novel gonadotropin, corifollitropin alfa. Given that corifollitropin alfa appears to result in pregnancy rates similar to those with conventional gonadotropins, whereas it may augment the number of oocytes retrieved (8), this long-acting FSH may be of particular interest for specific patient categories, because a single injection may substitute seven daily injections of conventional gonadotropins. In this regard, we may provide information that may be suitable for individualization of IVF treatment. Futhermore, owing to the ability of AMH and AFC to accurately identify women at risk of OHSS, the thresholds identified in the present study may undeniably help to eliminate the risk of this potential fatal complication.

In conclusion, allowing for the limitations of the present study, AMH and AFC appear to be the best predictors of ovarian response in women treated with corifollitropin alfa. This study indicates that this new long-acting FSH may be safely administered in women with AMH values <3.52 ng/mL and AFC < 16 because the likelihood of OHSS in these patients categories is significantly reduced. In women with values exerting those thresholds, close monitoring is indicated to prevent and avoid this iatrogenic complication.

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