Predictive factors for ovarian response in a corifollitropin alfa/GnRH antagonist protocol for controlled ovarian stimulation in IVF/ICSI cycles

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Abstract

Background: This secondary analysis aimed to identify predictors of low (<6 oocytes retrieved) and high ovarian response (>18 oocytes retrieved) in IVF patients undergoing controlled ovarian stimulation with corifollitropin alfa in a gonadotropin-releasing hormone (GnRH) antagonist protocol.

Methods: Statistical model building for high and low ovarian response was based on the 150 μg corifollitropin alfa treatment group of the Pursue trial in infertile women aged 35–42 years (n = 694).

Results: Multivariable logistic regression models were constructed in a stepwise fashion (P <0.05 for entry). 14.1 % of subjects were high ovarian responders and 23.2 % were low ovarian responders. The regression model for high ovarian response included four independent predictors: higher anti-Müllerian hormone (AMH) and antral follicle count (AFC) increased the risk, and higher follicle-stimulating hormone (FSH) levels and advancing age decreased the risk of high ovarian response. The regression model for low ovarian response also included four independent predictors: advancing age increased the risk, and higher AMH, higher AFC and longer menstrual cycle length decreased the risk of low ovarian response.

Conclusions: AMH, AFC and age predicted both high and low ovarian responses, FSH predicted high ovarian response, and menstrual cycle length predicted low ovarian response in a corifollitropin alfa/GnRH antagonist protocol.

Trial registration number: NCT01144416, Protocol P06029

Keywords: Predictive modelling, Ovarian response, Corifollitropin alfa, GnRH antagonist

Introduction

In assisted reproductive technology, both very low and very high ovarian responses to ovarian stimulation have been associated with increased cancellation rates and compromised pregnancy and live birth rates [1, 2]. A high ovarian response also increases the risk for development of ovarian hyperstimulation syndrome (OHSS) [3]. Early identification of potential low and high responders is relevant to enable individualization of the ovarian stimulation treatment regimen [4].

The majority of studies on predictors of ovarian response have analyzed patients treated with recombinant (r) follicle-stimulating hormone (FSH) in long gonadotropin-releasing hormone (GnRH) agonist protocols. Systematic reviews have identified anti-Müllerian hormone (AMH), antral follicle count (AFC) and basal FSH as predictors of low ovarian response and AMH and AFC as predictors of high ovarian response in these protocols [5, 6], although the independence of these markers has not always been tested. AFC, basal FSH, luteinizing hormone (LH) and AMH have been identified as common prognostic factors for low or high ovarian response in rFSH GnRH antagonist protocols [7, 8].

Corifollitropin alfa is a novel recombinant gonadotropin, a single dose of which is capable of initiating and sustaining multifollicular growth during the first 7 days of ovarian stimulation as a replacement for 7 daily injections with rFSH. The treatment regimen retains the
capacity for flexibility to individualize treatment after
day 7 [9]. A retrospective cohort study in young women
receiving infertility care [11]. The Pursue trial showed that
in women aged 35–42 years, a single injection of 150 µg
corifollitropin alfa was noninferior to daily injections of
300 IU rFSH for the first 7 days of ovarian stimulation
prior to in vitro fertilization (IVF) or intracytoplasmic
sperm injection (ICSI) in terms of the vital pregnancy
rate and was equally well tolerated with a low incidence
of OHSS [12].

The objective of the current study was to identify pre-
dictors of low and high ovarian response in IVF/ICSI
patients aged 35 to 42 years undergoing ovarian stimula-
tion with corifollitropin alfa in a GnRH antagonist
protocol, using data from the corifollitropin alfa arm of
the Pursue trial.

Materials and methods
This was a secondary analysis of data collected in the
Pursue trial (N = 1390) (Trial registration number:
NCT01144416; Protocol P06029), a double-blind, ran-
domized controlled trial of corifollitropin alfa versus
daily injections of rFSH [12]. The trial was conducted in
accordance with principles of Good Clinical Practice and
was approved by the appropriate institutional review
boards and regulatory agencies (Chesapeake IRB,
Columbia (http://www.chesapeakeirb.com/)). Written in-
fomed consent was provided by all subjects. Infertile
women aged 35–42 years with a body weight of ≥50 kg
and body mass index (BMI) ≥18 and ≤32 kg/m² received
either a single injection of 150 µg corifollitropin alfa or
daily injections of 300 IU rFSH for the first 7 days of
stimulation, followed by ≤300 IU/d rFSH starting on
stimulation day 8, if needed. GnRH antagonist treat-
ment, 0.25 mg/d ganirelix, was started on day 5 until
final oocyte maturation with 250 µg recombinant hu-
man chorionic gonadotropin [12]. Patients were ex-
cluded if they had a history of, or current, polycystic
ovary syndrome.

Validated immunoassays were performed at a cen-
tral laboratory on frozen serum samples to assess
FSH, LH, estradiol (E₂) and progesterone (P) concen-
trations as previously described [13]. Assessment of
AMH was carried out using the validated Active
AMH Gen II ELISA pre-mix assay from Beckman
Coulter, Inc. (Brea, California, USA).

Limits of high and low ovarian response used in
the current analyses were set at >18 oocytes retrieved
and <6 oocytes retrieved, respectively.

Statistical methods
Initially, separate logistic regression models were con-
structed for high ovarian response (>18 oocytes retrieved
or cycle canceled by the investigator because of too high
response) and low ovarian response (<6 oocytes re-
trieved or cycle canceled due to insufficient response).
Age was included as the first variable in both models.
Other candidate prognostic factors were age at menar-
che (years), average menstrual cycle length (days), dur-
ation of infertility (years), BMI (kg/m²), AFC and serum
levels of FSH (IU/L), LH (IU/L), E₂ (pmol/L), P (nmol/L)
and AMH (ng/mL) on day 1 of stimulation. For each
candidate predictor, the association with high and low
ovarian response was assessed using a χ² test (the score
test in a logistic regression model including only that
predictor).

Multivariate logistic regression models were constructed
in a stepwise fashion (P < 0.05 for entry and P > 0.05 for
removal). Ten subjects with missing values (1.5 %) were
excluded from model building, but were included in the
estimation of the final model with missing covariate values
imputed. For both outcomes the receiver operating char-
acteristic (ROC) curve was plotted and the area under the
curve (AUC, c-statistic) was calculated. This was done for
the final model as well as for the intermediate models.
These values were denoted ‘apparent’ AUCs. Optimism-
corrected values were calculated using leave-one-out
cross-validation (where the regression coefficients were
re-estimated with each subject left out and then combined
with the subject’s covariate values in order to mimic the
prediction of the outcome for each subject). The ‘optimal’
point on the ROC curve providing the best trade-off be-
tween sensitivity and specificity and the associated ‘opt-
timal’ probability cutoff were identified. Sensitivity,
specificity, positive predictive value and negative predict-
tive value at the optimal cutoff were calculated.

Additionally, a combined model was constructed to predict
both high and low ovarian by including the pre-
dictors that appeared in both models for the separate
endpoints. The impact of leaving out prognostic factors
that appeared in only one of the models was investi-
gated. In the combined model, the regression coefficient
of a given factor was allowed to differ between the out-
comes of high and low ovarian response (i.e., propor-
tional odds was not assumed).

External model validation was not possible as Pursue
was the only study with corifollitropin alfa for which
AMH measurements were available. Instead, models
were internally validated by bootstrapping [14]. A total
of 500 samples from 686 were drawn with replacement
from the data set analyzed and for each sample, a logis-
tic regression model was fitted for high, and separately,
for low ovarian response using the stepwise approach
described above. Each model was validated using the
subjects not included in the bootstrap sample (on average, 36.8 %) [15]. Validation focused on discrimination—the ability of the model to distinguish between subjects with and without the event of interest, and calibration—the correspondence between the predicted event probabilities and observed proportions. Discrimination was measured by the AUC (or c-statistic) and calibration was measured by the calibration slope. Both quantities were obtained by fitting a logistic regression model in the validation sample with a single covariate for the so-called linear predictor, a combination of covariate values (from subjects in the validation sample) and regression coefficients (from the model constructed in the bootstrap sample). The calibration slope is the regression coefficient of the linear predictor, which should be close to unity. If the calibration slope is markedly less than one, this suggests that predictions should be ‘shrunken’ toward the mean when applied to future patients. The distribution of AUCs and calibration slopes was summarized over the 500 validation samples.

Finally, we compared our models with those developed by Polyzos et al. for excessive (>20 oocytes retrieved) and poor ovarian response (<6 oocytes retrieved). It should be noted, however, that the Polyzos et al. models were based on younger women from a single European center [10].

All analyses were performed using SAS PC version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results
In this study population, 14.1 % of women were high ovarian responders (>18 oocytes retrieved) and 23.2 % were low ovarian responders (<6 oocytes retrieved). Descriptive statistics of potential predictors for ovarian response are shown in Table 1. These analyses showed that age at baseline, menstrual cycle length, AFC, FSH and AMH had a strong ($P < 0.001$) association with both high and low ovarian response.

High ovarian response
The logistic regression model for high ovarian response included four independent predictors (Table 2). Higher AMH concentrations and AFCs increased the risk for high ovarian response and higher FSH levels and advancing age decreased the risk. The apparent AUC of the ROC curve for the complete model predicting high ovarian response was 0.888 (Fig. 1). Correcting for the optimism associated with measuring the performance of the model in the same data set in which the model was constructed, the AUC was 0.880 (Table 2).

Table 2 and Fig. 1 also show that high ovarian response cannot be predicted by age alone (apparent AUC = 0.613). Adding AMH strongly increased the ability of the model to separate patients with high ovarian response from those without high ovarian response (AUC = 0.864). Further inclusion of AFC and FSH also increased the performance of the model, but to a lesser extent (AUC = 0.888). The sensitivity and specificity of the final model were 84 % and 80 %, respectively (Table 3). The regression equation for the final model is given in Table 3 (first row). The equation can be used to calculate the probability for high ovarian response for any patient, given her age, AMH, AFC and FSH. For a 38-year-old patient with AMH = 1.8 ng/mL, AFC = 11 and FSH = 7.5 IU/L, the

Table 1 Descriptive statistics of potential predictors (covariates) for ovarian response and their univariate correlation with high and low ovarian response

| Covariate                        | Overall (n = 686) | Low (<6 oocytes) (n = 159) | Normal (6–18 oocytes) (n = 430) | High (>18 oocytes) (n = 97) | High versus normal/low (P-value) | Low versus normal/high (P-value) |
|----------------------------------|-------------------|-----------------------------|---------------------------------|----------------------------|---------------------------------|---------------------------------|
| Age at baseline, y, mean (SD)    | 38.0 (2.2)        | 38.6 (2.2)                  | 37.9 (2.1)                      | 37.3 (2.1)                 | <0.001                          | <0.001                          |
| Age at menarche, y, mean (SD)    | 12.9 (1.5)        | 12.6 (1.4)                  | 12.9 (1.5)                      | 13.1 (1.6)                 | 0.097                           | 0.026                           |
| Average menstrual cycle length, days, mean (SD) | 28.2 (1.7) | 27.5 (1.5)                  | 28.3 (1.7)                      | 28.7 (1.7)                 | <0.001                          | <0.001                          |
| Duration of infertility, y, mean (SD) | 2.8 (2.8)      | 2.5 (2.3)                   | 2.9 (2.8)                       | 3.2 (3.2)                  | 0.169                           | 0.100                           |
| BMI at baseline, kg/m², mean (SD) | 25.1 (3.6)     | 25.1 (3.6)                  | 25.1 (3.7)                      | 25.0 (3.4)                 | 0.705                           | 0.893                           |
| AFC at day 1 of stimulation, n, mean (SD) | 10.8 (4.0)   | 7.8 (3.1)                   | 11.2 (3.6)                      | 14.5 (3.4)                 | <0.001                          | <0.001                          |
| FSH at day 1 of stimulation, IU/L, median | 6.9            | 8.2                         | 6.9                             | 6.1                        | <0.001                          | <0.001                          |
| LH at day 1 of stimulation, IU/L, median | 4.6           | 4.2                         | 4.7                             | 4.7                        | 0.555                           | 0.089                           |
| Estradiol at day 1 of stimulation, pmol/L, median | 140.6         | 140.2                       | 141.5                           | 138.4                      | 0.163                           | 0.981                           |
| Progesterone at day 1 of stimulation, nmol/L, median | 1.9          | 1.9                         | 1.9                             | 2.0                        | 0.984                           | 0.849                           |
| AMH at day 1 of stimulation, ng/mL, median | 1.5            | 0.5                         | 1.6                             | 3.2                        | <0.001                          | <0.001                          |

Note: 8 subjects who did not have oocyte retrieval (for reasons other than too low or too high ovarian response according to the investigator) were excluded from the analysis

SD standard deviation, BMI body mass index, AFC antral follicle count, FSH follicle-stimulating hormone, LH luteinizing hormone, AMH anti-Müllerian hormone
linear predictor $LP = -2.676$ and the probability for high ovarian response is 0.064, or 6.4%. For another 38-year-old patient with AMH = 0.8 ng/mL, AFC = 8 and FSH = 8.5 IU/L, the LP = -4.136 and the probability for high ovarian response is 0.016, or 1.6%.

Low ovarian response

The multivariable regression model for low ovarian response also included four independent predictors (Table 4). Advancing age increased the risk for low ovarian response and higher AMH, higher AFC and longer menstrual cycle length decreased the risk. The apparent AUC of the ROC curve for the complete model predicting low ovarian response was 0.886 (Fig. 2). The optimism-corrected AUC was 0.877 (Table 4).

Table 4 and Fig. 2 again show that low ovarian response cannot be predicted by age alone (apparent AUC = 0.605). Adding AMH strongly increased the discriminative ability of the model (AUC = 0.871), whereas further inclusion of AFC and menstrual cycle length also increased the performance of the model (AUC = 0.886). The sensitivity and specificity of the final model were 77% and 87%, respectively (Table 3). The regression equation for the final model is given in Table 3 (second row). For a 38-year-old patient with AMH = 1.8 ng/mL, AFC = 11 and a menstrual cycle length of 28 days, the linear predictor $LP = -2.548$ and the probability for low ovarian response is 0.073, or 7.3%. For the 38-year-old patient with AMH = 0.8 ng/L, AFC = 8 and FSH = 8.5 IU/L, the LP = -0.359 and the probability for low ovarian response is 0.411, or 41.1%.

Combined model

The regression models for high and low ovarian response had three predictors in common: age, AMH and AFC. The added value of FSH in the model for high ovarian response, although statistically significant, was not overwhelming. The same is true for menstrual cycle length in the model for low ovarian response. Without these factors, the AUC would decrease by only 0.006 and 0.004 for high and low ovarian response, respectively. Although age could also be dropped from the model without losing much predictive power, this factor was kept in the model as it is readily available. It should be noted that predicting high and low ovarian response based on the combined regression model should be based on different regression equations (Table 3, third and fourth rows). For the 38-year-old patient with AMH = 1.8 ng/mL and AFC = 11, the linear predictors for high and low ovarian response are $-2.504$ and $-2.550$, respectively and the associated probabilities are 7.6% and 7.2%, respectively (the estimates based on previous models were 7.3% and 7.3%, respectively). The remaining
85.2 % is the probability of a normal ovarian response between six and 18 oocytes.

Interpretation and application of the model would be simpler if age, AMH and AFC were classified as ‘high’ or ‘low,’ for example, by using a threshold that optimizes sensitivity and specificity for each single factor. For high ovarian response, these thresholds are age ≤37 years, AMH ≥2.24 ng/mL and AFC ≥13 (details not shown). For low ovarian response, the values are age ≥39 years, AMH ≤1.03 ng/mL and AFC ≤9. However, it is well known that dichotomization of continuous covariates leads to loss of information. Indeed, the AUC of the simpler model for high ovarian response drops to 0.867 (from 0.882) and the AUC of the simpler model for high ovarian response drops to 0.841 (also from 0.882). For this reason, the simpler models were not pursued further.

Model validation
The bootstrap validation of the model for high ovarian response (including variable selection) resulted in a median AUC of 0.895 in the validation samples (2.5 and 97.5 percentage points: 0.862 and 0.923). The median calibration slope was 0.990 (0.964–1.004). The validation of the model for low ovarian response based on the same 500 bootstrap samples resulted in a median AUC of 0.890 (0.857–0.917) and a median calibration slope of 0.937 (0.557–1.461). These results suggested good discrimination and calibration for high and low ovarian response.

Comparison with the model of Polyzos et al.
Our findings agree with those of Polyzos et al. [10] in that AMH and AFC are important predictors of ovarian response. Polyzos et al. developed models for excessive ovarian response (>20 oocytes retrieved) and poor ovarian response (<3 oocytes retrieved) based on AMH and AFC. The linear predictor for excessive ovarian response based on our data would be LP = −7.287 + 0.664 × AMH + 0.260 × AFC (details not shown), rather similar to the regression equation of Polyzos et al. (z = −6.782 + 0.557 × AMH + 0.172 × AFC).

Our linear predictor for poor ovarian response, LP = 0.964 − 2.710 × AMH − 0.167 × AFC, however, is different from their regression equation (z = 2.161 − 0.991 × AMH − 0.171 × AFC). The main reason is that the percentage of poor responders in our data set is markedly lower than reported by Polyzos et al. (6.7 % versus 34.3 %). This difference could not be accounted for by possibly different values of AMH and AFC in our population. The percentages of excessive response were similar (9.5 % versus 8.6 %). Using the linear predictors of Polyzos et al. in our data resulted in calibration slopes of 1.31 and 1.72 for excessive and poor response, respectively. These were statistically significantly different from one (P = 0.032 and P = 0.0032, respectively), suggesting that these predictors should not be used for older women. Predictive models inevitably reflect the data set from which they are derived, which is why we made the validation effort.

Discussion
In the population of women in the Pursue trial aged 35–42 years old undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol, the predictive factors for high ovarian stimulation were age, AFC, basal
FSH and AMH, factors previously identified from rFSH GnRH agonist and antagonist protocols [5–8]. In the older patient population in the Pursue trial [12], increased menstrual cycle length was identified as a factor that decreased the risk of low ovarian response. Women with a history of polycystic ovary syndrome were excluded. Compared with younger women (18–36 years old) undergoing ovarian stimulation with rFSH in a GnRH antagonist protocol, in the current analyses, increased LH and BMI [16] were not identified as predictors of high ovarian response [8].

In this study, AMH concentrations were measured on frozen serum samples using the Active AMH Gen II ELISA pre-mix assay. For stored samples, there is no difference between the pre-mix and post-mix protocols in AMH concentrations, as complement degradation has already occurred resulting in minimal interference in the assay [17].

Limits of high (>18 oocytes retrieved) and low (<6 oocytes retrieved) ovarian response used in the current analyses were selected as subjects with more than 18 oocytes recovered have an increased risk of OHSS [3] and those with fewer than six oocytes recovered have a compromised chance of pregnancy [1, 2]. These limits are consistent with previous publications on excessive and low ovarian response [7, 8].

In a retrospective analysis of a prospective randomized trial in which patients aged 18–36 years were treated with corifollitropin alfa or rFSH in a GnRH antagonist protocol, the ongoing pregnancy success rates in high responders (186 subjects with >18 oocytes) were at least as high as in patients with fewer than 18 oocytes [18]. This difference from the Sunkara analysis [1] may be related to the fact that these were women with a normal menstrual cycle and body weight range, and those with extremes in AFC and with polycystic ovary syndrome were excluded. Also, the Sunkara analysis was mainly an analysis of GnRH agonist cycles [1].

The current analyses of older women undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol uphold that age of the subject, AFC and AMH are strong predictors of ovarian response, as indicated in younger women undergoing ovarian stimulation with rFSH in a GnRH agonist or antagonist protocol.

We conclude that in women aged 35 to 42 years undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol, AMH, AFC and age at the start of stimulation were prognostic for both high and low ovarian response, in addition to FSH for high ovarian response and menstrual cycle length for low ovarian response.

Abbreviations
AF: Antral follicle count; AMH: Anti-Müllerian hormone; AUC: Area under the curve; BMI: Body mass index; E2: Estradiol; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; ICSI: Intracytoplasmic sperm injection; IVF: In vitro fertilization; LH: Luteinizing hormone; OHSS: Ovarian hyperstimulation syndrome; P: Progesterone; r: Recombinant; ROC: Receiver operating characteristic.

Competing interests
SO has received travel and honoraria fees from Merck & Co., Inc. SMN has received consultancy fees from Merck & Co., Inc., Merck Serono, Ferring Pharmaceuticals, Beckman Coulter and Roche Diagnostics. PV is a former employee of MSD BV, Oss. BJS is a current employee of Merck & Co., Inc., Kenilworth, NJ and may own stock/stock options in the company.

Authors’ contributions
SO and BJS took part in the conception and design of the study and acquisition of data. PV and BJS took part in analysis of the data and drafting the manuscript. All authors took part in the interpretation of data, critical
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